Gdański Uniwersytet Medyczny

Rozprawa doktorska

Wpływ liczby powtórzeń i czasu trwania okresowych ruchów kończyn podczas snu na częstość i zmienność rytmu serca oraz wartości ciśnienia tętniczego – analiza retrospektywna

The impact of the number of repetitions and duration of periodic limb movements during sleep on heart rate variability, heart rate, and blood pressure – a retrospective analysis

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Wyrażam głęboką wdzięczność

Profesorowi dr. hab. Mariuszowi Siemińskiemu, mojemu promotorowi,
za wspólną drogę, cenne wskazówki oraz nieustanne wsparcie
w trakcie realizacji niniejszej rozprawy doktorskiej.

Profesorowi dr. hab. Pawłowi Winklewskiemu, mojemu przełożonemu,
za inspirację, wiarę we mnie i pomoc, które były dla mnie
bezcennym źródłem motywacji oraz rozwoju naukowego.

Doktor Małgorzacie Grzywińskiej, mojej promotor pomocniczej,
za życzliwość, wsparcie i gotowość do dzielenia się swoim czasem i wiedzą.

Współautorom artykułów wchodzących w skład niniejszej rozprawy,
za inspirującą współpracę.

Moim Rodzicom, Piotrowi i Leosiowi,
za nieustające oparcie, cierpliwość i siłę,
dzięki którym mogłam zrealizować tę rozprawę.

SPIS TREŚCI

WYKAZ PRAC WCHODZĄCYCH W SKŁAD ROZPRAWY DOKTORSKIEJ / LIST OF MANUSCRIPTS INCLUDED IN THE DOCTORAL DISSERTATION

Małkiewicz Marta A., Malinowski Krzysztof S., Grzywińska Małgorzata, Partinen Eemil
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Heart Rate Variability and Interoception in Periodic Limb Movements in Sleep: Interference with Psychiatric Disorders?

Journal of Clinical Medicine, 2024; vol. 13, nr 20, art. ID 6129, s. 1–13,
DOI: 10.3390/jcm13206129
IF 3,000 | MNiSW: 140 | praca poglądowa/przeglądowa

Małkiewicz Marta A., Grzywińska, Małgorzata, Malinowski, Krzysztof S., Partinen Eemil,
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Effect of Series of Periodic Limb Movements in Sleep on Blood Pressure, Heart Rate and High Frequency Heart Rate Variability

Neurologia i Neurochirurgia Polska, 2024; vol. 58, nr 2, s. 167–175
DOI: 10.5603/pjnns.95117
IF 2,900 | MNiSW: 100 | praca oryginalna

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Partinen Markku, Pyrzowski Jan, Wszędybył-Winklewska Magdalena

Time-Dependent Autonomic Dysregulation and Co-Activation Induced by Periodic Limb Movements in Sleep

Journal of Clinical Medicine, 2025; vol. 14, nr 6, art. ID 1940, s. 1–15
DOI: 10.3390/jcm14061940
IF 3,000 | MNiSW: 140 | praca oryginalna

POZOSTAŁY DOROBEK NAUKOWY

Publikacje naukowe nie wchodzące w skład rozprawy doktorskiej

Lp.	Publikacja	Czasopismo (rok)	IF	MNiSW	Pierwszy autor
1	Relative cerebral blood transit time decline and neurological improvement in patients after internal carotid artery stenting	Advances in Experimental Medicine and Biology (2019)	2,450	5	nie
2	Blood–brain barrier permeability and physical exercise	Journal of Neuroinflammation (2019)	5,793	100	tak
3	Substances of abuse and the blood–brain barrier: interactions with physical exercise	Neuroscience & Biobehavioral Reviews (2020)	8,989	200	tak
4	The role of melatonin and melatonin receptor agonist in the prevention of sleep disturbances and delirium in intensive care unit: a clinical review	Sleep Medicine (2020)	3,492	100	nie
5	Mild poikilocapnic hypoxia increases very low frequency haemoglobin oxygenation oscillations in prefrontal cortex	Biological Research (2021)	7,634	140	nie

Grant NCN Preludium

Kierowanie projektem badawczym finansowanym przez Narodowe Centrum Nauki w ramach grantu PRELUDIUM 2017 realizowanego na podstawie umowy nr UMO-2019/33/N/NZ5/02815 pt.: „Wpływ leczenia inhibitorami wychwytu zwrotnego serotoniny oraz wysiłkiem fizycznym na szczelność bariery krew–mózg, stężenie wybranych neurotransmiterów kory przedczołowej i hipokampa, szlak kynureninowy oraz nastrój u chorych na depresję”.

Uczestnictwo w konferencjach naukowych i szkoleniach

- Streszczenie konferencyjne zgłoszone i zaprezentowane podczas 13th International Conference on Cerebral Vascular Biology (CVB 2019), Miami. Tytuł abstraktu: *Association between relative computed tomography indicators of cerebral microperfusion and clinical symptoms reported by patients undergoing internal carotid artery stenting*.
- Streszczenie konferencyjne zgłoszone i zaprezentowane podczas European Psychiatric Association Congress (EPA) 2023. Tytuł abstraktu: *Series of periodic limb movements in sleep and heart rate variability*.
- Staż zagraniczny zrealizowany w ramach programu wymiany European Federation of Psychiatric Trainees (EFPT). Uczestnictwo w „Sleep and Circadian Neurophysiology Programme”, realizowanym w Psychiatric Clinic Vrapče w Zagrzebiu (Chorwacja), w terminie 11–25 maja 2020 r.

Specjalizacja w dziedzinie psychiatrii

Uzyskanie tytułu specjalisty w dziedzinie psychiatrii w 2023 roku.

Wskaźniki bibliometryczne dla dorobku naukowego

- Łączna liczba publikacji: 8
- Łączny Impact Factor: 36,758
- Łączna punktacja MNiSW: 925 punktów
- Indeks Hirscha (H-index): 4
- Łączna liczba cytowań: 254,
  w tym 249 cytowań po wyłączeniu autocytowań (wg danych na dzień 16.12.2025)
- Pierwsze autorstwo: 5 publikacji
- 2 publikacje w czasopismach z pierwszego decyla Journal Citation Reports (D1):
    - *Neuroscience & Biobehavioral Reviews*
    - *Journal of Neuroinflammation*

SŁOWA KLUCZOWE / KEYWORDS

Okresowe ruchy kończyn podczas snu (PLMS), zmienność rytmu serca (HRV), układ autonomiczny (ANS), koaktywacja autonomiczna, interocepcja, zespół niespokojnych nóg (RLS), regulacja sercowo-naczyniowa, zaburzenia psychiczne, ryzyko sercowo-naczyniowe

Periodic limb movements in sleep (PLMS), heart rate variability (HRV), autonomic nervous system (ANS), autonomic co-activation, interoception, restless legs syndrome (RLS), cardiovascular regulation, psychiatric disorders, cardiovascular risk

STRESZCZENIE W JĘZYKU POLSKIM

PLMS – okresowe ruchy kończyn podczas snu

RLS – zespół niespokojnych nóg

AASM – Amerykańska Akademia Medycyny Snu

HRV – zmienność rytmu serca

HF-HRV – składowa wysokiej częstotliwości zmienności rytmu serca

LF-HRV – składowa niskiej częstotliwości zmienności rytmu serca

HR – częstość akcji serca

BP – ciśnienie tętnicze

SBP – skurczowe ciśnienie tętnicze

DBP – rozkurczowe ciśnienie tętnicze

PLMI – wskaźnik okresowych ruchów kończyn podczas snu

ANS – autonomiczny układ nerwowy

PSG – badanie polisomnograficzne

AHI – wskaźnik bezdechów i spłyceń oddechu

EEG – elektroencefalografia

EOG – elektrookulografia

EMG – elektromiografia

EKG – elektrokardiografia

RR – odstęp RR w zapisie EKG (czas pomiędzy kolejnymi zespołami QRS)

PTT – czas przejścia fali tętna

ACC – przednia część zakrętu obręczy

PFC – kora przedczołowa

1. WPROWADZENIE

Okresowe ruchy kończyn podczas snu (PLMS, *Periodic Limb Movements in Sleep*) stanowią jedno z częściej opisywanych zaburzeń ruchowych snu. Charakteryzują się powtarzalnymi, mimowolnymi ruchami kończyn dolnych, obejmującymi zwykle grzbietowe zgięcie stopy, wyprost palucha oraz zgięcie w stawach kończyn dolnych. Pojedynczy epizod trwa 0,5–10 sekund i pojawia się w odstępach 5–90 sekund. Zgodnie z kryteriami AASM stosowanymi w diagnostyce polisomnograficznej, kolejne ruchy występujące w odstępie krótszym niż 90 sekund klasyfikuje się jako serię PLMS, natomiast przerwa równa lub dłuższa niż 90 sekund wyznacza początek nowej sekwencji. Organizacja epizodów w powtarzalne serie jest charakterystycznym elementem PLMS i może mieć znaczenie dla interpretacji ich następstw fizjologicznych.

PLMS obserwuje się u większości pacjentów z zespołem niespokojnych nóg, a także w innych zaburzeniach snu oraz wybranych chorobach neurologicznych. W literaturze opisano również ich współwystępowanie z niektórymi zaburzeniami psychicznymi, choć zakres i charakter tych zależności pozostają słabiej poznane. Niezależnie od kontekstu klinicznego, liczne badania wskazują, że epizodom PLMS towarzyszą krótkotrwałe zmiany w czynności autonomicznego układu nerwowego, przejawiające się m.in. przyspieszeniem czynności serca, wzrostem ciśnienia tętniczego oraz zmianami parametrów zmienności rytmu serca (HRV). Typowo opisuje się obniżenie składowej wysokiej częstotliwości (HF-HRV) oraz względny wzrost wartości niskoczęstotliwościowych (LF-HRV), co interpretowane bywa jako przejściowa przewaga aktywności współczulnej towarzysząca epizodom ruchowym.

Zmienność rytmu serca (HRV) jest jednym z podstawowych, nieinwazyjnych narzędzi oceny regulacji autonomicznej. Komponent wysokiej częstotliwości odzwierciedla przede wszystkim aktywność przywspółczulną, natomiast składowa niskiej częstotliwości pozostaje pod wpływem zarówno mechanizmów współczulnych, jak i odruchu z baroreceptorów. Parametry HRV pozwalają na analizę krótkotrwałych zmian równowagi autonomicznej towarzyszących epizodom PLMS i stanowią ważne uzupełnienie innych miar fizjologicznych. W piśmiennictwie zwraca się także uwagę, że zaburzenia HRV oraz regulacji autonomicznej opisywano u osób z wybranymi zaburzeniami psychicznymi, zwłaszcza afektywnymi i lękowymi. Dodatkową płaszczyzną możliwych powiązań jest interocepcja, rozumiana jako percepcja sygnałów wewnętrznych organizmu, której nieprawidłowości opisywano zarówno w PLMS, jak i w niektórych zaburzeniach psychicznych. Zjawiska te mogą wskazywać na pewne wspólne mechanizmy regulacyjne, choć ich charakter pozostaje przedmiotem dalszych badań.

W ostatnich latach zwrócono uwagę na możliwość występowania tzw. koaktywacji autonomicznej, polegającej na równoczesnym pobudzeniu gałęzi współczulnej i przywspółczulnej. Opisywano ją w różnych kontekstach fizjologicznych i klinicznych, natomiast jej znaczenie w zaburzeniach ruchowych snu nie zostało dotychczas jednoznacznie określone. Wyniki przedstawione w niniejszej rozprawie wskazują, że elementy koaktywacji mogą pojawiać się również w przebiegu PLMS, co sugeruje, że wzorzec odpowiedzi autonomicznej w tych epizodach może być bardziej złożony, niż zakładają tradycyjne modele oparte wyłącznie na chwilowej dominacji aktywności współczulnej. Obserwacja ta może stanowić istotne uzupełnienie dotychczasowej wiedzy na temat dynamiki autonomicznej w przebiegu PLMS.

PLMS pozostają zjawiskiem istotnym z perspektywy medycyny snu, kardiologii, neurologii oraz wybranych obszarów psychiatrii. Zmiany parametrów HRV, HR i BP obserwowane w trakcie epizodów ruchowych mogą mieć znaczenie dla zrozumienia mechanizmów ich krótkotrwałych następstw hemodynamicznych oraz potencjalnych implikacji klinicznych. HRV może w tym kontekście pełnić rolę parametru integrującego, umożliwiającego ocenę funkcjonowania autonomicznego układu nerwowego w różnych stanach klinicznych.

Dotychczasowe badania dotyczące PLMS koncentrowały się głównie na analizie ich częstości (PLMI). Znacznie mniej uwagi poświęcono parametrom jakościowym, takim jak czas trwania poszczególnych ruchów, oraz właściwościom sekwencyjnym, obejmującym liczbę kolejnych epizodów w serii. Rzadko analizowano także krótkookresową dynamikę odpowiedzi autonomicznych, w tym zmiany HRV, HR i BP w kolejnych epizodach ruchowych, mimo że parametry te mogą dostarczać kluczowych informacji o regulacji autonomicznej.

Publikacje składające się na niniejszą rozprawę obejmują opracowanie przeglądowe oraz dwa badania empiryczne dotyczące regulacji autonomicznej w odniesieniu do okresowych ruchów kończyn podczas snu. Rozprawa stanowi uzupełnienie dotychczasowej wiedzy poprzez analizę wpływu liczby powtórzeń i czasu trwania epizodów PLMS na wybrane parametry autonomiczne i sercowo-naczyniowe, z uwzględnieniem dynamiki krótkotrwałych zmian.

2. CELE PRACY

Celem niniejszej rozprawy było zbadanie, w jaki sposób wybrane cechy okresowych ruchów kończyn podczas snu (PLMS)- przede wszystkim liczba kolejnych epizodów w serii oraz czas trwania pojedynczych ruchów wiążą się z krótkotrwałymi zmianami parametrów odzwierciedlających aktywność autonomicznego układu nerwowego i układu sercowo-naczyniowego, takich jak zmienność rytmu serca (HRV), częstość akcji serca (HR) oraz ciśnienie tętnicze (BP). Część empiryczną uzupełniono przeglądem literatury dotyczącym możliwych powiązań PLMS z regulacją autonomiczną oraz interocepcją.

Publikacja 1 (praca przeglądowa – Heart Rate Variability and Interoception in Periodic Limb Movements in Sleep: Interference with Psychiatric Disorders? J Clin Med. 2024)

Cel: Przedstawienie i krytyczna analiza dostępnych badań dotyczących powiązań okresowych ruchów kończyn podczas snu (PLMS) z regulacją autonomiczną, w szczególności ze zmiennością rytmu serca oraz interocepcją, a także omówienie ich możliwych odniesień do wybranych zaburzeń psychicznych.

Cel szczegółowy: Przedstawienie i syntetyczne omówienie badań wskazujących, że zarówno w PLMS, jak i w niektórych zaburzeniach psychicznych obserwuje się zbliżone zaburzenia regulacji autonomicznej, w tym obniżone wartości parametrów HRV. W artykule omówiono również koncepcję interocepcji jako potencjalnego elementu łączącego funkcjonowanie autonomiczne z przetwarzaniem emocjonalnym. Analiza literatury wykazała, że rola HRV i interocepcji w powiązaniach między PLMS a funkcjonowaniem psychicznym pozostaje niewystarczająco poznana, co podkreśla potrzebę dalszych badań nad tym, w jaki sposób czynniki te mogą kształtować zależności między PLMS a objawami psychicznymi.

Publikacja 2 (praca oryginalna – Effect of Series of Periodic Limb Movements in Sleep on Blood Pressure, Heart Rate and High Frequency Heart Rate Variability. Neurol Neurochir Pol 2023)

Cel: Ocena krótkotrwałych zmian parametrów regulacji autonomicznej i układu sercowo-naczyniowego w kolejnych epizodach serii PLMS, analizowanych w bardzo krótkich, następujących po sobie oknach czasowych. Analizę przeprowadzono na dużym zbiorze epizodów PLMS pozyskanych retrospektywnie z zapisów polisomnograficznych, co umożliwiło ocenę powtarzalnych wzorców odpowiedzi autonomicznej.

Cel szczegółowy: Celem szczegółowym była ocena, czy:

1. kolejne epizody w serii PLMS wiążą się ze stopniowymi zmianami parametrów autonomicznych, w tym składowej wysokiej częstotliwości HRV (HF-HRV), ocenianych w krótkich, nakładających się oknach czasowych;
2. w przebiegu serii PLMS dochodzi do modyfikacji parametrów hemodynamicznych, takich jak częstość akcji serca (HR) oraz skurczowe i rozkurczowe ciśnienie tętnicze (BP);
3. obserwowany wzrost HF-HRV przy jednoczesnym braku istotnych zmian HR i BP może odzwierciedlać bardziej złożoną odpowiedź autonomiczną, obejmującą elementy współwystępowania aktywności współczulnej i przywspółczulnej.

Publikacja 3 (praca oryginalna – Time-Dependent Autonomic Dysregulation and Co-Activation Induced by Periodic Limb Movements in Sleep. J Clin Med 2025)

Cel: Ocena, czy czas trwania pojedynczych epizodów PLMS wpływa na przebieg krótkotrwałych zmian w parametrach autonomicznych i hemodynamicznych. Analiza została przeprowadzona na retrospektywnie zebranych zapisach polisomnograficznych, co pozwoliło na porównanie odpowiedzi fizjologicznej pomiędzy epizodami krótszymi i dłuższymi.

Cel szczegółowy:

1. ocena, czy epizody PLMS różniące się czasem trwania wykazują odmienne zmiany w parametrach zmienności rytmu serca (HRV) ze szczególnym uwzględnieniem składowej wysokiej częstotliwości (HF-HRV);
2. analiza, czy czas trwania epizodów PLMS wiąże się z różnym nasileniem zmian hemodynamicznych, obejmujących skurczowe i rozkurczowe ciśnienie tętnicze (SBP, DBP) oraz częstość akcji serca (HR);
3. sprawdzenie, czy dłużej trwające epizody PLMS wywołują taki profil odpowiedzi autonomicznej, który może sugerować współistnienie elementów aktywacji

współczulnej i przywspółczulnej, co wskazywałoby na bardziej złożony wzorzec regulacji autonomicznej niż modele oparte wyłącznie na przejściowej aktywacji układu współczulnego.

Podsumowanie

Nadrzędnym celem rozprawy było lepsze zrozumienie, jak funkcjonuje regulacja autonomiczna w przebiegu okresowych ruchów kończyn podczas snu (PLMS). Ujęcie to obejmowało zarówno analizę teoretyczną, jak i wyniki własnych badań. W części przeglądowej omówiono dotychczasowe dane dotyczące zależności między PLMS, zmiennością rytmu serca (HRV), interocepcją oraz wybranymi zaburzeniami psychicznymi, wskazując na możliwe mechanizmy, które mogłyby łączyć te obszary.

Dwa badania empiryczne pozwoliły szczegółowo ocenić krótkotrwałe zmiany w parametrach autonomicznych i hemodynamicznych, uwzględniając zarówno liczbę kolejnych epizodów w serii, jak i czas trwania pojedynczych ruchów. Uzyskane wyniki pokazują, że odpowiedź autonomiczna w przebiegu PLMS może być bardziej złożona, niż wynika to z tradycyjnych ujęć opartych wyłącznie na krótkotrwałej aktywacji układu współczulnego.

Wnioski z pracy sugerują, że PLMS warto rozpatrywać nie tylko w kontekście zaburzeń snu, lecz także jako zjawisko powiązane z regulacją autonomiczną istotną dla zdrowia sercowo-naczyniowego i funkcjonowania psychicznego. Wskazano również obszary, które wymagają dalszych badań, zwłaszcza dotyczące roli HRV i interocepcji oraz ich potencjalnego znaczenia klinicznego.

4. OMÓWIENIE PUBLIKACJI WCHODZĄCYCH W SKŁAD ROZPRAWY DOKTORSKIEJ

Publikacja 1

Pierwsza publikacja ma charakter przeglądowy i koncentruje się na powiązaniach między okresowymi ruchami kończyn podczas snu (PLMS), regulacją autonomiczną, zmiennością rytmu serca (HRV), interocepcją oraz wybranymi zaburzeniami psychicznymi. W pracy zwrócono uwagę, że PLMS, choć formalnie klasyfikowane jako zaburzenie ruchowe snu — wiążą się z istotnymi zmianami w funkcjonowaniu autonomicznego układu nerwowego, co odzwierciedlają m.in. obniżone wartości HRV oraz zaburzenia równowagi pomiędzy aktywnością współczulną i przywspółczulną.

W przeglądzie zestawiono wyniki badań wskazujące, że zbliżony profil zaburzeń autonomicznych opisuje się również u osób z depresją i zaburzeniami lękowymi. Obniżona HRV, zmieniona reaktywność autonomiczna i trudności w regulacji emocjonalnej pojawiają się zarówno w tych zaburzeniach, jak i w PLMS, co może sugerować częściowo wspólny mechanizm neurobiologiczny.

Istotnym elementem publikacji jest omówienie interocepcji, rozumianej jako zdolność do odbioru i interpretacji sygnałów płynących z wnętrza organizmu. Wskazano, że nieprawidłowości w zakresie interocepcji opisywano zarówno w PLMS, jak i w wybranych zaburzeniach psychicznych, a ich podłożem mogą być zaburzenia funkcjonowania struktur korowych odpowiedzialnych za integrację informacji somatycznych i emocjonalnych. W tym kontekście podkreślono rolę kory wyspy, przedniej części zakrętu obręczy (ACC) oraz obszarów przedczołowych jako głównych ośrodków integrujących sygnały autonomiczne i emocjonalne.

Na podstawie przeglądu literatury przedstawiono model, w którym zaburzenia regulacji autonomicznej, obniżone wartości HRV oraz nieprawidłowa interocepcja mogą stanowić wspólne podłoże zarówno dla PLMS, jak i dla części zaburzeń psychicznych. Jednocześnie podkreślono, że PLMS poprzez fragmentację snu oraz przejściowe pobudzenie autonomiczne mogą wpływać na nasilenie objawów psychicznych, przyczyniając się do utrwalenia dysregulacji autonomicznej.

W podsumowaniu wskazano na potrzebę dalszych badań nad tym, w jakim stopniu parametry HRV oraz różne wymiary interocepcji mogą pomóc w lepszym zrozumieniu regulacji autonomicznej u pacjentów z PLMS oraz czy mogą mieć wartość kliniczną w ocenie współwystępujących zaburzeń psychicznych.

Publikacja 2

Publikacja ta przedstawia wyniki badania własnego dotyczącego krótkotrwałych zmian parametrów hemodynamicznych i autonomicznych w odpowiedzi na kolejne PLMS występujące w obrębie analizowanych serii ruchów**.** W badaniu oceniano, czy liczba następujących po sobie PLMS w serii wiąże się z systematycznymi zmianami zmienności rytmu serca, częstości akcji serca oraz ciśnienia tętniczego. Analizę oparto na retrospektywnie pozyskanych zapisach polisomnograficznych pacjentów z zespołem niespokojnych nóg, co pozwoliło na ocenę ponad tysiąca epizodów PLMS i uchwycenie bardzo dynamicznych zmian fizjologicznych towarzyszących narastaniu serii ruchów.

Do analizy włączono pięciu pacjentów z rozpoznanym RLS, u których zarejestrowano łącznie 1 348 PLMS. Uwzględniono wyłącznie epizody niewywołujące przebudzeń. Z badania wykluczono osoby z chorobami sercowo-naczyniowymi, metabolicznymi, zaburzeniami psychicznymi oraz pacjentów przyjmujących leki wpływające na układ autonomiczny. Wykluczono również pacjentów ze wskaźnikiem bezdechów i spłyceń oddechu (AHI) ≥ 5, aby uniknąć wpływu zaburzeń oddychania na parametry autonomiczne.

W zapisie polisomnograficznym rejestrowano m.in. wielokanałowe EEG, EOG, EMG bródkowe i obustronne EMG mięśni piszczelowych przednich, a także trzyodprowadzeniowy zapis EKG. Czynność oddechową monitorowano przy pomocy kaniuli donosowej, pasów oddechowych i pulsoksymetru. Ciśnienie tętnicze mierzono metodą beat-to-beat z wykorzystaniem czasu przejścia fali tętna (PTT). Częstość rytmu serca wyliczano na podstawie automatycznej detekcji szczytów QRS.

Parametry autonomiczne i hemodynamiczne — skurczowe i rozkurczowe ciśnienie tętnicze (SBP, DBP), częstość rytmu serca (HR) oraz zmienność rytmu serca w paśmie wysokiej częstotliwości (HF-HRV) oceniano dla kolejnych pojedynczych interwałów RR, analizowanych w blokach po 10 interwałów.

Dla każdego z 10 kolejnych interwałów RR obliczano wszystkie wymienione parametry w trzech sytuacjach:

- w 10 interwałach RR poprzedzających początek pierwszej serii PLMS,
- w 10 interwałach RR rozpoczynających pierwszą serię PLMS,
- w kolejnych dziesięciointerwałowych blokach po każdym PLMS w serii.

Tak zdefiniowane segmenty umożliwiły uchwycenie zmian zachodzących w bardzo krótkich odstępach czasowych równolegle z narastaniem liczby PLMS w serii. Dzięki temu możliwa była szczegółowa ocena dynamiki odpowiedzi autonomicznej, a nie jedynie pojedynczych wartości przed i po epizodzie.

Analiza wykazała, że wraz z kolejnymi PLMS w serii nie dochodziło do istotnych zmian ani w częstości rytmu serca, ani w wartościach skurczowego i rozkurczowego ciśnienia tętniczego. Wynik ten pozostaje w pewnym kontraście do wcześniejszych prac, w których opisywano wyraźnie nasilone reakcje hemodynamiczne w przebiegu PLMS.

Odmienny obraz uzyskano natomiast w zakresie HRV. W miarę narastania liczby PLMS w serii obserwowano systematyczny, statystycznie istotny wzrost komponentu HF-HRV. Najbardziej wyraźne nasilenie tego zjawiska pojawiało się po ośmiu PLMS w jednej serii, co wskazuje, że odpowiedź przywspółczulna narasta wraz z postępem serii.

Taki wzorzec, czyli wzrost aktywności przywspółczulnej przy braku równoległych zmian hemodynamicznych sugeruje, że odpowiedź autonomiczna na PLMS może mieć bardziej złożony charakter, obejmujący współistnienie elementów pobudzenia współczulnego i przywspółczulnego**.** To właśnie takie współwystępowanie, czyli koaktywacja autonomiczna, może wyjaśniać, dlaczego rosnące HF-HRV nie przekłada się na spadek HR czy ciśnienia tętniczego, pobudzenie współczulne może bowiem równoważyć efekt przywspółczulny na poziomie sercowo-naczyniowym.

Wyniki tej publikacji wpisują PLMS w szerszy kontekst zaburzeń równowagi autonomicznej. Uzyskany profil odpowiedzi: rosnące HF-HRV bez zmian HR i BP, stoi w opozycji do prostych modeli, w których PLMS traktowane są wyłącznie jako epizody towarzyszącej im aktywacji współczulnej Zamiast tego wskazuje on na możliwość występowania bardziej subtelnych, naprzemiennych lub współbieżnych reakcji obu gałęzi ANS.

W praktyce klinicznej zjawisko koaktywacji ma istotne znaczenie. Jednoczesne pobudzenie układu współczulnego i przywspółczulnego może sprzyjać zaburzeniom rytmu serca, co w połączeniu z obserwacjami epidemiologicznymi sugerującymi zwiększone ryzyko migotania przedsionków u pacjentów z PLMS nadaje wynikom badania realny wymiar kliniczny.

Praca została przez Redakcję opatrzona artykułem redakcyjnym na zaproszenie (ang. invited editorial) podkreślającym jej znaczenie teoretyczne i kliniczne. Publikacja podkreśla potrzebę dalszych prac dotyczących autonomicznych następstw PLMS, zwłaszcza z zastosowaniem metod pozwalających na jednoczesną ocenę obu gałęzi ANS oraz ich interakcji.

Publikacja 3

Publikacja ta przedstawia wyniki kolejnego badania własnego dotyczącego autonomicznej odpowiedzi na okresowe ruchy kończyn podczas snu, tym razem ze szczególnym uwzględnieniem wpływu czasu trwania pojedynczych PLMS na dynamikę odpowiedzi autonomicznej. Celem analizy było sprawdzenie, czy dłużej trwające PLMS wywołują odmienne zmiany hemodynamiczne i autonomiczne niż ruchy krótsze oraz czy czas trwania PLMS może modulować stopień współwystępowania aktywacji współczulnej i przywspółczulnej. Badanie oparto na retrospektywnej analizie zapisów polisomnograficznych pięciu pacjentów z zespołem niespokojnych nóg, co pozwoliło na ocenę łącznie 1 348 PLMS i prześledzenie zmian fizjologicznych zachodzących w bezpośrednim następstwie kolejnych epizodów ruchowych.

Zastosowano ten sam protokół rejestracji i kryteria włączenia/wyłączenia, jak w badaniu opisanym w Publikacji 2.

Parametry autonomiczne i hemodynamiczne: skurczowe i rozkurczowe ciśnienie tętnicze (SBP, DBP), częstość rytmu serca (HR) oraz zmienność rytmu serca w paśmie wysokiej częstotliwości (HF-HRV) oceniano dla kolejnych pojedynczych interwałów RR, analizowanych w blokach po 10 interwałów. Dla każdego z 10 kolejnych RR obliczano wszystkie wymienione parametry w trzech sytuacjach:

- w 10 interwałach RR poprzedzających początek pierwszej serii PLMS,
- w 10 interwałach RR rozpoczynających pierwszą serię PLMS,

- w kolejnych dziesięciointerwałowych blokach po każdym PLMS w serii.

Wyniki analizy wykazały, że wzrost HF-HRV pojawiał się w odpowiedzi na PLMS niezależnie od czasu trwania ruchu, co wskazuje na istotny udział aktywacji przywspółczulnej. Jednocześnie dla krótszych PLMS (poniżej mediany 2,1 s) nie obserwowano istotnych zmian SBP ani DBP, natomiast dłuższe ruchy (>2,1 s) wiązały się już z wyraźnym, istotnym statystycznie wzrostem zarówno SBP, jak i DBP. Brak zmian HR przy równoczesnym wzroście HF-HRV i wzroście ciśnienia w przypadku dłuższych PLMS sugeruje współistnienie aktywacji współczulnej i przywspółczulnej, czyli autonomiczną koaktywację.

Taki obraz odpowiedzi autonomicznej stanowi rozszerzenie wcześniejszych obserwacji, zgodnie z którymi PLMS mogą uruchamiać jednocześnie mechanizmy współczulne i przywspółczulne. Badanie to pokazuje jednak, że czas trwania PLMS jest czynnikiem modulującym tę odpowiedź, dłuższe epizody wywołują silniejszą odpowiedź hemodynamiczną, będącą prawdopodobnie efektem większego udziału aktywacji współczulnej, która równocześnie „nakłada się" na narastający wzrost aktywności przywspółczulnej.

W konsekwencji wyniki te sugerują, że czas trwania pojedynczych PLMS może być markerem nasilenia autonomicznej dysregulacji. Obserwowany wzorzec, zwłaszcza w przypadku dłuższych ruchów, może odzwierciedlać rosnące ryzyko niestabilności autonomicznej, która u pacjentów z chorobami układu krążenia lub innymi współistniejącymi zaburzeniami mogłaby zwiększać podatność na zdarzenia kardiologiczne.

Publikacja ta stanowi ważny krok w kierunku lepszego zrozumienia, jak czas trwania PLMS wpływa na równowagę autonomiczną, oraz wskazuje, że ocena długości ruchów, obok ich częstości, może mieć znaczenie w bardziej precyzyjnej ocenie ryzyka u pacjentów z PLMS.

5. WNIOSKI

W niniejszej rozprawie przeanalizowano okresowe ruchy kończyn podczas snu (PLMS) z trzech perspektyw: ich związku z regulacją autonomiczną, możliwych powiązań ze zdrowiem psychicznym oraz krótkotrwałych zmian hemodynamicznych towarzyszących tym epizodom.

Pierwsza publikacja – o charakterze przeglądowym, pozwoliła umieścić PLMS w szerszym kontekście funkcjonowania autonomicznego układu nerwowego. Przedstawiono dane sugerujące, że zarówno u osób z PLMS, jak i u pacjentów z niektórymi zaburzeniami psychicznymi występują podobne trudności w regulacji autonomicznej, obejmujące obniżoną zmienność rytmu serca oraz zaburzenia interocepcji. Literatura wskazuje, że zjawiska te mogą się wzajemnie wzmacniać i wpływać zarówno na przebieg PLMS, jak i na funkcjonowanie emocjonalne. Podkreślono również znaczenie interocepcji jako procesu łączącego percepcję sygnałów fizjologicznych z regulacją emocji.

Druga publikacja – badanie własne, dotyczyła krótkotrwałych zmian parametrów autonomicznych w trakcie serii PLMS. Wykazano, że wraz z kolejnymi epizodami PLMS rosła aktywność przywspółczulna (rozumiana jako wzrost HF-HRV), przy jednoczesnym utrzymywaniu się stabilnych wartości ciśnienia tętniczego oraz częstości akcji serca. Sugeruje to, że odpowiedź autonomiczna na PLMS jest bardziej złożona, niż zakładają tradycyjne modele oparte wyłącznie na pobudzeniu współczulnym, i może obejmować równoczesną aktywację obu gałęzi układu autonomicznego – zjawisko określane jako koaktywacja autonomiczna.

Trzecia publikacja koncentrowała się na znaczeniu czasu trwania pojedynczych PLMS. Wykazano, że dłuższe ruchy (powyżej 2,1 sekundy) wiązały się z wyraźniejszym wzrostem ciśnienia tętniczego oraz silniejszą odpowiedzią autonomiczną, obejmującą elementy aktywacji zarówno współczulnej, jak i przywspółczulnej. Wyniki te podkreślają, że nie tylko liczba ruchów, lecz również ich długość wpływa na sposób, w jaki organizm reaguje na PLMS, co wskazuje na konieczność uwzględniania parametrów czasowych w analizach tego zjawiska.

Jednym z najważniejszych atutów rozprawy jest jej innowacyjny charakter. W pracy zastosowano analizę odpowiedzi autonomicznej w wyjątkowo krótkich, następujących po sobie oknach czasowych, co stanowi rzadko wykorzystywane podejście w badaniach PLMS i pozwoliło uchwycić subtelną, szybko zmieniającą się dynamikę parametrów takich jak HF-HRV, HR i BP, niewidoczną w tradycyjnych analizach opartych na uśrednianiu sygnału. Wyniki rozprawy dostarczyły także pierwszych empirycznych przesłanek sugerujących możliwość występowania koaktywacji autonomicznej w przebiegu PLMS, co stanowi odejście od dominujących w literaturze ujęć, w których epizody te interpretowane są głównie jako przejaw przejściowej aktywacji współczulnej. Dodatkowo wprowadzono ocenę jakościowych cech PLMS, takich jak czas trwania pojedynczych ruchów czy ich pozycja w sekwencji, czyli parametrów dotychchczas praktycznie nieobecnych w badaniach koncentrujących się głównie na wskaźniku PLMI. W efekcie zaproponowano podejście, w którym PLMS traktowane są jako dynamiczny proces hemodynamiczno-autonomiczny, a nie jedynie zjawisko ruchowe, co otwiera nowe kierunki interpretacji dla badań nad regulacją autonomiczną i potencjalnym ryzykiem sercowo-naczyniowym.

Ograniczenia pracy również wymagają uwzględnienia. Liczebność próby w badaniach empirycznych była niewielka (pięciu pacjentów z RLS), co ogranicza możliwość uogólniania wyników. Analiza miała charakter retrospektywny i opierała się na danych z jednego ośrodka, co wiąże się z ryzykiem błędu selekcji i niejednorodności badanej populacji. Aktywność współczulna oceniana była jedynie pośrednio — na podstawie zmian ciśnienia tętniczego i braku możliwości rejestracji bezpośrednich wskaźników neurofizjologicznych — co ogranicza precyzję wnioskowania o mechanizmach odpowiedzi autonomicznej. Badania dotyczyły wyłącznie krótkotrwałych zmian hemodynamicznych i nie obejmowały dalszych konsekwencji klinicznych.

Pomimo tych ograniczeń, łączne wyniki wskazują, że PLMS nie są zjawiskiem ograniczonym wyłącznie do obszaru medycyny snu. Wykazują liczne powiązania z regulacją autonomiczną, mogą wpływać na jakość snu oraz odzwierciedlać szerszy kontekst funkcjonowania fizjologicznego i psychicznego. Analiza HRV w krótkich oknach czasowych oraz wybrane aspekty interocepcji mogą stanowić przydatne narzędzia diagnostyczne i monitorujące u pacjentów z PLMS.

Uzyskane wyniki wskazują także na konieczność dalszych, prospektywnych badań na większych grupach chorych, obejmujących bezpośrednie wskaźniki aktywności współczulnej oraz długoterminowe konsekwencje kliniczne. Wyniki te otwierają również przestrzeń do badań nad możliwością modyfikowania równowagi autonomicznej w tej populacji — zarówno metodami niefarmakologicznymi (treningi regulacji autonomicznej, interwencje behawioralne, neuromodulacja), jak i potencjalnie w przyszłości metodami farmakologicznymi ukierunkowanymi na precyzyjne modulowanie odpowiedzi autonomicznej towarzyszącej PLMS.

OTHER SCIENTIFIC ACHIEVEMENTS

Scientific publications not included in the doctoral dissertation

No.	Publication	Journal (year)	IF	MNiSW	First author
1	Relative cerebral blood transit time decline and neurological improvement in patients after internal carotid artery stenting	Advances in Experimental Medicine and Biology (2019)	2.450	5	no
2	Blood–brain barrier permeability and physical exercise	Journal of Neuroinflammation (2019)	5.793	100	yes
3	Substances of abuse and the blood–brain barrier: interactions with physical exercise	Neuroscience & Biobehavioral Reviews (2020)	8.989	200	yes
4	The role of melatonin and melatonin receptor agonist in the prevention of sleep disturbances and delirium in the intensive care unit: a clinical review	Sleep Medicine (2020)	3.492	100	no
5	Mild poikilocapnic hypoxia increases very low frequency haemoglobin oxygenation oscillations in the prefrontal cortex	Biological Research (2021)	7.634	140	no

NCN Preludium Grant

Leadership of a research project funded by the National Science Centre (NCN, Poland) within the PRELUDIUM 2017 grant scheme, carried out under grant agreement no. UMO-2019/33/N/NZ5/02815, entitled:
"The effects of treatment with selective serotonin reuptake inhibitors and physical exercise on blood–brain barrier integrity, the concentrations of selected neurotransmitters in the prefrontal cortex and hippocampus, the kynurenine pathway, and mood in patients with depression."

Attendance at scientific conferences and training courses

- Conference abstract submitted and presented at the 13th International Conference on Cerebral Vascular Biology (CVB 2019), Miami. Abstract title: *Association between relative computed tomography indicators of cerebral microperfusion and clinical symptoms reported by patients undergoing internal carotid artery stenting.*
- Conference abstract submitted and presented at the European Psychiatric Association Congress (EPA) 2023. Abstract title: *Series of periodic limb movements in sleep and heart rate variability.*
- International internship completed within the Exchange Programme of the European Federation of Psychiatric Trainees (EFPT). Participation in the "Sleep and Circadian Neurophysiology Programme", carried out at the Psychiatric Clinic Vrapče in Zagreb, Croatia, during 11–25 May 2020.

Specialization in Psychiatry

Obtaining the title of specialist in psychiatry in 2023.

Bibliometric indicators of scientific achievements

- Total number of publications: 8
- Total Impact Factor: 36.758
- Total MNiSW score: 925 points
- Hirsch index (H-index): 4

- Total number of citations: 254**,**
  including 249 citations excluding self-citations
  (according to data as of 16 December 2025)
- First authorship: 5 publications
- Two publications in first-decile (D1) Journal Citation Reports journals:
  - *Neuroscience & Biobehavioral Reviews*
  - *Journal of Neuroinflammation*

SUMMARY IN ENGLISH

1. LIST OF ABBREVIATIONS

PLMS – Periodic Limb Movements in Sleep

RLS – Restless Legs Syndrome

AASM – American Academy of Sleep Medicine

HRV – Heart Rate Variability

HF-HRV – High-Frequency Component of Heart Rate Variability

LF-HRV – Low-Frequency Component of Heart Rate Variability

HR – Heart Rate

BP – Blood Pressure

SBP – Systolic Blood Pressure

DBP – Diastolic Blood Pressure

PLMI – Periodic Limb Movement Index

ANS – Autonomic Nervous System

PSG – Polysomnography

AHI – Apnea–Hypopnea Index

EEG – Electroencephalography

EOG – Electrooculography

EMG – Electromyography

ECG – Electrocardiography

RR – RR interval (time between consecutive QRS complexes)

PTT – Pulse Transit Time

ACC – Anterior Cingulate Cortex

PFC – Prefrontal Cortex

2. INTRODUCTION

Periodic limb movements in sleep (PLMS) constitute one of the most frequently described sleep-related movement disorders. They are characterized by recurrent, involuntary movements of the lower limbs, typically involving dorsiflexion of the foot, extension of the great toe, and flexion at the lower limb joints. Individual movements last between 0.5 and 10 seconds and recur at intervals of 5–90 seconds. According to AASM criteria used in polysomnographic diagnostics, movements occurring less than 90 seconds apart are classified as a PLMS series, whereas a pause of 90 seconds or longer marks the beginning of a new sequence. The organization of PLMS into repetitive series is a defining feature of this phenomenon and may be relevant for interpreting their physiological consequences.

PLMS are observed in most patients with restless legs syndrome, as well as in other sleep disorders and selected neurological conditions. Their co-occurrence with certain psychiatric disorders has also been reported, although the extent and nature of these associations remain insufficiently understood. Across clinical contexts, numerous studies indicate that PLMS are accompanied by transient changes in autonomic nervous system activity, reflected in brief increases in heart rate, rises in blood pressure, and alterations in heart rate variability (HRV). A typical pattern includes a reduction in the high-frequency component of HRV (HF-HRV) and a relative increase in low-frequency values (LF-HRV), which is often interpreted as a transient shift toward sympathetic dominance during movement episodes.

Heart rate variability is one of the fundamental, non-invasive markers of autonomic regulation. The high-frequency component primarily reflects parasympathetic activity, whereas the low-frequency component is influenced by both sympathetic mechanisms and baroreflex function. HRV parameters enable the assessment of short-term autonomic fluctuations accompanying PLMS and serve as an important complement to other physiological measures. The literature further highlights that disturbances in HRV and autonomic regulation have been described in individuals with selected psychiatric disorders, particularly affective and anxiety conditions. An additional domain of potential overlap is interoception- the perception and interpretation of internal bodily signals, which has been reported to be altered both in PLMS and in certain psychiatric disorders. These phenomena may suggest shared regulatory mechanisms, although their precise nature requires further investigation.

Recent years have brought increasing attention to the possibility of autonomic coactivation, understood as the concurrent engagement of sympathetic and parasympathetic branches of the autonomic nervous system. Although described in various physiological and clinical contexts, its relevance to sleep-related movement disorders has not been clearly established. The findings presented in this dissertation indicate that elements of coactivation may also emerge during PLMS, suggesting that the autonomic response pattern in these episodes may be more complex than traditional models based solely on transient sympathetic activation would predict. This observation may provide an important addition to current understanding of autonomic dynamics in PLMS.

PLMS remain a clinically relevant phenomenon within the fields of sleep medicine, cardiology, neurology, and certain areas of psychiatry. Changes in HRV, heart rate, and blood pressure occurring during movement episodes may offer insights into the mechanisms underlying their short-term hemodynamic consequences and potential clinical implications. In this context, HRV may serve as an integrative marker of autonomic nervous system functioning across diverse clinical conditions.

To date, research on PLMS has focused primarily on their frequency (PLMI). Considerably less attention has been devoted to qualitative parameters such as the duration of individual movements or the sequential properties of PLMS, including the number of consecutive episodes within a series. Moreover, the short-term dynamics of autonomic responses, including changes in HRV, heart rate, and blood pressure across consecutive movements have been explored only rarely, despite the fact that such analyses may yield essential insights into autonomic regulation.

The publications included in this dissertation comprise a review article and two empirical studies examining autonomic regulation in relation to periodic limb movements in sleep. The dissertation expands existing knowledge by analyzing how both the number of successive movements and the duration of individual PLMS episodes influence selected autonomic and cardiovascular parameters, with particular attention to short-term dynamic changes.

3. AIMS OF THE STUDY

The main aim of this dissertation was to examine how selected characteristics of periodic limb movements during sleep (PLMS), in particular the number of consecutive episodes within a series and the duration of individual movements relate to short-term fluctuations in parameters reflecting autonomic and cardiovascular activity, including heart rate variability (HRV), heart rate (HR), and blood pressure (BP). The empirical work was complemented by a review of the literature addressing potential links between PLMS, autonomic regulation, and interoception.

Publication 1. (Review – Heart Rate Variability and Interoception in Periodic Limb Movements in Sleep: Interference with Psychiatric Disorders? J Clin Med. 2024)

Objective:

To provide a comprehensive and critical analysis of studies investigating associations between PLMS, autonomic regulation, with particular emphasis on heart rate variability (HRV) and interoception, as well as to discuss the potential relevance of these mechanisms to selected psychiatric conditions.

Specific objective:

To summarise and interpret research demonstrating that PLMS and certain psychiatric disorders exhibit comparable patterns of autonomic dysregulation, including reduced HRV. The article also considers interoception as a potential framework linking autonomic processes with emotional and cognitive functioning. The review highlights that the contribution of HRV and interoception to the relationship between PLMS and psychological symptoms remains insufficiently understood, underscoring the need for further investigation into the mechanisms through which these factors may shape such associations.

Publication 2. (Original Research – Effect of Series of Periodic Limb Movements in Sleep on Blood Pressure, Heart Rate and High Frequency Heart Rate Variability. Neurol Neurochir Pol 2023)

Objective:

To characterise short-term changes in autonomic and cardiovascular parameters across successive PLMS episodes within a series, analysed in very brief, sequential time windows. The study utilised a large dataset of retrospectively identified PLMS episodes derived from polysomnographic recordings, allowing for the examination of reproducible patterns of autonomic responsiveness.

Specific objective:

To determine whether:

1. consecutive PLMS episodes are accompanied by progressive alterations in autonomic indices, including the high-frequency component of HRV (HF-HRV), assessed in short, overlapping windows;
2. the progression of PLMS series is associated with modifications in hemodynamic parameters such as heart rate (HR) and systolic and diastolic blood pressure (BP);
3. the observed increase in HF-HRV, in the absence of significant changes in HR and BP, may reflect a more complex pattern of autonomic engagement involving concurrent sympathetic and parasympathetic activation.

Publication 3. (Original Research – Time-Dependent Autonomic Dysregulation and Co-Activation Induced by Periodic Limb Movements in Sleep. J Clin Med 2025)

Objective:

To determine whether the duration of individual PLMS episodes influences short-term autonomic and hemodynamic responses. The analysis was conducted on retrospectively collected polysomnographic recordings, enabling the comparison of physiological reactions to shorter and longer PLMS episodes.

Specific objective:

To evaluate whether:

1. PLMS episodes differing in duration elicit distinct patterns of HRV changes, with particular emphasis on the high-frequency component (HF-HRV);
2. episode duration is associated with differential hemodynamic changes, including variations in systolic and diastolic blood pressure (SBP, DBP) and heart rate (HR);
3. longer PLMS episodes evoke autonomic response profiles indicative of simultaneous sympathetic and parasympathetic activation, suggesting a more complex regulatory pattern than that proposed by models emphasising transient sympathetic activation alone.

Summary

The central aim of this dissertation was to advance the understanding of autonomic regulation in the context of periodic limb movements during sleep (PLMS). This objective was approached through both theoretical analysis and empirical investigation. The review article synthesised current knowledge on the relationships among PLMS, heart rate variability (HRV), interoception, and selected psychiatric disorders, identifying potential mechanisms that may link these domains.

The two empirical studies provided detailed insights into short-term autonomic and hemodynamic dynamics, incorporating both the number of consecutive PLMS within a series and the duration of individual episodes. The findings demonstrate that autonomic responses to PLMS exhibit greater complexity than implied by traditional interpretations that focus solely on transient sympathetic activation.

Taken together, the results suggest that PLMS should be considered not only within the framework of sleep disorders but also as a phenomenon closely related to autonomic functioning, with relevance for cardiovascular health and psychological well-being. The findings further identify areas requiring continued research, particularly concerning the role of HRV and interoception and their potential clinical applications.

4. DESCRIPTION OF THE PUBLICATIONS INCLUDED IN THE DOCTORAL THESIS

Publication 1.

The first publication is a review article that examines the relationships among periodic limb movements in sleep (PLMS), autonomic regulation, heart rate variability (HRV), interoception, and selected psychiatric disorders. The review highlights that PLMS, although formally classified as a sleep-related movement disorder, are associated with notable alterations in autonomic nervous system function, reflected in reduced HRV and disturbances in the balance between sympathetic and parasympathetic activity.

The article summarizes evidence showing that a similar pattern of autonomic dysregulation is also described in individuals with depression and anxiety disorders. Reduced HRV, altered autonomic reactivity, and difficulties in emotional regulation appear both in these psychiatric conditions and in PLMS, suggesting that a partially shared neurobiological mechanism may exist.

A key component of the review is the discussion of interoception, understood as the ability to perceive and interpret signals originating within the body. The article notes that abnormalities in interoceptive processing have been reported both in PLMS and in certain psychiatric disorders, potentially linked to dysfunction in cortical regions responsible for integrating somatic and emotional information. In this context, the review emphasizes the role of the insular cortex, the anterior cingulate cortex (ACC), and prefrontal areas as central nodes in the integration of autonomic and emotional signals.

Based on the literature, the publication proposes a model in which autonomic dysregulation, reduced HRV, and impaired interoception may form a common foundation for PLMS and for some psychiatric disorders. It also suggests that PLMS, through sleep fragmentation and transient autonomic activation, may exacerbate psychiatric symptoms and contribute to the persistence of autonomic imbalance.

The review concludes by underscoring the need for further studies to clarify how HRV parameters and different dimensions of interoception may enhance the understanding of autonomic regulation in patients with PLMS, and whether these measures may have clinical value in assessing co-occurring psychiatric conditions.

Publication 2.

This publication presents the results of an original study examining short-term changes in hemodynamic and autonomic parameters in response to successive PLMS occurring within analyzed movement series. The study investigated whether the number of consecutive PLMS within a series was associated with systematic changes in heart rate variability, heart rate, and blood pressure. The analysis was based on retrospectively collected polysomnographic recordings from patients with restless legs syndrome, which allowed the assessment of more than one thousand PLMS and the capture of rapid physiological changes accompanying the progression of a series.

Five patients with diagnosed RLS were included, with a total of 1,348 PLMS recorded. Only episodes not associated with arousals were analyzed. Individuals with cardiovascular, metabolic, or psychiatric disorders, as well as patients taking medications affecting autonomic function, were excluded. Participants with an apnoea–hypopnoea index (AHI) ≥ 5 were also excluded to avoid the influence of respiratory disturbances on autonomic parameters.

The polysomnographic recordings included multichannel EEG, EOG, chin EMG, bilateral EMG of the anterior tibialis muscles, and a three-lead ECG. Respiratory activity was monitored with a nasal cannula, thoracic and abdominal belts, and pulse oximetry. Blood pressure was measured beat-to-beat using pulse transit time (PTT), and heart rate was derived from automatic QRS detection.

Autonomic and hemodynamic parameters: systolic and diastolic blood pressure (SBP, DBP), heart rate (HR), and high-frequency heart rate variability (HF-HRV) were evaluated for successive individual RR intervals, analyzed in blocks of ten intervals.

For each of the 10 consecutive RR intervals, all parameters were calculated in three conditions:
1. in the 10 RR intervals preceding the onset of the first PLMS series,
2. in the 10 RR intervals marking the beginning of the first series, and
3. in subsequent ten-interval blocks following each PLMS within the series.

This approach made it possible to detect changes occurring over very short time scales, parallel to the increasing number of PLMS within a series. As a result, the study captured the fine-grained dynamics of autonomic responses, rather than only comparing values before and after individual events.

The analysis demonstrated that successive PLMS in a series were not accompanied by significant changes in heart rate or in systolic and diastolic blood pressure. This finding contrasts with several previous reports describing more pronounced hemodynamic reactions to PLMS.

A different pattern emerged in the HRV measures. As the number of PLMS increased within a series, a systematic and statistically significant rise in HF-HRV was observed. The most pronounced increase appeared after the eighth PLMS in a series, indicating that parasympathetic activity intensified as the series progressed.

This pattern: rising parasympathetic activity without parallel hemodynamic changes suggests that the autonomic response to PLMS may be more complex than typically assumed and may involve the simultaneous activation of sympathetic and parasympathetic branches. Such coexistence, referred to as autonomic coactivation, may explain why increasing HF-HRV does not lead to a reduction in heart rate or blood pressure: sympathetic activation may counterbalance the parasympathetic effects at the cardiovascular level.

The findings place PLMS within the broader context of autonomic imbalance. The observed response: rising HF-HRV in the absence of changes in HR or BP, challenges simplified models depicting PLMS solely as episodes of sympathetic activation. Instead, the results point to the possibility of more nuanced and overlapping reactions within the autonomic nervous system.

Clinically, autonomic coactivation is relevant. The simultaneous activation of sympathetic and parasympathetic pathways can create cardiac arrhythmias, which together with epidemiological observations suggesting an elevated risk of atrial fibrillation in individuals with PLMS, gives the findings tangible clinical importance.

The manuscript was accompanied by an invited editorial commissioned by the Editorial Board, highlighting its theoretical and clinical significance. The publication underscores the need for further research into the autonomic consequences of PLMS, particularly studies using methods capable of assessing both autonomic branches and their interactions.

Publication 3.

This publication presents the results of another original study examining the autonomic response to periodic limb movements during sleep, this time with particular focus on the influence of the duration of individual PLMS episodes on the dynamics of autonomic regulation. The aim of the analysis was to determine whether longer-lasting PLMS elicit different autonomic and hemodynamic changes compared with shorter episodes, and whether movement duration may modulate the degree of simultaneous sympathetic and parasympathetic activation. The study was based on a retrospective analysis of polysomnographic recordings from five patients with restless legs syndrome, which enabled the evaluation of 1,348 PLMS episodes and the assessment of physiological changes occurring directly after each movement.

The same recording protocol and inclusion/exclusion criteria were applied as in the study described in Publication 2.

Autonomic and hemodynamic parameter: systolic and diastolic blood pressure (SBP, DBP), heart rate (HR), and high-frequency heart rate variability (HF-HRV) were assessed for individual RR intervals, analyzed in blocks of ten intervals.

For each set of ten consecutive RR intervals, all parameters were calculated in three contexts:

1. during the ten RR intervals preceding the onset of the first PLMS series,
2. during the ten RR intervals marking the beginning of the first PLMS series,
3. in subsequent blocks of ten RR intervals following each PLMS within the series.

This segmentation allowed for the identification of rapid changes occurring in very short time windows as the number of PLMS within a series increased. As a result, it was possible to examine the dynamics of the autonomic response rather than simply comparing values before and after individual movements.

The analysis showed that heart rate and both systolic and diastolic blood pressure did not change significantly as additional PLMS occurred within a series. This finding contrasts with earlier studies reporting pronounced hemodynamic responses during PLMS.

A different pattern emerged for HRV. As the number of PLMS within a series increased, HF-HRV rose systematically and significantly, with the most marked increase observed after the eighth PLMS. This indicates that parasympathetic activity intensified progressively as the series continued.

Such a pattern: rising parasympathetic activity without parallel hemodynamic changes suggests that the autonomic response to PLMS may be more complex than traditionally assumed, involving elements of both sympathetic and parasympathetic activation. This coexistence, referred to as autonomic coactivation, may explain why increasing HF-HRV does not result in a reduction in heart rate or blood pressure: sympathetic activation may counterbalance the parasympathetic influence at the cardiovascular level.

The study's findings place PLMS within a broader context of autonomic imbalance. The observed response pattern- rising HF-HRV without changes in HR or BP contradicts simplified models conceptualizing PLMS solely as episodes of sympathetic arousal. Instead, the results point to the possibility of alternating or concurrent activation of both branches of the autonomic nervous system.

Clinically, autonomic coactivation is relevant because it may increase susceptibility to cardiac arrhythmias. The simultaneous activation of sympathetic and parasympathetic pathways may create proarrhythmic conditions, which, combined with epidemiological data suggesting a higher risk of atrial fibrillation in individuals with PLMS—lends practical significance to these observations.

This publication underscores the need for further studies on the autonomic consequences of PLMS, particularly those employing methods capable of assessing both autonomic branches and their interactions in parallel.

5. SUMMARY

This dissertation examined periodic limb movements in sleep (PLMS) from three perspectives: their relationship with autonomic regulation, their potential connections with mental health, and the short-term hemodynamic changes accompanying these episodes.
The first publication- a review article situated PLMS within the broader context of autonomic nervous system functioning. It presented evidence suggesting that individuals with PLMS and patients with certain psychiatric disorders share similar difficulties in autonomic regulation, including reduced heart rate variability (HRV) and disturbances in interoception. The literature indicates that these phenomena may reinforce one another and influence both the course of PLMS and emotional functioning. The review also emphasized the role of interoception as a process linking the perception of physiological signals with emotional regulation.

The second publication- an original study focused on short-term changes in autonomic parameters during PLMS sequences. It demonstrated that parasympathetic activity (HF-HRV) increased with successive PLMS episodes, while blood pressure and heart rate remained stable. This pattern suggests that the autonomic response to PLMS is more complex than traditional models based solely on sympathetic activation, and may involve simultaneous activation of both branches of the autonomic nervous system- a phenomenon referred to as autonomic co-activation.

The third publication examined the significance of the duration of individual PLMS episodes. It showed that longer movements (exceeding 2.1 seconds) were associated with more pronounced increases in blood pressure and a stronger autonomic response incorporating elements of both sympathetic and parasympathetic activation. These findings indicate that

not only the number of movements but also their duration influences physiological reactions to PLMS, highlighting the need to consider temporal parameters in analyses of this phenomenon.

One of the major strengths of the dissertation is its innovative character. The studies employed analysis of autonomic responses in exceptionally short, consecutive time windows, an approach rarely used in PLMS research, which enabled the detection of subtle, rapidly evolving changes in parameters such as HF-HRV, HR, and BP, undetectable in conventional averaged analyses. The dissertation also provided the first empirical evidence suggesting the possibility of autonomic co-activation during PLMS, representing a departure from dominant interpretations in the literature, in which these episodes are described primarily as transient sympathetic activations. Moreover, the work introduced an evaluation of qualitative PLMS features, such as episode duration and their position within a sequence- parameters largely absent from previous studies that focused mainly on PLMI. Consequently, PLMS were conceptualized as a dynamic hemodynamic–autonomic process rather than merely a motor phenomenon, opening new interpretative directions for research on autonomic regulation and potential cardiovascular risk.

The study's limitations must also be acknowledged. The sample size in the empirical investigations was small (five patients with RLS), limiting the generalizability of the findings. The analysis was retrospective and based on data from a single center, which is associated with a risk of selection bias and heterogeneity of the studied population.

Sympathetic activity was assessed only indirectly, through blood pressure changes and without access to direct neurophysiological markers restricting the precision of conclusions regarding autonomic mechanisms. Additionally, the studies focused solely on short-term hemodynamic changes and did not include long-term clinical outcomes.

Despite these limitations, the combined findings indicate that PLMS are not confined solely to the domain of sleep medicine. They exhibit multiple associations with autonomic regulation, may affect sleep quality, and may reflect a broader context of physiological and psychological functioning. Short-window HRV analysis and selected aspects of interoception may serve as useful diagnostic and monitoring tools in patients with PLMS.

These results also highlight the need for prospective studies on larger patient cohorts, including direct measures of sympathetic activity and long-term clinical consequences. Furthermore, they open avenues for exploring the possibility of modulating autonomic balance in this population, both through non-pharmacological approaches (autonomic regulation training, behavioral interventions, neuromodulation) and, potentially in the future, through pharmacological strategies aimed at precise modulation of autonomic responses accompanying PLMS.

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PUBLIKACJE WCHODZĄCE W SKŁAD ROZPRAWY DOKTORSKIEJ / MANUSCRIPTS INCLUDED IN THE DOCTORAL DISSERTATION

Journal of
Clinical Medicine

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Review

Heart Rate Variability and Interoception in Periodic Limb Movements in Sleep: Interference with Psychiatric Disorders?

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Abstract: Periodic limb movements in sleep (PLMS) are a prevalent disorder characterized by rhythmic, involuntary movements of the lower limbs, such as dorsiflexion of the ankle and extension of the big toe, occurring in periodic intervals during sleep. These movements are often linked to disrupted autonomic nervous system (ANS) activity and altered interoception. Interoception involves perceiving internal bodily states, like heartbeat, breathing, hunger, and temperature, and plays a crucial role in maintaining homeostasis and the mind–body connection. This review explores the complex relationships between PLMS, heart rate variability (HRV), ANS dysregulation, and their impact on psychiatric disorders. By synthesizing the existing literature, it provides insights into how ANS dysregulation and altered interoceptive processes, alongside PLMS, contribute to psychiatric conditions. The review highlights the potential for integrated diagnostic and therapeutic approaches and presents a cause-and-effect model illustrating the mutual influence of psychiatric disorders, ANS dysregulation, PLMS, and interoception.

Keywords: periodic limb movements in sleep; heart rate variability; autonomic nervous system; cardiovascular interoception; psychiatric disorders

Citation: Małkiewicz, M.A.; Malinowski, K.S.; Grzywińska, M.; Partinen, E.; Partinen, M.; Pyrzowski, J.; Wszędybył-Winklewska, M. Heart Rate Variability and Interoception in Periodic Limb Movements in Sleep: Interference with Psychiatric Disorders? *J. Clin. Med.* **2024**, *13*, 6129. https://doi.org/10.3390/jcm13206129

Academic Editor: Daniel Álvarez

Received: 22 August 2024
Revised: 23 September 2024
Accepted: 8 October 2024
Published: 14 October 2024

1. Introduction

Periodic limb movements in sleep (PLMS) are involuntary, stereotyped movements of the lower limbs that occur in a periodic interval pattern during sleep, typically involving dorsiflexion of the ankle, extension of the big toe, and occasional flexion of the knee and hip. PLMS are present in 80% of patients with restless leg syndrome (RLS) but also in particular sleep disorders, psychiatric diseases, and neurological pathologies. Emerging evidence suggests a potential link between PLMS and psychiatric disorders, particularly anxiety and depression.

While PLMS primarily pertains to sleep disturbances, its relationship with psychiatric disorders is multifaceted. The role of autonomic nervous system (ANS) impairment in PLMS has been widely investigated, particularly the involvement of the sympathetic nervous system. This review aims to explore the relationship between ANS activity in

PLMS and mental diseases by examining heart rate variability (HRV). HRV reflects the intracardiac activity of the ANS and, thus, the complexity of the regulatory mechanisms of the cardiovascular system. HRV may, therefore, indirectly serve as a marker of ANS health. Disease processes, aging, lifestyle, and external environmental and neuropsychological conditions may lead to disturbances in the autonomic regulation of the heart rate (HR) and thus influence HRV [1,2]. Smoking cigarettes or excessive alcohol consumption reduces HRV, while an active lifestyle, regular physical exercise, and practicing relaxation methods, including meditation, increase HRV parameters [3]. The findings highlight the importance of understanding the autonomic control of HR and its implications in the context of PLMS and mental psychiatric disorders. While some studies have reported ANS dysfunction in PLMS and psychiatric conditions based on HRV analysis, the underlying pathogenesis and the precise relationship between PLMS, mental diseases, and ANS activity remain to be fully elucidated.

Interoception, which involves the perception of internal bodily states, adds another layer of complexity to our understanding of these relationships. Interoception entails the recognition of feelings related to body functions per the cardiovascular system (such as heartbeat), breathing, hunger, thirst, temperature, and other visceral experiences. It helps maintain the stability of the internal environment (homeostasis) but also plays a significant role in the mind–body connection by managing emotions and making decisions based on the internal state [4].

By synthesizing the existing literature, this review provides insights into how ANS dysregulation, altered interoceptive processes, and PLMS collectively contribute to psychiatric disorders, emphasizing the potential for integrated diagnostic and therapeutic approaches. For a better thematization of the discussed topic, we formulated a cause-and-effect sequence, which, in the form of a closed circle, covers the mutual influence of psychiatric disorders, ANS dysregulation, PLMS, and interoception (Figure 1).

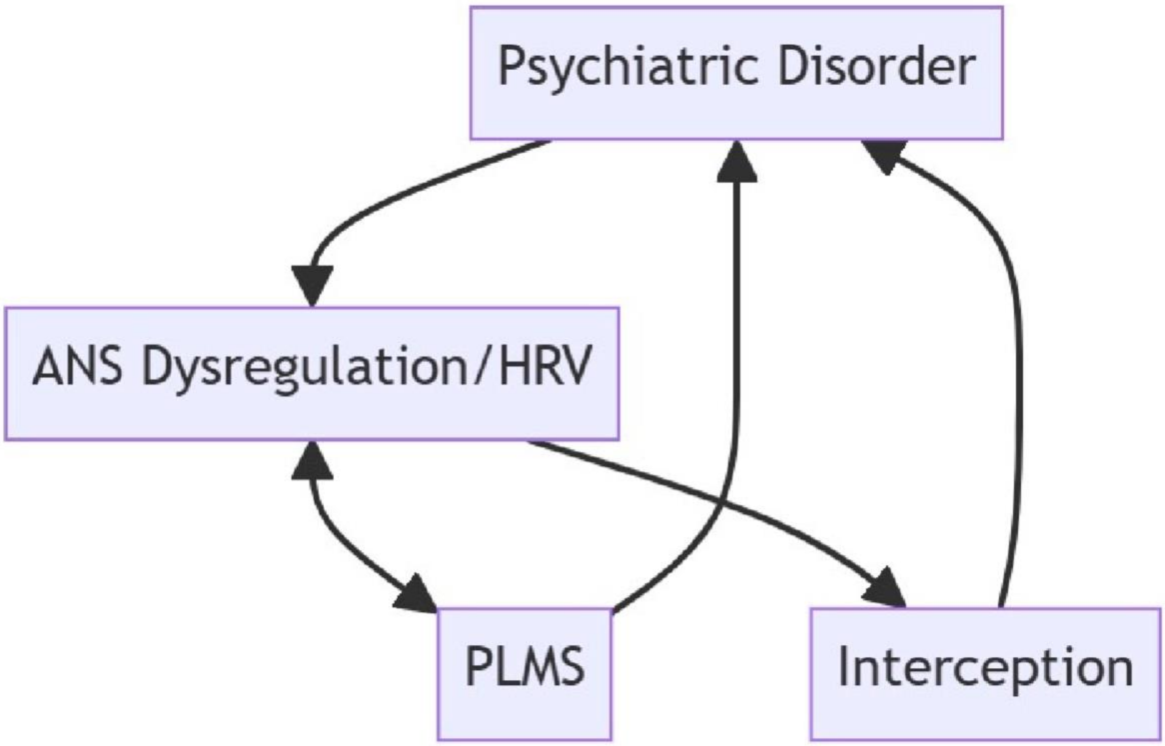

Figure 1. The intricate interplay between psychiatric disorders, ANS/HRV dysregulation, PLMS, and interoception; ANS—autonomic nervous system, HRV—heart rate variability, PLMS—periodic limb

movements in sleep. Note: At the core of this interconnected web lies a bidirectional relationship. Psychiatric disorders contribute to ANS and HRV dysregulation, which, in turn, influence the manifestation of PLMS. Simultaneously, PLMS can exacerbate psychiatric symptoms, creating a feedback loop. Interoception—the perception of internal bodily sensations—acts as a pivotal link, influencing and being influenced by both psychiatric disorders and ANS dysregulation. This circular relationship underscores the dynamic nature of the interactions, emphasizing the mutual influence and feedback loops among these elements, illustrating the multifaceted nature of the relationship between psychiatric health, autonomic function, sleep movement disorders, and the perception of internal bodily states.

2. Psychiatric Disorders and ANS Dysregulation (HRV)

The timing of adjacent cardiac cycles is variable both at rest and in states of arousal. Intracardiac ANS fibers constitute the efferent pathway of the cardiac reflexes involved in the complex regulatory mechanisms of heart function. HRV is the result of biological oscillators that generate repetitive rhythms. The frequency and amplitude of these oscillations are a valuable indicator of the body's functional state and ability to adapt to changing environmental conditions [5]. The basic variable analyzed is the NN (normal to normal) interval [i.e., standardized R-wave peak to R-wave peak (RR) intervals, verified for the correctness of their determination]. On their basis, parameters regarding the average length of the RR interval (i.e., the average duration of the cardiac cycle), as well as the total and short- and long-term variability, are determined [6]. Time domain analysis is based on computational methods of mathematical statistics. This is the oldest method and, at the same time, characterized by the least complexity. The second class of methods is based on analysis of the frequency domain using a non-parametric method, the discrete Fourier "transform", or a parametric method based on autoregression. Harmonic analysis involves separating a complex rhythm into components that are harmonic curves with different frequencies and amplitudes. Spectral analysis calculates the contribution of individual harmonic frequencies to the total irregularity of the recording and presents them in the form of a signal power density spectrum [7]. The low-frequency (LF) component of HRV reflects the combined impact of both the sympathetic and parasympathetic nervous systems, whereas the high-frequency (HF) component is chiefly under the control of parasympathetic signals transmitted to the heart via the vagal nerve.

HRV reflects the variation in heartbeat intervals, regulated by the ANS, and is influenced by physiological factors. Studies show that while a healthy heart exhibits complex nonlinear dynamics and long-range correlations, the reduction of HRV in some medical conditions leads to a reduction in its complexity by disrupting these patterns [8,9].The inclusion of nonlinear HRV measures that evaluate data structure and organization shows promise for improving HRV interpretation. Assessing chaotic and nonlinear dynamics in HRV can be used for understanding the complex behavior of the cardiovascular system, particularly its adaptive responses to physiological and pathological conditions. While traditional time- and frequency-domain measures of HRV are useful, they often fail to capture the intricate dynamics of heart rate regulation. Nonlinear methods, inspired by chaos theory and fractal mathematics, can provide deeper insights into the complex variability of heart rate signals [10].

Cardiac regulation via the ANS involves a complex interplay between higher brain regions and brainstem centers responsible for autonomic functions. The ANS is a multifaceted neural network that orchestrates the involuntary physiological processes essential for maintaining homeostasis. Its intricate regulation involves a dynamic interplay between higher brain regions, brainstem centers, and neural circuits. The rostral ventrolateral region of the medulla oblongata (RVLM) plays an important role in generating and regulating sympathetic activity in the cardiovascular system [11]. Neurons in the RVLM have the ability to generate rhythmic action potentials and determine tonic central sympathetic activity. The RVLM receives information from peripheral receptors, including pulmonary baroreceptors and mechanoreceptors, arterial chemoreceptors, inspiratory neurons, central chemodetectors, and ergoreceptors [12].

Moreover, projections from higher structures of the nervous system reach the RVLM area. Influences coming from the prefrontal cortex, amygdala, hypothalamus, and hippocampus are involved in emotional and defensive reactions [13]. The cerebral cortex, particularly areas involved in cognitive, emotional, and behavioral control, plays a crucial role in modulating the activity of the brainstem ANS centers. The prefrontal cortex (PFC), including the dorsolateral prefrontal cortex (DLPFC) and ventromedial prefrontal cortex (VMPFC), is associated with executive functions, decision-making, and emotion regulation. It sends top-down signals to the brainstem, including the medullary and pontine centers involved in autonomic control. The PFC can influence the balance between sympathetic and parasympathetic tone, impacting HR, blood pressure (BP), and other autonomic responses. This regulation allows the ANS to adapt to changes in the external environment and internal physiological needs. Dysregulation within these networks can contribute to the physiological and psychological symptoms of mental disorders [10].

In mental disorders such as depression and anxiety, alterations in PFC activity can disrupt the balance between sympathetic and parasympathetic activity. Dysfunctional PFC connectivity within the default mode network (DMN) and cognitive control network may be implicated in these disorders. Irregularities within the DMN, encompassing the PFC, posterior cingulate cortex, and other associated regions, have been implicated in various psychiatric disorders [14,15]. Altered connectivity within the DMN can impact self-referential thinking and emotion processing, potentially influencing ANS function. Dysregulation within the DMN is observable in conditions such as anxiety disorders, mood disorders, and schizophrenia [11,12]. In mental disorders, disruptions in these neural networks can result in altered ANS responses to emotional and physiological cues. These disruptions may lead to heightened sympathetic arousal, reduced parasympathetic activity, and an overall imbalance in ANS functioning, which can manifest as physical symptoms and impact emotion regulation. Understanding these neural network dysregulations is crucial for developing targeted interventions aimed at restoring ANS balance in individuals with mental disorders.

Impaired physiological and emotional regulation, as indicated by a reduced resting HRV, has been linked to heightened physiological and emotional responses when exposed to stress [16,17]. Reduced HRV, often indicative of ANS dysfunction, is linked to various psychiatric conditions, including anxiety, depression, schizophrenia, and post-traumatic stress disorder [18]. This decrease in HRV appears to signify a reduction in cardiac vagal tone and an increase in sympathetic activity among individuals experiencing anxiety and depression. In the context of healthy adults, HRV demonstrates a correlation with positive mood, and this association is influenced by the routine implementation of cognitive–emotion regulation strategies [19]. Increased HRV serves as a defensive barrier, attenuating the negative impact of stressors [20]. Conversely, individuals with depression and anxiety demonstrate reduced HRV when compared to those without these conditions [21,22]. Additionally, women demonstrate an elevated baseline HRV compared to men, manifested by increased power in the HF band, indicating enhanced parasympathetic activity and improved emotion regulation [23]. Conversely, individuals with schizophrenia exhibit a heightened sympathetic nervous system and parasympathetic nervous system activity, reflected in reduced HRV parameters. HF HRV was significantly reduced in patients with schizophrenia relative to healthy controls [24–26]. Furthermore, recent research indicates a correlation between diminished HRV and heightened severity of both positive and negative symptoms in schizophrenia. Investigations have delved into the prospect of utilizing HRV as a potential biomarker for schizophrenia [27].

In summary, abnormalities in HRV exhibit a close association with the neural networks operating within the ANS. Dysfunction in neural control, arising from both central and peripheral components, has the potential to perturb the delicate equilibrium between sympathetic and parasympathetic activity. This disruption results in discernible alterations in HRV, as evidenced in conditions such as PLMS and various psychiatric disorders. The assessment of HRV and a comprehensive understanding of its neural foundation yield valuable clinical insights. These insights may serve as a basis for interventions aimed at reinstating autonomic balance, with the ultimate goal of enhancing overall health outcomes.

3. ANS Dysregulation and PLMS

Although HRV reflects the neurogenic regulation of HR, lower parameters of HRV analysis have indicated a reduction in autonomic regulation. Therefore, should we expect altered HRV in PLMS, which is associated with ANS dysfunction? Information from the existing literature highlights a reduction in HRV in individuals with PLMS, coupled with a rise in sympathetic tone leading to transient autonomic disturbances during sleep [28–30].

PLMS can increase daytime sleepiness and subjective sleep disturbances in patients with obstructive sleep apnea due to heightened sympathetic activation [31]. Individuals with insomnia often exhibit signs of autonomic dysfunction, particularly with diminished vagal activity. Yet, practicing slow, controlled breathing can help boost vagal function and enhance sleep quality [31].

Disturbances in HR and BP signify alterations in ANS function in the pathophysiology of PLMS. This heightened sympathetic activity has the potential to disrupt the architecture of sleep, thereby contributing to sleep-related symptoms. Barone et al. conducted a study that identified changes in HRV in PLMS patients, revealing a significant reduction in HF HRV and an elevation of very low-frequency HRV [32]. Previous studies have also reported an increase in very low-frequency HRV, LF HRV, and the LF/HF ratio during PLMS events [27,29,30,33,34]. In a specific investigation [35], an elevation in very-low-frequency HRV and LF HRV was observed several tens of seconds before the onset of the PLMS period, followed by a subsequent decrease in HF HRV fluctuation. These results would, therefore, indicate a partial withdrawal of intracardiac parasympathetic activity, most likely in favor of sympathetic activity.

Traditionally, the sympathetic and parasympathetic branches of the ANS are considered to have opposing actions: sympathetic activation accelerates HR, while parasympathetic activation tends to decelerate it. This balance between the two branches is crucial for maintaining cardiovascular stability. This does not mean, however, that the heart cannot be simultaneously stimulated with sympathetic and parasympathetic activity, which may lead to the so-called "autonomic conflict" [36]. In our last study, we observed that following eight PLMS in a series, HF HRV was increased with no decrease in HR and BP [37]. The increased HF HRV suggested an increase in intracardiac parasympathetic activity, but the lack of change in HR and BP indicated a parallel, antagonistic SNS effect on the heart. Such a coactivation proposes a scenario where sympathetic and parasympathetic activities increase simultaneously, challenging the conventional notion of a reciprocal relationship. Such a phenomenon may have implications for our understanding of autonomic regulation, especially in specific contexts such as the occurrence of successive PLMS. Coactivation of the sympathetic and parasympathetic systems might indicate a more intricate regulatory mechanism, potentially reflecting a dynamic adaptation to specific pathophysiological demands. The precise mechanisms driving this coactivation in PLMS and its implications for cardiovascular health and overall physiological homeostasis will likely be subjects of further investigation.

As indicated above, psychiatric disorders may be an independent cause of ANS dysfunction, as reflected by an altered HRV. However, can ANS dysfunction constitute the basis for PLMS and thus be a bridge connecting mental dysfunctions with PLMS? Numerous studies have demonstrated that individuals with depression and anxiety disorders exhibit reduced HRV compared to healthy controls. This diminished HRV is often associated with increased sympathetic activity, which may exacerbate sleep disturbances, including PLMS. Conversely, the sleep disruption caused by PLMS can further exacerbate mood disorders, creating a vicious cycle. There is also evidence of shared neurobiological pathways between ANS function, sleep regulation, and mood regulation. Dysfunctions in neurotransmitter systems such as serotonin, norepinephrine, and dopamine can affect both ANS activity and mood regulation [38]. Moreover, chronic ANS dysregulation, along with sleep disruption caused by PLMS, may contribute to systemic inflammation. Inflammation is increasingly recognized as a contributing factor in the development of psychiatric disorders, particularly mood disorders like depression [39]. Moreover, addressing ANS dysregulation and sleep disturbances caused by PLMS through lifestyle modifications, relaxation techniques, and medications (e.g., dopamine agonists for PLMS) may indirectly improve psychiatric symptoms.

4. PLMS and Psychiatric Disorders

Finally, we can close the proposed cause-and-effect circle by describing the impact of PLMS on psychiatric disorders. Various psychiatric disorders, such as anxiety, depression, attention-deficit hyperactivity disorder (ADHD), and schizophrenia, have a higher prevalence of RLS, PLMS, or both [40–42]. It is highly probable that increased severity of RLS is closely associated with mood symptoms, including the recurring nature and diagnostic characteristics of major depressive disorders [43]. The interplay between the severity of psychiatric symptoms and PLMS represents a complex and multifaceted domain of investigation within the medical literature. Emerging evidence suggests a complex relationship between PLMS and psychiatric disorders, particularly anxiety and depression [44]. The presence of PLMS-related sleep disruptions may contribute to the development or exacerbation of anxiety symptoms [45]. Similarly, an increased risk of depression has been observed in individuals with PLMS [45]. The disrupted sleep patterns and associated daytime impairment may contribute to the onset or persistence of depressive symptoms.

The relationship between PLMS and anxiety/depression appears to be bidirectional. While PLMS-related sleep disturbances can worsen psychiatric symptoms, the presence of anxiety or depression can also lead to sleep disruption, creating a cycle of mutual influence [46,47]. Anxiety-related symptoms, such as heightened arousal and stress, may contribute to the manifestation of PLMS and disrupted sleep, and individuals with PLMS may be at a heightened risk of developing anxiety disorders [48]. Sleep disturbances, daytime fatigue, and physiological changes associated with PLMS could contribute to anxiety symptoms [49].

Some studies suggest an increased prevalence of sleep-related movement disorders, including PLMS, in individuals with schizophrenia [40]. However, the specific relationship between the severity of schizophrenia symptoms and the occurrence of PLMS is not yet fully elucidated. Medications commonly used in the treatment of schizophrenia, such as antipsychotics, can have effects on sleep architecture and may influence the occurrence of PLMS [50]. The relationship between medication use, symptom severity, and sleep disturbances is complex. Moreover, some studies suggest a link between ADHD severity and RLS symptoms, and more severe ADHD symptomatology was associated with RLS [42]. In general, sleep disturbances, including PLMS, can exacerbate symptoms of psychiatric disorders and negatively impact the overall well-being of individuals. Poor sleep quality may contribute to the severity of psychiatric symptoms and impact daily functioning [49].

5. ANS Dysregulation and Interoception

Interoception refers to the perception and awareness of the internal state of the body, including sensations related to heartbeat, respiration, and other physiological processes [51]. Dysregulation of the ANS may be related to disturbances in the activity of individual branches of the ANS, as well as imbalances between them. Anxiety disorders and depression may be associated with impaired functioning of the ANS and thus change an individual's ability to perceive internal sensations. The correlation between HRV and interoception finds its primary basis in the influence of the ANS on both phenomena. HRV serves as an indicator of the dynamic equilibrium between the sympathetic (fight-or-flight) and parasympathetic (rest-and-digest) branches of the ANS [52]. An elevated HRV suggests a more adaptable and responsive ANS, which is intricately linked to heightened interoceptive awareness. Researchers have explored the relationship between HRV and interoception in various clinical and psychological contexts [53]. Understanding this association can provide insights into how ANS regulation influences our perception of internal bodily states and may have implications for mental health and the management of conditions related to autonomic dysfunction.

The brain plays a vital role in interoception, encompassing the processing of signals associated with HR. Regions like the insula and anterior cingulate cortex are crucial in integrating and interpreting interoceptive signals, including those originating from the cardiovascular system [54]. In initial studies, it was observed that individuals who perceive heartbeats differently exhibit distinct heartbeat-evoked potential (HEP) waves (i.e., HEPs). HEP is measured in relation to the R-wave in an electrocardiogram (ECG) test and is thought to reflect the brain's processing of cardiac activity during behavior in the brain during an electroencephalogram (EEG) [55].

HEP refers to a specific brain response or electrical signal elicited by the heartbeat. This phenomenon is associated with interoception. EEGs are employed to record the brain's electrical activity, enabling researchers to measure HEPs with a high level of precision [56]. HEPs are connected to mental disorders through their role in interoception [57,58]. Interoception plays a crucial role in our emotional and physiological self-awareness. Therefore, abnormalities or dysregulations in HEPs can be associated with various mental disorders, such as anxiety disorders, depression, or somatization [44,45]. Additionally, some studies have explored the potential of biofeedback interventions, incorporating techniques like controlled breathing, relaxation exercises, and meditation to enhance HRV [59]. However, at present, the available data do not conclusively establish whether paced respiration or subjective relaxation alone is necessary or sufficient for achieving positive outcomes with HRV biofeedback.

6. Interoception and Psychiatric Disorders

Interoception is closely related to the connection between mind and body, which is related to the interplay of psychological and physiological processes [51,60]. Practices that promote mindfulness and body awareness, such as meditation and biofeedback, can positively impact both interoception and HRV, contributing to improved autonomic regulation and, therefore, mental health [61]. While the existing literature on this topic is limited in scope, a synthesis of these studies suggests that integrating biofeedback with relaxation and meditation strategies may lead to an augmentation of HRV and increased parasympathetic activity [62]. It is essential to acknowledge the constraints of the reviewed literature, and these limitations underscore the need for further research in this area to explore its full potential.

HR, being a fundamental component of cardiovascular function, plays a significant role in interoception [63]. Individuals can consciously or subconsciously perceive their own heartbeats, and this awareness contributes to their overall sense of bodily self-awareness [64]. Variability in cardiac interoceptive sensitivity can influence how individuals interpret and respond to physiological cues related to HR. Fluctuations in HR are frequently linked to emotional states, stress, and arousal. Being aware of these HR changes contributes to emotional awareness, which has a pivotal role in cognitive function [53]. Interoceptive attention is a component of both emotion regulation and higher cognitive functions [51]. It allows individuals to recognize and interpret the physical sensations associated with emotions. For example, when you feel anxious, you may become aware of a racing heart or shallow breathing. Recognizing these bodily sensations can be a key step in managing and regulating emotional responses. Interoceptive attention also involves higher cognitive functions. The ability to consciously focus on and interpret internal bodily sensations requires cognitive processes such as attention, self-awareness, and self-thinking about one's own thinking. Higher cognitive functions are responsible for recognizing and making sense of these sensations, as well as using this information to make decisions or engage in cognitive processes related to emotional and physical well-being [65]. Cortical areas involved in emotion processing, such as the amygdala and VMPFC, wield influence over the autonomic response to emotional stimuli [65]. The amygdala, for instance, can elicit sympathetic responses to perceived threats, while the VMPFC can mitigate these responses through inhibitory connections with brainstem autonomic centers [66]. Cortical regions engaged in higher cognitive functions, encompassing memory, attention, and perception, indirectly modulate the ANS [65]. Cognitive processes associated with stress, vigilance, and awareness can activate or suppress autonomic responses mediated by the brainstem [67].

Altered interoceptive processes have been observed in psychiatric disorders, influencing emotional experiences and contributing to symptom severity. The cingulate cortex, particularly the anterior cingulate cortex, serves as a crucial bridge between cognitive and emotional processes and autonomic control. It possesses the ability to regulate the brainstem nuclei governing ANS functions, thereby impacting HRV and visceral responses. The insular cortex, a hub for interoception, enables the brain to monitor and interpret internal bodily states. Its intricate connections with brainstem regions allow for real-time adjustments of autonomic responses based on perceived visceral sensations [68,69]. Dysfunctions within the insular cortex can disrupt autonomic equilibrium, contributing to psychiatric disorders [69].

Understanding how interoception processes interact with psychiatric conditions offers insights into their shared pathophysiological mechanisms. In simpler terms, individuals with higher HRV tend to be more attuned to their internal bodily sensations, such as heartbeat, breathing, and digestive processes. This enhanced interoceptive awareness can have implications for emotion regulation, stress response, and overall well-being.

7. Interoception and PLMS

Currently, available knowledge about the direct relationship between interoception and PLMS is limited. Although there is no well-established direct link between interoception and PLMS, it is important to note that both phenomena are based on neurobiological mechanisms with the involvement of the ANS system. Sleep disorders, including those associated with PLMS, can affect the way we perceive internal body sensations. The object of the study by Sandri et al. was an assessment of interoception in people with RLS [70]. The results indicated reduced interoceptive accuracy (measured by a heartbeat tracking task) in RLS patients. Additionally, interoceptive accuracy is negatively correlated with nocturnal eating behavior [70]. The neurobiological mechanisms underlying the relationship between impaired interoception and PLMS are unknown, but considering that PLMS is associated with disturbed sleep, it can be assumed that factors related to sleep and sleep disorders may play an important role here.

Sleep disorders have the potential to impact the ANS responsible for overseeing involuntary bodily functions, such as heart rate regulation. Conditions such as insomnia may induce imbalances in autonomic activity, potentially influencing the perception of internal bodily sensations, particularly in the context of cardiac interoception. Insomnia, characterized by challenges in falling or staying asleep, is frequently linked to elevated arousal levels. This heightened state of arousal can result in an individual's awareness of internal sensations [71]. The examination of interoceptive sensitivity involves assessing the cerebral cortical response to an individual's heartbeat using HEP measurement. Research by Yishul Wei et al. indicated that people suffering from insomnia had an altered HEP amplitude via frontal electrodes compared to a control group [71]. Increased neural activity temporally related to heartbeats was noted in the anterior cingulate cortex/medial frontal cortex. This implies that these individuals exhibited inadequate adjustment of the brain's reaction to regularly recurring heartbeats [71,72]. Moreover, the interconnection of stress and sleep has potential implications for the field of sleep and emotion research. Of note, the effects of sleep deprivation on ANS dysregulation may result in dysregulation characterized by changes in sensitivity and response to stress. As a result, changes in arousal levels or interoceptive signals may affect the ability to process emotionally relevant information [73]. The relationship between cardiac interoception and PLMS is unclear, and research in this area is ongoing. However, it seems that sleep disorders associated with PLMS play a potential role. The interplay between cardiovascular interoception and sleep is bidirectional, with changes in one system influencing the other.

8. The Complex Interplay of Physiological, Neurobiological, and Psychological Factors Involved in PLMS and Psychiatric Disorders—Summary

The vicious circle begins as psychiatric disorders and neurological conditions, such as PLMS, give rise to disturbances in both interoception and HRV. These disturbances, in turn, contribute to the exacerbation of symptoms associated with psychiatric disorders and PLMS.

This relationship can be characterized multimodally. Shared neurochemical pathways as perturbations in dopaminergic neurons have been implicated in both PLMS and mood disorders [45,74]. Dopamine, a neurotransmitter crucial for mood regulation, may exhibit dysregulation in individuals with PLMS, potentially contributing to mood-related symptoms. Notably, PLMS frequently co-occurs with RLS, which is associated with mood disorders such as depression and anxiety. Consequently, psychiatric symptomatology frequently seen in RLS patients can indirectly be linked to PLMS in cases of co-occurrence. This reduction in quality of life can intensify feelings of distress and exacerbate psychiatric symptomatology. Then, prolonged sleep disruption, as observed in PLMS, can disrupt emotion regulation and mood stability, as sleep plays a pivotal role in modulating emotion processes [73]. The cumulative effect of PLMS-induced sleep disruption, coupled with the discomfort associated with limb movements, significantly diminishes an individual's overall quality of life. RLS can instigate a chain reaction, ultimately linking to impaired cardiac regulation and the potential development of cardiovascular disease (Figure 2).

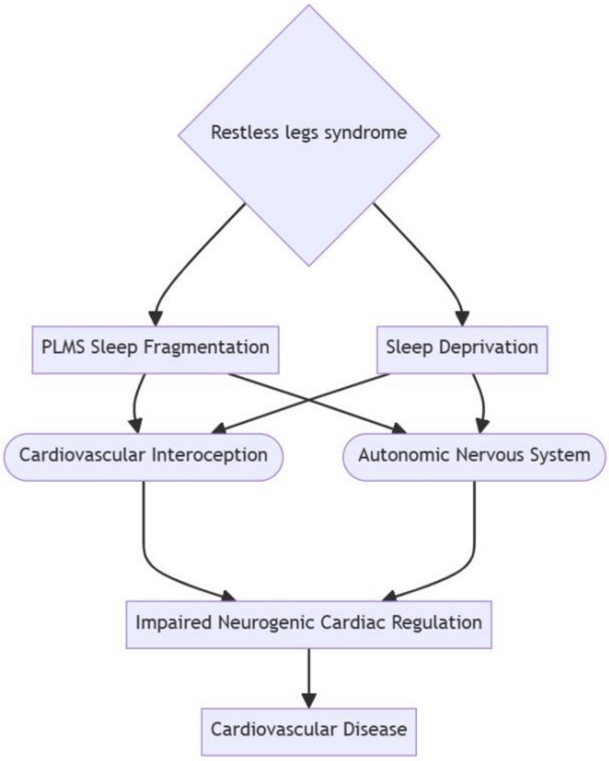

Figure 2. RLS initiates a chain of events leading to PLMS, sleep fragmentation, and sleep deprivation; RLS—restless leg syndrome, PLMS—periodic limb movements in sleep. Note: These events disrupt the ANS and alter interoception. The compromised ANS and impaired interoception contribute to disrupted neurogenic cardiac regulation, potentially leading to cardiovascular disease. This closed-loop sequence highlights the interdependence and sequential impact of RLS on cardiovascular health.

9. Clinical Implications and Future Research

Understanding the intricate interplay between HRV, ANS dysregulation, PLMS, and psychiatric disorders has clinical implications. Monitoring HRV and ANS activity in individuals with PLMS and comorbid psychiatric conditions may provide insights into treatment strategies. Interventions targeting ANS regulation, such as biofeedback and relaxation techniques, may have therapeutic potential in managing PLMS-related sleep disturbances and improving mental health outcomes. While the existing literature on this topic is limited in scope, a synthesis of these studies suggests that integrating biofeedback with relaxation and meditation strategies may lead to an augmentation of HRV and increased parasympathetic activity. Overall, the limitations of past studies underscore the need for further research in this area to explore its full potential.

10. Conclusions

In summary, this review underscores the need for a comprehensive approach to assessing and managing individuals with comorbid PLMS and psychiatric disorders. The interplay between PLMS, ANS dysregulation, HRV abnormalities, and psychiatric disorders represents a multifaceted and evolving field of study. HRV serves as a valuable indicator of ANS activity, reflecting the balance between sympathetic and parasympathetic branches. Reduced HRV often signifies ANS dysregulation, characterized by a heightened sympathetic tone and reduced parasympathetic influence. Interoception, on the other hand, involves the awareness and perception of internal bodily states, including autonomic responses. It plays a crucial role in emotion processing and self-regulation.

The relevance of this manuscript lies in its potential to enhance the understanding of the interactions between periodic limb movements during sleep (PLMS), heart rate variability (HRV), and psychiatric disorders, offering important insights for clinical practice. The review highlights how PLMS, a condition often co-occurring with sleep disturbances and psychiatric conditions, can be associated with autonomic nervous system (ANS) dysregulation, as reflected by changes in HRV. This understanding can assist clinicians in identifying at-risk individuals for mental health conditions based on physiological markers, such as HRV, even before more obvious symptoms appear. HRV could act as a non-invasive biomarker for assessing the effects of PLMS on the ANS and psychiatric health. This opens up opportunities for clinical applications like early diagnosis; monitoring HRV in patients with sleep complaints may aid in the early detection of autonomic dysfunction and psychiatric disorders.

Furthermore, understanding the physiological impact of PLMS on HRV and the autonomic nervous system could enable more personalized therapeutic approaches, addressing both the psychological and physiological aspects of the condition. Additionally, tracking treatment efficacy through changes in HRV over time could provide a valuable metric for evaluating the effectiveness of interventions for PLMS and associated psychiatric disorders.

In light of these possibilities, further research is warranted to elucidate the underlying mechanisms and establish effective interventions that target ANS regulation. Such efforts could transform clinical paradigms, promoting a more holistic approach to mental health and sleep disorders, ultimately fostering a deeper understanding of how physiological markers can guide tailored treatments for improved patient outcomes.

Author Contributions: Conceptualization, M.A.M., E.P. and M.P.; methodology, M.A.M. and K.S.M.; software, J.P.; validation, E.P., M.P. and M.W.-W.; formal analysis, M.G. and M.W.-W.; investigation, M.A.M. and K.S.M.; resources, J.P.; data curation, M.A.M.; writing—original draft preparation, M.A.M.; writing—review and editing, M.A.M.; visualization, M.G.; supervision, M.W.-W.; project administration, J.P.; funding acquisition, M.A.M. All authors have read and agreed to the published version of the manuscript.

Funding: Marta A. Małkiewicz is supported by the Polish National Science Centre (NCN) grant Preludium, number 2019/33/N/NZ5/02815.

Data Availability Statement: No new data were created or analyzed in this study.

Conflicts of Interest: Markku Partinen reports other from Bioprojet, other from Takeda, other from Idorsia, other from Umecrine, personal fees and other from Orion-Pharma, outside the submitted work. The other authors declare no conflicts of interest.

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RESEARCH PAPER

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Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2024, Volume 58, no. 2, pages: 167–175
DOI: 10.5603/pjnns.95117

ISSN: 0028-3843, e-ISSN: 1897-4260

Effect of series of periodic limb movements in sleep on blood pressure, heart rate and high frequency heart rate variability

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ABSTRACT

Introduction. The phenomenon known as periodic limb movements in sleep (PLMS) has been linked to a change in autonomic nervous system (ANS) activity and its effect on circulatory regulation. Autonomic dysfunction or dysregulation in patients with PLMS has been described in some domains; however, any relationship between heart rate variability (HRV) and PLMS has not been clearly established. HRV analysis is a recognised, non-invasive research method that describes the influence of the ANS on heart rate (HR). The aim of our study was to further investigate the dysregulation of autonomic HR control in patients with PLMS.

Material and methods. We undertook a retrospective analysis of the polysomnographic (PSG), demographic and medical data of five patients with a total number of 1,348 PLMS. We analysed HR, HRV HF, systolic blood pressure (SBP), and diastolic blood pressure (DBP) for 10 heartbeats before the series of PLMS and 10 consecutive heartbeats as beat-to-beat measurements. The presented method of using successive, short, 10 RR interval segments refers to the time-frequency measurement, which is very clear and useful for presenting changes in the calculated parameters over time and thereby illustrating their dynamics. This method allowed us to assess dynamic changes in HRV HF during successive PLMS series. Statistical analysis was performed using IBM SPSS Statistics (v. 28.0.0.0). The Kruskal-Wallis test was performed to find statistically significant changes from baseline.

Results. No statistically significant changes in HR, SBP, or DBP were found in our group, although an increase in the value of the HRV HF was noted, suggesting an increase in intracardiac parasympathetic activity during the subsequent series of PLMS.

Conclusions. Our study indicates an increase in parasympathetic activity during the appearance of successive PLMS, which, with the simultaneous lack of changes in HR, may suggest an increase in sympathetic activity, and therefore the appearance of so-called 'autonomic co-activation' resulting in the possibility of life-threatening cardiac events.

Clinical implications. Our findings add to the literature information regarding HRV in PLMS, and highlight the need for further studies to elucidate the effects of these conditions on the ANS, and on cardiovascular health.

Keywords: periodic limb movements in sleep, periodic movement disorder of sleep, heart rate variability, autonomic nervous system, sleep-related movement disorder, autonomic co-activation

(*Neurol Neurochir Pol 2023; 57 (2): 167–175*)

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Received: 11.04.2023 Accepted: 05.07.2023 Early publication date: 05.09.2023

Introduction

Periodic limb movements in sleep (PLMS) are defined as repetitive and stereotypical movements of the lower limbs occurring during sleep in a periodic pattern. They typically involve dorsiflexion of the ankle, extension of the big toe, and occasional flexion of the knee and hip [1]. A single movement may last from 0.5 to 10 s; however, the movements manifest in a series of four or more single movements separated by intervals of 5-90 s [1]. PLMS are present in 80% of patients with restless leg syndrome (RLS) [2], but also co-occur with a range of sleep disorders including obstructive sleep apnoea, insomnia, narcolepsy [3], and neurological pathologies associated with REM sleep behaviour disorder [4]. Interestingly, PLMS have also been associated with diverse psychiatric diseases in numerous studies. Longitudinal data demonstrates that patients with PLMS have an increased risk of depression and anxiety, and of dementia [5, 6].

It should be noted, however, that it remains unclear how a series of PLMS affects the autonomic nervous system (ANS), cardiovascular system, and mental health.

PLMS has been linked to a change in ANS activity and its effect on circulatory regulation. PLMS are regarded as being accompanied by an increase in HR preceding the occurrence of leg movements during PLMS. Cortical and sympathetic activations are supposed to lead these changes [7–11], supporting the association between PLMS and cardiovascular and hypertensive risks [12]. This sympathetic overactivity can lead to surges in nocturnal blood pressure (BP) and HR [13]. There have been some reports that PLMS onset is heralded by a significant increase of HR and BP [14, 15]. Indeed, the increase in systolic blood pressure (SBP) [14] and diastolic blood pressure (DBP) has been widely discussed in the literature [14–16]. PLMS are supposed to be followed by an increase in HR which starts immediately after the onset of leg movement and rises in the first few seconds after the limb movement [14, 15, 17].

Basic haemodynamic parameters, such as systolic and diastolic blood pressure, but also more sophisticated methods of assessing extracardiac regulation of heart rhythms such as HRV, can be used to assess the autonomic regulation of circulation. HRV analysis is a well-recognised, non-invasive research method that describes the influence of the ANS on HR. HRV analysis determines the contribution of total HR components that are dependent on endogenous oscillators of HR regulation. The basic components of the heart rhythm are affected by the sympathetic and parasympathetic activity of the ANS, which determines the short- and long-term variability of the sinus rhythm. HRV analysis also indicates the contribution of the respiratory component to the heart rhythm. Physiological respiratory irregularity is a change in HR that is closely related to the phase of breathing.

In general, high HRV is regarded as an index of cardiovascular health [18]. Moreover, low HRV parameters are related to diverse psychiatric illnesses including major depressive disorder [19], bipolar disorder [20], anxiety disorder [21], schizophrenia [22] and Parkinson's Disease (PD) [23, 24]. PLMS are frequently observed in individuals with PD, and are often accompanied by dysautonomia and cognitive impairment, which are among the non-motor symptoms associated with PD [24, 25]. Cardiovascular ANS dysautonomia in PD involve abnormalities such as decreased HRV and impaired baroreflex sensitivity which may contribute to the increased risk of cardiovascular events in individuals with PD [24]. It is possible that the dysregulation of autonomic cardiovascular control in PD could impact upon cerebral blood flow and oxygenation, and contribute to neuroinflammation and neurodegeneration, thus affecting cognitive function [24].

HRV may be considered to be a link between psychiatric and neurological disorders, cardiovascular diseases, and mortality [26]. HRV has recently been reported to show associations with suicide attempts [26, 27]. HRV analysis has found wide recognition in medical research as a non-invasive method of assessing HR regulation and an indicator assessing the risk of serious cardiovascular events. It is reasonable to postulate that the sympathetic activation and HRV alterations associated with PLMS may play a role in the occurrence of desaturation episodes during sleep, potentially worsening stroke outcomes [28].

Conducting further research to explore the connection between PLMS, desaturation episodes, and stroke outcomes could offer valuable insights into the underlying pathophysiology and clinical implications of PLMS-related cardiovascular dysautonomia.

Smoking and excessive alcohol consumption reduce HRV, while conversely an active lifestyle, regular physical exercise, and the use of relaxation methods including meditation, raise HRV parameters.

Data from the literature indicates that HRV decreases in PLMS with a concomitant increase in sympathetic tone [29–31]. Some studies additionally have indicated decreased vagal activity [32]. Altered HRV in PLMS patients was also the result of the study by Barone et al., who observed a significant reduction of HRV HF (high-frequency HRV) and elevation of very-low-frequency HRV (HRV VLF) [11]. Previous reports have indicated elevation of HRV VLF, HRV LF and LF/HF in the period of a PLMS event [7, 13, 31, 33]. In one study [7], the increase of HRV VLF and HRV LF was described several tens of seconds before the beginning of the period with PLMS, with a subsequent increase of HRV HF fluctuation. However, Izzi et al. [34] found no significant difference in HRV in RLS patients with PLMS.

Clinical rationale for the study

Autonomic dysfunction or dysregulation in patients with PLMS reflecting in HRV has been described in some domains; however, detailed studies on this subject are limited and results are conflicting. Therefore, the aim of this study was to verify the hypothesis that a series of PLMS is connected with a higher range of abnormalities in SBP and DBP, with particular interest in HRV HF scores before the series of PLMS and after the end of the series.

In the current work, we have applied an innovative approach to the assessment of autonomic regulation of the heart rhythm, including the measurement of the dynamics of changes in HR regulation indices during successive PLMS series.

Material and methods

We analysed polysomnographic (PSG) recordings from five patients (three males and two females) aged 32–62 with PLMS at the Vitalmed Helsinki Sleep Clinic, Helsinki, Finland. All of the patients had a diagnosis of RLS that had been verified by an experienced neurologist. The original studies were approved by the local ethics committees and all subjects provided informed written consent.

Each subject underwent a single night PSG study. Patients did not undergo any pharmacological therapies that might influence or induce PLMS, such as antipsychotics, sedatives, antidepressants, lithium, B-blockers, or Ca-blockers. Patients with renal disease, diabetes mellitus, depression, anxiety disorder, heart disease, psychotic disorder, or arrhythmia were excluded. Patients with an apnoea/hypopnoea index ≥ 5 were also excluded.

Treatments for other conditions, including drugs for hypertension, were stable for ≥ 2 weeks preceding the PSG. Inclusion and exclusion criteria are set out in Table 1.

All PSG recordings were performed with a SOMNOscreen plus PSG system (Somnomedics, Randersacker, Germany).

The following parameters were included in the PSG examination. Recordings included eight EEG leads, two bilateral electro-oculogram leads (EOG), bilateral chin electromyographic (EMG) leads, and two surface EMG of the left and right anterior tibialis muscles (for recording periodic limb movements). Electrocardiograms were recorded via three precordial leads. The sleep respiratory pattern was assessed with a nasal cannula, thoracic and abdominal strains, and a finger oximeter.

The PSG recording included beat-to-beat BP measurements performed automatically, using pulse transit time (PTT) [35]. The BP measurements were collected continuously (beat-to-beat).

To assess heart rhythm, QRS peaks were detected, and then the HR was calculated directly from the RR interval (RRi) automatically. ECG was recorded at a sampling rate of 4 kH.

We also assessed the stage of sleep and the duration of limb movement in each PLMS. The total number of analysed PLMS samples was 1,348. All the measurements were noninvasive, did not disturb sleep, and were unnoticeable by the patients. No awakenings were noted during the study in the sample group.

PLMS were scored following the standard criteria of the American Academy of Sleep Medicine (AASM) [36]. PLMS were included if they increased at least 8 μV above the resting line in EMG with a duration of 0.5–10 s before a drop in EMG to < 2 μV above the resting line. The episodes were defined as PLMS only when four or more such episodes appeared separated by intervals of 5-90 s. In this study, only PLMS were considered, and patients with PLMS with arousals in PSG were excluded from the study.

A series of PLMS was defined as a group of consecutive PLMS with an interval between leg movements shorter than 90 s. A leg movement appearing 90 s or more after the previous one was designated as the beginning of a new series or as a single leg movement.

The episodes of PLMS > 10 s were regarded as a PLMS series, and in the case of each patient there were no single PLMS, as they occurred only as series. The PLMS series was stopped when a limb movement appeared with an interval of < 10 s [37]. Limb movements overlapping with any breath event were not considered as PLMS. Movements appearing sooner than 0.5 s before the beginning of, or no more than 0.5 s after the end of, a breath event were not recognised as PLMS. A total of 1,348 PLMS without arousals were selected from the PSGs.

Methods

The first step was to identify the appropriate ECG fragments for further analysis. Based on these records, RRi were calculated and used to determine HRV in the short-term variability band — HRV HF. For each time series, we assessed also the mean HR, SBP and DBP.

All measurements were computed from a segment of 10 RR intervals immediately preceding the first PLMS series (baseline; –1), and at the start of the first PLMS series (point 0), as well as from subsequent 10 RR interval segments located after each successive PLMS series from 1 to 10 (Fig. 1).

Determination of the HRV HF parameter allowed the assessment of short-term HRV, represented by changes in high frequency (0.15–0.4 Hz) [38]. Short-term variability is

Table 1. Inclusion and exclusion criteria applied in study

Inclusion criteria	Exclusion criteria
Age 18-65	Age < 18
Diagnosis of RLS	Age > 65
PLMS without arousal	PLMS with arousal
Treatment of non-excluded medical conditions stable for ≥ 2 weeks preceding PSG	Respiratory events
	Apnoea/hypopnoea index ≥ 5
	Antipsychotics, sedatives, antidepressants, lithium, B-blockers, or Ca-blockers intake
	Renal diseases, diabetes mellitus, depression, anxiety disorders, heart diseases, psychotic disorders, and arrhythmias diagnosis

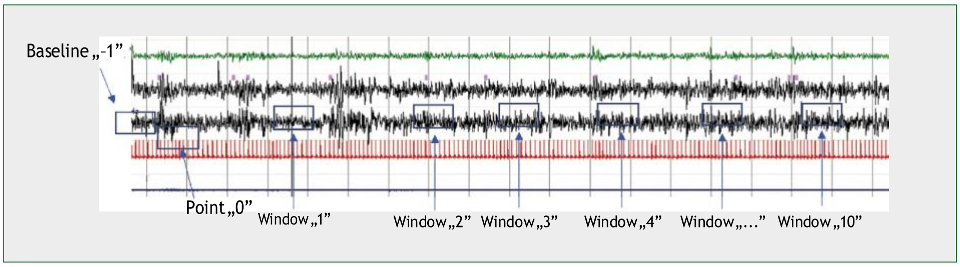

Figure 1. Demonstration of PLMS in a series; point 0 indicates start of 1st PLMS in series. Time window location (1–10) was assessed as 10 RR intervals after each PLMS (1–10). Baseline indicates point of 10 RR intervals before start of series. For each RR interval in window and baseline, value of HR, SBP, DBP and HRV HF was assessed

representative of parasympathetic influences on heart rhythm. The choice of HRV HF estimation was dictated by short time windows, which in turn were determined by the nature of the records.

The presented method of using successive, short, 10 RR interval segments refers to the time-frequency measurement, which is very clear and useful for presenting changes in the calculated parameters over time and thereby illustrating their dynamics. Calculation of HRV analysis parameters from many consecutive short time windows is widely used in time-frequency analysis. Using this method allowed us to assess any dynamic changes in HRV HF during successive PLMS series. To the best of our knowledge, we are the first to study dynamic changes in intracardiac ANS activity in conjunction with PLMS.

All tested parameters: HR, HRV HF, and BP (SBP and DBP) were averaged for all subsequent PLMS series. Moreover, the value of data was subtracted from the baseline rate, defined as the value of data before leg movement (in point "–1"), to obtain the rate of change for each data type.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (v. 28.0.0.0). A one-sample test was performed to check if these measurements differed significantly from each other. The analysis showed that only SBP changes had no statistically significant change ($p = 0.0589$; the other parameters had $p < 0.05$). None of the data had a normal distribution (normality test $p < 0.001$). The Kruskal–Wallis test was performed to find statistically significant changes from baseline. This analysis was carried out to compare responses to leg movement from each type of data compared to baseline values (before PLMS). The statistically significant changes showed data from HRV_HF between series "–1" and series "9" ($p = 0.026$).

Results

We found no statistically significant changes in HR, SBP, or DBP in our group (Tab. 2, 3). In the assessed group of patients, HRV HF changed after the series of eight PLMS (Fig. 2). The average of the evoked change in HRV HF, calculated as

Table 2. Average value of parameters obtained for each PLMS, where "–1" is period before beginning of limb movement ("0")

Movement	HR	SBP	DBP	HRV HF
-1	59.22	127.84	69.53	307.08
0	58.02	125.81	68.86	354.96
1	59.72	127.60	70.82	356.43
2	58.43	126.42	70.33	358.02
3	59.28	126.84	70.98	357.55
4	58.02	127.12	71.11	362.38
5	58.67	126.24	69.83	364.65
6	57.24	124.53	69.21	377.45
7	55.96	125.56	70.01	446.98
8	57.26	126.53	69.58	472.44
9	56.46	125.69	69.26	476.50
10	58.00	126.28	68.85	475.32

DBP — diastolic blood pressure, HR — heart rate; HRV HF — heart rate variability high frequency; SBP — systolic blood pressure

Table 3. Average changes in value (difference between value of each parameter and mean value before PLMS) of parameters obtained for each PLMS, where "–1" is period before beginning of limb movement ("0")

Movement	HR change	SBP change	DBP change	HRV HF change
-1	0.00	0.03	-0.05	0.03
0	-0.28	-0.43	-0.51	0.42
1	1.42	1.33	1.45	1.89
2	0.14	0.17	0.96	3.48
3	0.99	0.65	1.61	3.01
4	-0.72	-1.14	1.19	5.05
5	-0.08	0.23	-0.08	7.31
6	-2.29	0.78	0.71	11.86
7	-2.19	-0.46	0.83	22.50
8	-1.05	0.48	1.74	24.87
9	-1.85	-0.36	1.43	28.94
10	-0.11	0.25	0.91	32.13

DBP — diastolic blood pressure, HR — heart rate; HRV HF — heart rate variability high frequency; SBP — systolic blood pressure

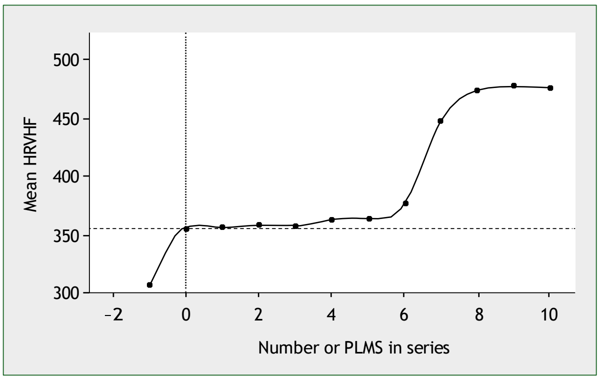

Figure 2. Average of evoked HRV HF for each PLMS. Horizontal dashed line represents mean HRV before limb movement, while vertical dashed line marks beginning of limb movement. HRV HF — heart rate variability high frequency; PLMS — periodic limb movements in sleep

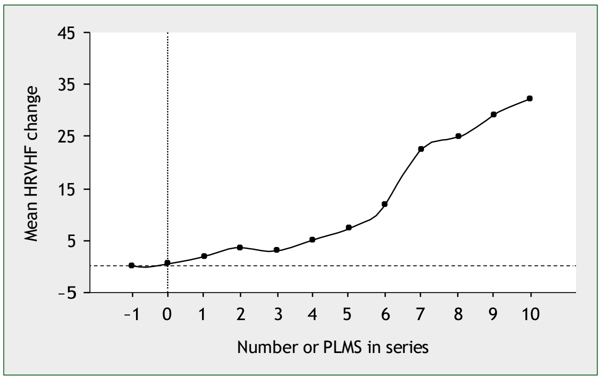

Figure 3. Average change in evoked HRV HF (calculated as difference between each HRV and mean HRV before limb movement) for each PLMS. Horizontal dashed line represents mean HRV before limb movement, while vertical dashed line marks beginning of limb movement. HRV HF — heart rate variability high frequency; PLMS — periodic limb movements in sleep; HR — .heart beats/ /min; HR change calculated as difference between actual HR and mean HR before leg movement; HR baseline calculated as mean HR before leg movement; SBP/DBP/HRV HF baseline calculated as difference between actual value and mean value before leg movement; movement calculated as number of series, where "−1" is before start of movement and "0" is start of movement

the difference between each HRV and mean HRV before leg movement for each PLMS, also increased after the series of eight PLMS (Fig. 3).

Discussion

The main finding of our study is that following eight PLMS in a series, HRV HF increased with no increase in HR and BP. To the best of our knowledge, we are the first to report such an effect.

We focused on sequential PLMS series and related changes in BP, HR and HRV HF. Previous research has analysed a single PLMS or limited numbers of PLMS patterns [7, 14, 29]. In our research, we focused on all the PLMS events during sleep in all five patients.

The results that we present do not indicate a significant and systematic increase in systolic and diastolic blood pressure as well as HR during subsequent series of PLMS. These results contradict some reports that have recorded both an increase in HR and in BP before PLMS. It has been reported that as much as 99% of PLMS is associated with changes in HR [39]. Increases in HR and BP are associated with increased sympathetic arousal, sometimes in combination with arousal in EEG, shortly before the onset of periodic limb movement [30, 40]. In our study however, PLMS with arousals were excluded, which could explain the lack of changes in HR and BP.

Sympathetic hyperactivity may also have an important effect on BP, increasing it up to 30 mmHg [41]. On the other hand, although our results did not indicate a change in HR and BP, we do not rule out an increase in intracardiac sympathetic activity. We believe that the increase in sympathetic activity was marked, as it counterbalanced the increase in intracardiac parasympathetic activity, which resulted in no change in HR and BP.

Since our results indicate a significant increase in short-term variability, expressed by the HRV HF, we hypothesise an increase in intracardiac parasympathetic activity, alongside the appearance of successive PLMS series. We postulate a simultaneous increase in intracardiac sympathetic and parasympathetic activity.

Although this assumption does not contradict the traditional view of the role of the ANS in the establishment of HR, associated with the opposing action of the sympathetic and parasympathetic systems on the heart rhythm, it does suggest the co-activation of the sympathetic and parasympathetic systems in such a way that they occur in parallel with each other.

Almost 30 years ago, Pagani et al. [42] proposed that HRV analysis be applied to evaluate the balance between two branches of the ANS. This was related to three core statements: 1) the power spectral density (PSD) of the HF component can be taken as an index of cardiac parasympathetic tone; 2) the PSD of the LF component may be a marker of cardiac sympathetic outflow; and 3) the balance between the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) can be assessed as the LF/HF ratio, usually interpreted as the relative SNS contribution to the control of HR. Surprisingly, despite evidence to the contrary [43–45], these measures are still extensively used to index the so-called 'sympathovagal balance'. The concept of autonomic balance and its LF/HF mathematical expression is based on the traditional doctrine of autonomic reciprocity.

The traditional view of the SNS and PNS is that they function in opposition to each other. The SNS is often considered the 'fight or flight' system, while the PNS is responsible for 'rest and digest' or 'feed and breed' activities [46]. The SNS is activated by exercise, cold and anxiety to divert bloodflow away from the gastro-intestinal tract and skin (via vasoconstriction) to the brain, heart, skeletal muscles and lungs. In addition, SNS activation increases HR and myocardial contractility, further enhancing bloodflow to the brain and skeletal muscles [47].

According to this doctrine, the sympathetic and parasympathetic branches of the ANS are subjected to reciprocal central nervous control, in the sense that increased activation of one system is accompanied by inhibition of the other [48]. This view, however, seems somewhat simplistic. Instead, the SNS and PNS interact in a dynamic fashion, and either reciprocity or co-activation of both branches may occur [44, 49].

Baroreflex represents a typical physiological example of reciprocal activation of the ANS. It allows for a powerful and quick, but not precisely controlled, response to a rise/decline in BP through activation of PNS or SNS outflow to the heart, respectively [47]. However, the SNS/PNS relation seems to be more like the yin-yang principle where the interrelation of opposites is essential, and the SNS and PNS are indispensable to each other [50, 51]. Examples of SNS/PNS co-activation include: peripheral chemoreflex (PChR) [50], trigemino-cardiac reflexes (TCRs) [52, 53], panic disorder [54], emotional sadness [55], and visceral pain [56], to name but a few.

Sympathetic and parasympathetic co-activation, however, can lead to life-threatening cardiovascular events [57]. This is due to the parasympathetic chromotropic effect, slowing down the speed of conduction of excitation between the atria and ventricles, which can cause partial or complete atrioventricular block or even lead to asystole for several seconds. On the other hand, an increase in sympathetic activity directed at ventricular cells may lead to the appearance of ectopic areas and associated ventricular extrasystoles. These are just a few examples of cardiac arrhythmias that may occur. There are also studies confirming the connection between a higher prevalence of cardiac arrhythmia such as atrial fibrillation in PLMS [58–60]. Any causal role for PLMS in the pathogenesis of cardiovascular diseases including arrhythmias requires further investigation.

In general, a regular cardiac rhythm is maintained by a strictly regulated balance of sympathetic and vagal tone. Simultaneous co-activation of both branches of the ANS is associated with a potential risk of cardiac arrhythmia [61] and might determine a possible additive notable risk factor of cardiovascular disease in PLMS patients. According to Koo et al., both sympathetic and parasympathetic activity are likely to be hyperactive in patients with PLMS and in older men with PLMS and structural heart disease, or in those who in the absence of anti-arrhythmic medication are more prone to cardiac arrhythmias [58].

Our data, combined with earlier reports suggesting sympathetic activity, may potentially highlight the co-activation of both the sympathetic and parasympathetic divisions of the ANS, determining possible autonomic dysregulation. Sasai et al. have also described a consecutive elevation of HRV HF fluctuation after these changes, suggesting that parasympathetic nervous activity becomes unstable, which is consistent with our findings [7].

There are some limitations to our work. Short time windows did not allow us to calculate the long-term variability of HRV. Spectral power in the low frequency (LF) range corresponds to HR changes of 2.4–9 beats per minute (0.04–0.15 Hz). Originally, the LF band was thought to be an indicator of intracardiac sympathetic activity. However, the assumption of a simple relationship between the sympathetic activity and HRV in the low frequency range was not confirmed in further studies. Intracardiac parasympathetic activity may contribute to some extent in the LF component. This is evidenced by research related to the blockade of muscarinic receptors — M1, which leads not only to the reduction of the HF band, but also the low-frequency component — LF [62].

The use of AASM rules might be considered another limitation of this study. Although PSG recordings were scored accordingly to AASM guidelines, the new guidelines of the IRLSSG/WASM were considered as far as respiratory event-related leg movements were concerned. In selecting PLMS episodes which underwent further analysis, special attention was given to exclude events that might have been triggered by a respiratory event.

Finally, our sample size was small. Nevertheless, there were no PLMS related to the arousals criteria [63] defined as transient increases in higher frequency EEG activity occurring with increases of SNS activity. In addition, in all patients, changes in the HRV were in the same direction, an observation that actually strengthens our reasoning. The process of 1,348 leg movements and its influence on used parameters was analysed, which we believe support our inferences.

Clinical implications

The findings of our current study add to the literature information regarding HRV in PLMS, and highlight the need for further studies to elucidate the effects of these conditions on the ANS, and cardiovascular health. In particular, the effects of the PLMS series on the ANS should be more closely monitored.

Article information

Funding: *Marta A. Malkiewicz is supported by the Polish National Science Centre (NCN) grant Preludium, number 2019/33/N/NZ5/02815.*

Conflicts of interest: None.

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Journal of Clinical Medicine

Article

Time-Dependent Autonomic Dysregulation and Co-Activation Induced by Periodic Limb Movements in Sleep

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Abstract: Background: Periodic limb movements in sleep (PLMS) are characterised by repetitive, involuntary limb movements that occur during sleep and are often associated with autonomic nervous system dysregulation. While it is known that PLMS influence cardiovascular parameters, the exact role of heart rate variability (HRV) and the balance between sympathetic and parasympathetic activity remains unclear. Previous studies have suggested that longer PLMS events may trigger more pronounced autonomic responses, but the relationship between the duration of PLMS and autonomic dynamics has yet to be fully explored. This study aims to investigate the influence of PLMS duration on autonomic co-activation and its potential cardiovascular implications. **Methods:** A retrospective analysis was conducted on polysomnographic, demographic, and medical data from five patients, encompassing a total of 1348 PLMS events. We measured heart rate (HR), high-frequency HRV (HF-HRV), systolic blood pressure (SBP), and diastolic blood pressure (DBP) for 10 heartbeats before and 10 heartbeats after each PLMS series. A time–frequency approach was used, employing 10 RR interval segments to analyse HF-HRV dynamics. Statistical analysis was performed using IBM SPSS Statistics (v. 28.0.0.0), and the Kruskal–Wallis test was used to assess statistically significant deviations from baseline. **Results:** HF-HRV increased during PLMS, indicating enhanced parasympathetic activation. No significant changes in mean DBP or SBP were observed with leg movements of <2.1 s. However, with movements of >2.1 s, significant increases in DBP and SBP were noted, suggesting sympathetic activation. Longer PLMS events were associated with greater parasympathetic activity, while the absence of HR changes indicates concurrent sympathetic activation, supporting autonomic co-activation. **Conclusions:** Our study indicates that PLMS events lasting >2.1 s are linked to increased parasympathetic activity, likely accompanied by sympathetic activation. This simultaneous activation of both branches of the autonomic nervous system, referred to as autonomic co-activation, could lead to autonomic dysregulation and an increased risk of cardiovascular instability, including potentially life-threatening events.

Academic Editor: Giuseppe Lanza

Received: 21 January 2025
Revised: 3 March 2025
Accepted: 4 March 2025
Published: 13 March 2025

Citation: Malkiewicz, M.A.; Grzywinska, M.; Malinowski, K.S.; Partinen, E.; Partinen, M.; Pyrzowski, J.; Wszedybyl-Winklewska, M. Time-Dependent Autonomic Dysregulation and Co-Activation Induced by Periodic Limb Movements in Sleep. *J. Clin. Med.* **2025**, *14*, 1940. https://doi.org/10.3390/jcm14061940

Keywords: autonomic co-activation; autonomic nervous system; heart rate variability; periodic limb movements in sleep; PLMS duration; cardiovascular risk

1. Introduction

Periodic limb movements in sleep (PLMS) are involuntary, stereotyped movements of the lower limbs that occur in a periodic pattern during sleep, typically involving dorsiflexion of the ankle, extension of the big toe, and occasional flexion of the knee and hip. They are commonly observed in individuals with restless leg syndrome (RLS) [1]; however, they also occur in sleep disorders such as obstructive sleep apnoea, insomnia, and narcolepsy, as well as in neurological and psychiatric conditions, including neurodegenerative diseases, dementia, schizophrenia, and anxiety disorders [2–6]. Emerging evidence suggests a potential link between PLMS and psychiatric disorders, particularly anxiety and depression [7].

Additionally, PLMS have been identified as an independent risk factor for cardiovascular diseases, such as hypertension and stroke, with studies suggesting a possible link to increased cardiovascular and cerebrovascular risk [8].

As psychiatric and cardiovascular diseases become more prevalent, understanding PLMS and its potential impact on these conditions is increasingly important. Anxiety disorders are estimated to affect millions of people worldwide, while depression impacts more than 264 million individuals [9]. Cardiovascular diseases, including hypertension, heart disease, and stroke, are among the leading causes of death, accounting for a significant number of fatalities each year [9]. This underscores the growing relevance of studying PLMS, particularly in relation to these conditions, as gaining insight into its biological mechanisms could provide valuable clinical information [7].

The autonomic nervous system (ANS) plays a crucial role in regulating physiological responses during PLMS, with shifts in sympathetic and parasympathetic activity occurring in reaction to these movements. Sympathetic activation, commonly associated with PLMS, leads to elevated heart rate (HR) and blood pressure (BP), potentially increasing cardiovascular risk in affected individuals [10–12]. At the same time, parasympathetic activation may also occur, reflected by an increase in high-frequency HR variability (HF-HRV), suggesting parasympathetic involvement [13]. This simultaneous activation of both branches of the ANS during PLMS is termed autonomic co-activation. Such co-activation can disrupt the autonomic balance, leading to instability and potential cardiovascular consequences because both branches of the ANS are engaged without a dominant influence from either [13].

PLMS may potentially serve as an independent risk factor for cardiovascular diseases. Although transient elevations in BP and HR during PLMS episodes could contribute to the long-term development of hypertension [14], emerging evidence increasingly supports the notion that PLMS itself may represent an independent cardiovascular risk factor.

The frequency and intensity of PLMS episodes may influence the cardiovascular responses observed, but the role of episode duration remains underexplored.

Previous research has shown that PLMS affect autonomic regulation, particularly circulatory function. Sympathetic activation during PLMS leads to increases in nocturnal BP and HR, with significant rises in both at the onset of PLMS, peaking within seconds after each limb movement [14–16].

Our previous study, 'Effect of series of periodic limb movements in sleep on blood pressure, heart rate, and high-frequency heart rate variability', identified autonomic co-activation in PLMS, providing a foundation for understanding its cardiovascular effects [13]. The current study builds upon this by focusing on the duration of PLMS episodes. We hypothesise that longer PLMS episodes may have a distinct influence on autonomic regulation, potentially leading to more pronounced parasympathetic activity or greater autonomic conflict. The duration of these episodes could modulate the extent of autonomic instability, contributing to an increased risk of cardiovascular events. This hypothesis explores whether the duration of PLMS affects the balance between sympathetic and parasympathetic activity and whether prolonged or repeated activations lead to more significant autonomic dysregulation.

Our study aimed to identify a marker of autonomic dysfunction specifically in the context of PLMS, as autonomic disturbances during these episodes could be linked to cardiovascular implications across various clinical conditions.

By investigating the time-dependent nature of autonomic co-activation, this study aims to address critical questions: Does the duration of PLMS episodes influence the degree of autonomic conflict? Can longer PLMS episodes amplify autonomic instability, increasing the potential for cardiovascular disturbances even in the absence of overt cardiovascular disease? Understanding the time dependency of autonomic responses during PLMS may provide important insights into the physiological processes underlying the disorder and guide more precise clinical assessments for affected individuals.

2. Materials and Methods

We conducted a retrospective analysis of polysomnographic (PSG) data, along with demographic and medical information, from 5 patients who experienced a total of 1348 PLMS events. HR, HF HRV, systolic BP (SBP), and diastolic BP (DBP) were measured for 10 heartbeats prior to each PLMS series and for 10 subsequent heartbeats using beat-to-beat analysis. A time–frequency approach, using short segments of 10 RR intervals, was employed to track changes in the measured parameters over time, providing a dynamic perspective of autonomic activity.

Statistical analysis was performed using IBM SPSS Statistics (version 28.0.0.0), and the Kruskal–Wallis test was used to identify significant deviations from baseline values.

We analysed PSG recordings from five patients (three men and two women), aged 32 to 62 years, with PLMS at the Vitalmed Helsinki Sleep Clinic, Finland. All participants had a confirmed diagnosis of RLS made by an experienced neurologist. It is important to note that all individuals in this study had the non-neurodegenerative form of RLS.

The original studies were approved by the local ethics committee of the Medical University of Gdańsk (approval number NKBBN/388/2022), and all participants provided written informed consent.

Each participant underwent a single-night PSG study. None of the patients were receiving pharmacological treatments that could influence or induce PLMS, such as antipsychotics, sedatives, antidepressants, lithium, β-blockers, or calcium channel blockers. Patients with conditions such as renal disease, diabetes mellitus, depression, anxiety disorders, heart disease, psychotic disorders, or arrhythmias were excluded. Participants with an apnoea–hypopnoea index of ≥5 were also excluded.

Medications for other conditions, including those for hypertension, had been stable for at least 2 weeks prior to the PSG study. Detailed inclusion and exclusion criteria are provided in Table 1.

Table 1. Inclusion and exclusion criteria applied in the study.

Inclusion Criteria	Exclusion Criteria
Age of 18–65 years Diagnosis of RLS PLMS without arousal Treatment for non-excluded medical conditions stable for at least 2 weeks prior to the PSG study	Age of <18 years Age of >65 years PLMS with arousal Respiratory events Apnoea/hypopnoea index of ≥5 Use of antipsychotics, sedatives, antidepressants, lithium, β-blockers, or calcium channel blockers

2.1. Materials

All PSG recordings were conducted using a SOMNOscreen plus PSG system (Somnomedics, Randersacker, Germany).

The PSG examination included a comprehensive set of parameters: eight electroencephalographic (EEG) leads, two bilateral electro-oculographic leads, bilateral chin electromyographic (EMG) leads, and surface EMG electrodes placed on the left and right anterior tibialis muscles to monitor PLMS. ECG recordings were obtained using three precordial leads. Respiratory patterns during sleep were assessed using a nasal cannula, thoracic and abdominal effort belts, and a finger pulse oximeter.

The PSG recordings also featured continuous, beat-to-beat BP measurements, which were automatically collected using pulse transit time technology [17]. These non-invasive BP measurements were performed without disturbing the participants' sleep.

Heart rhythm was assessed by detecting QRS peaks in the ECG recording, from which HR was automatically calculated based on RR intervals. ECG signals were sampled at a high frequency of 4 kHz to ensure precision.

Sleep stages and the duration of each limb movement within PLMS events were analysed, with a total of 1348 PLMS samples included in the study. All measurements were performed non-invasively, ensuring they did not disrupt the participants' sleep, as no awakenings were observed in the sample group.

PLMS scoring followed the standard criteria outlined by the American Academy of Sleep Medicine (AASM) [18]. Movements were classified as PLMS if they exhibited an increase of at least 8 μV above the baseline EMG level, lasted between 0.5 and 10 s, and were followed by a reduction in EMG activity to less than 2 μV above the baseline. To qualify as PLMS, episodes had to consist of at least four movements occurring at intervals of 5–90 s. Only PLMS events without associated arousals were included in the study, and participants who exhibited PLMS with arousals were excluded.

A PLMS series was defined as a sequence of consecutive movements with intervals of <90 s between events. Movements separated by ≥90 s were considered the start of a new series or classified as isolated movements.

PLMS episodes lasting >10 s were classified as PLMS series. None of the participants exhibited isolated PLMS; all episodes occurred within the series. A PLMS series was considered complete if a limb movement was followed by an interval of <10 s [19]. Limb movements overlapping with respiratory events were excluded. Specifically, movements occurring within 0.5 s before the start of, or up to 0.5 s after the end of a respiratory event were not classified as PLMS. In total, 1348 non-arousal-associated PLMS events were selected for analysis.

2.2. Methods

The first step involved identifying suitable ECG segments for further analysis. RR intervals were derived from these segments and used to calculate short-term HF-HRV, which reflects parasympathetic modulation. For each time series, mean HR, SBP, and DBP were also assessed.

Measurements were taken at the following time points: 10 RR intervals immediately before the start of the first PLMS series (baseline; −1), 10 RR intervals at the onset of the first PLMS event in the series (point 0), and a subsequent 10 RR interval segments following each successive PLMS event from 1 to 10 (Figure 1).

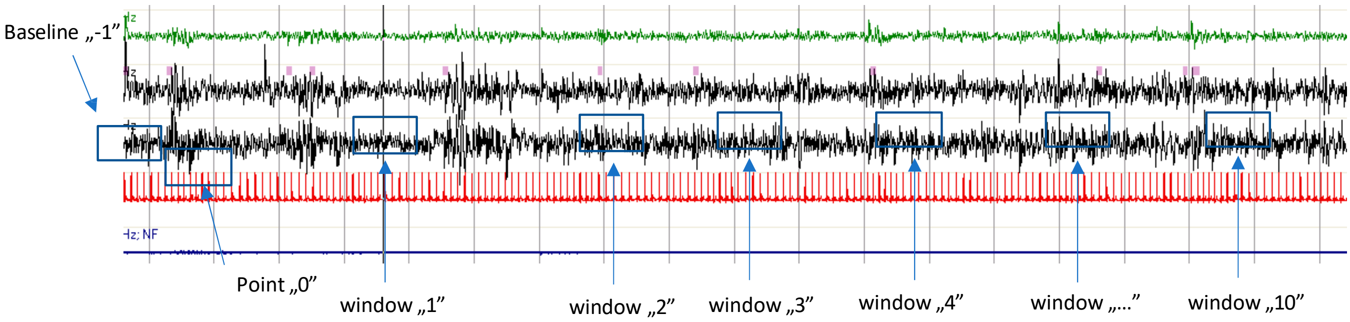

Figure 1. Illustration of PLMS occurring in a series. Point '0' denotes the onset of the first PLMS event in the sequence. Time windows (1–10) correspond to segments of 10 RR intervals following each subsequent PLMS event (1–10). Window ". . ." illustrates windows 5–9. The baseline is defined as the 10 RR intervals preceding the initiation of the series. For each RR interval within the baseline and time windows, values for HR, SBP, DBP, and HF-HRV were calculated, and the baseline values for HR, SBP, DBP, and HF-HRV were assessed.

HF-HRV was selected for its high sensitivity to parasympathetic modulation, making it ideal for analysing the brief intervals characteristic of PLMS occurrences. This method, which applies consecutive 10 RR interval segments, is consistent with established approaches in time–frequency analysis.

This approach effectively illustrates temporal dynamics in physiological parameters, providing a clear picture of their changes during consecutive PLMS events. To the best of our knowledge, this study is the first to examine dynamic fluctuations in ANS activity, specifically parasympathetic modulation, in relation to PLMS.

HR, HF-HRV, and BP parameters were averaged for each successive PLMS series. To evaluate changes relative to baseline, the values from each PLMS event were expressed as differences from the baseline measurement taken at point '−1'.

2.3. Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics (v. 28.0.0.0). A one-sample test was used to assess whether the measurements exhibited statistically significant differences. Among the parameters, changes in SBP were the only ones that did not reach statistical significance ($p = 0.0589$), whereas other parameters showed significant differences ($p < 0.05$). Normality testing revealed that the data were not normally distributed ($p < 0.001$).

Significant deviations from baseline were assessed using the Kruskal–Wallis statistical test. This test compared the responses of various parameters at different PLMS events against baseline values. HF-HRV values showed a statistically significant rise between the baseline measurement (series '−1') and series '9' ($p = 0.026$).

In this study, the median > 2.1 s approach was employed to evaluate how the duration of PLMS in series affects autonomic activity. The aim was to investigate whether longer phenomena (lasting >2.1 s) have a different impact on sympathetic and parasympathetic co-activation compared to shorter ones.

The analysis focused on differences in the duration of PLMS in series, classified based on the median duration of >2.1 s. Pairwise comparisons were performed as follows:

Comparison between the 1st and 10th movement in the series of PLMS: This comparison was aimed at evaluating the effect of the duration of the first movement (which may reflect the initial phase of the PLMS series) on subsequent movements, particularly the 10th movement, which typically occurs later in the series. We investigated whether differences in the duration of these movements (the first and the last) influenced autonomic activity, particularly with respect to the changing dynamics of sympathetic and parasympathetic activation.

Comparison between the 0th and 10th movement: Because the first movement in the series (the 0th movement) occurs in close proximity to the initial stage of sleep and the 10th movement represents a more advanced phase, this comparison aimed to assess the impact of differences in the duration of these two movements on autonomic activity. The hypothesis was that differences in the duration of these movements could influence autonomic response, possibly leading to changes in sympathetic and parasympathetic balance.

Pairwise comparisons were conducted to determine whether the duration of specific movements significantly influenced autonomic responses, particularly in the context of co-activation of both the sympathetic and parasympathetic systems. Additionally, this analysis aimed to assess how movement duration might affect autonomic balance and whether movements lasting >2.1 s could amplify co-activation, leading to greater autonomic instability.

3. Results

The horizontal dashed line represents the baseline mean HF-HRV before the limb movement occurs, serving as a reference point. The vertical dashed line marks the onset of the limb movement, visually distinguishing the pre-movement and post-movement phases. The plot illustrates the evoked changes in HF-HRV, allowing for an analysis of how the autonomic response (in terms of parasympathetic activation) varies during leg movements.

The increase in HF-HRV was statistically significant ($p < 0.01$) (Figure 2), indicating enhanced parasympathetic activation during PLMS. However, there was no statistically significant difference ($p > 0.01$) in the mean DBP change when the median time of leg movement was <2.1 s (Table 2), (Figure 3). Similarly, no significant difference ($p > 0.01$) was observed in the mean SBP change under the same condition (Table 2), (Figure 4). By contrast, when the median time of leg movement exceeded 2.1 s, the increase in HF-HRV was also observed (Figure 5), but also in both the mean DBP change ($p < 0.01$) (Table 3), (Figure 6) and the mean SBP change ($p < 0.01$) (Table 3), (Figure 7). This pattern suggests the involvement of sympathetic activation during prolonged episodes, supporting the hypothesis of autonomic co-activation, where both sympathetic and parasympathetic branches of the ANS are simultaneously engaged without clear dominance. This finding is important because it challenges the traditional view of SNS and PNS functioning in opposition. Instead, it highlights a more complex interaction where both branches are activated together, potentially leading to autonomic dysregulation.

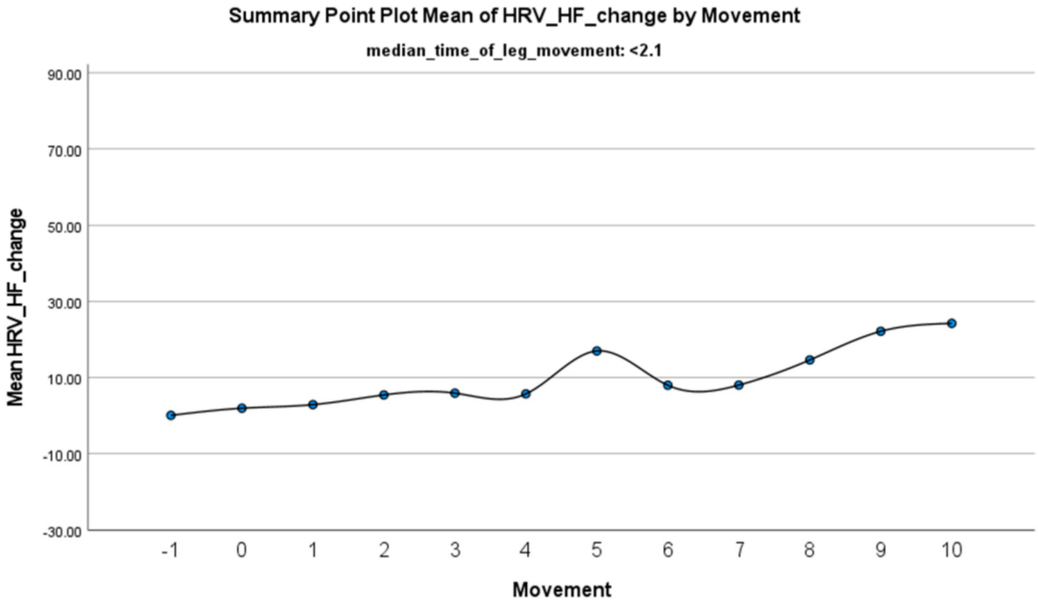

Figure 2. Summary of the mean change in HF-HRV during PLMS with leg movements lasting <2.1 s. The vertical axis represents the mean change in HF-HRV, calculated as the difference between each HRV value and the mean HRV before the limb movement. The horizontal axis indicates the movement series, with '−1' marking the time immediately before the start of the movement and '0' indicating the beginning of the movement. 'Movement' on the *x*-axis refers to leg movement.

Table 2. Presentation of statistical results of the one-sample test for the condition where median_time_of_leg_movement < 2.1 s. Only DBP_change and HF-HRV_change demonstrated statistically significant differences ($p < 0.05$).

One-Sample Test						
	Test Value = 0					
	t	df	Sig. (Two-Tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
HR_change	−0.251	839	0.802	−0.05357	−0.4722	0.3651
SBP_change	0.510	839	0.610	0.17869	−0.5084	0.8658
DBP_change	3.195	839	0.001	0.49464	0.1907	0.7986
HF-HRV_change	14.411	839	0.000	8.38750	7.2451	9.5299

Table 3. Presentation of statistical results of the one-sample test for the condition where median_time_of_leg_movement > 2.1 s. SBP_change, DBP_change, and HF-HRV_change demonstrated statistically significant differences ($p < 0.05$).

One-Sample Test						
	Test Value = 0					
	t	df	Sig. (Two-Tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
HR_change	−1.600	425	0.110	−0.63427	−1.4136	0.1451
SBP_change	3.961	425	0.000	0.55000	0.2771	0.8229
DBP_change	4.490	425	0.000	1.27512	0.7170	1.8333
HF-HRV_change	7.322	425	0.000	14.26103	10.4325	18.0895

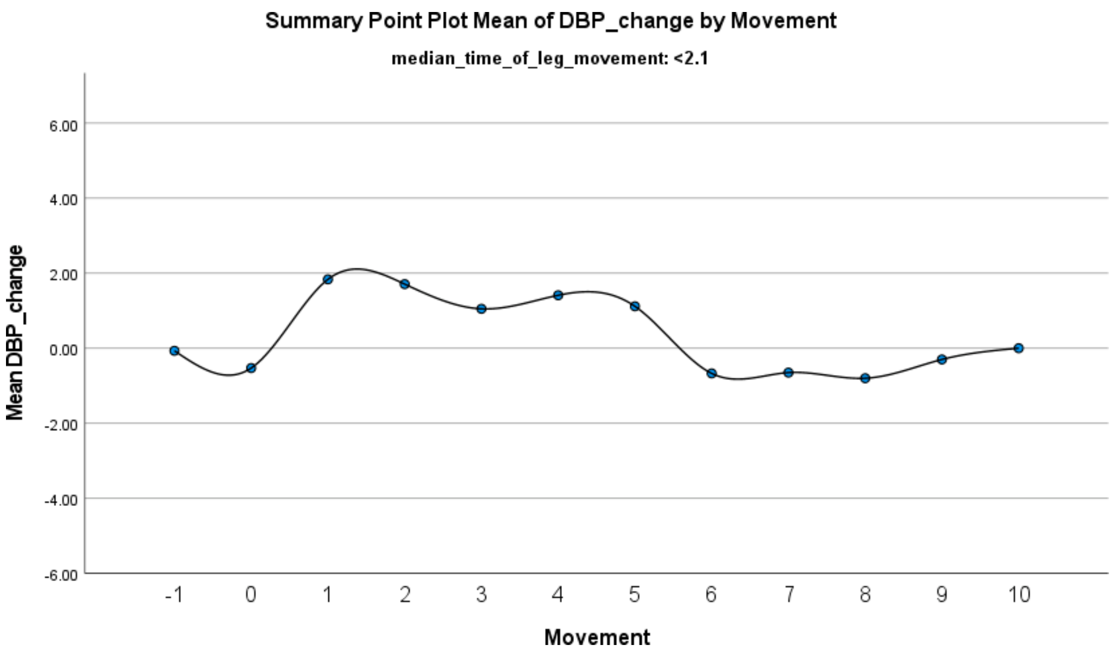

Figure 3. Summary of the mean change in DBP during PLMS with leg movements lasting <2.1 s. The vertical axis represents the mean change in DBP, calculated as the difference between each DBP value and the mean DBP before the limb movement. The horizontal axis indicates the movement series, with '−1' marking the time immediately before the start of the movement and '0' indicating the beginning of the movement. 'Movement' on the *x*-axis refers to leg movement.

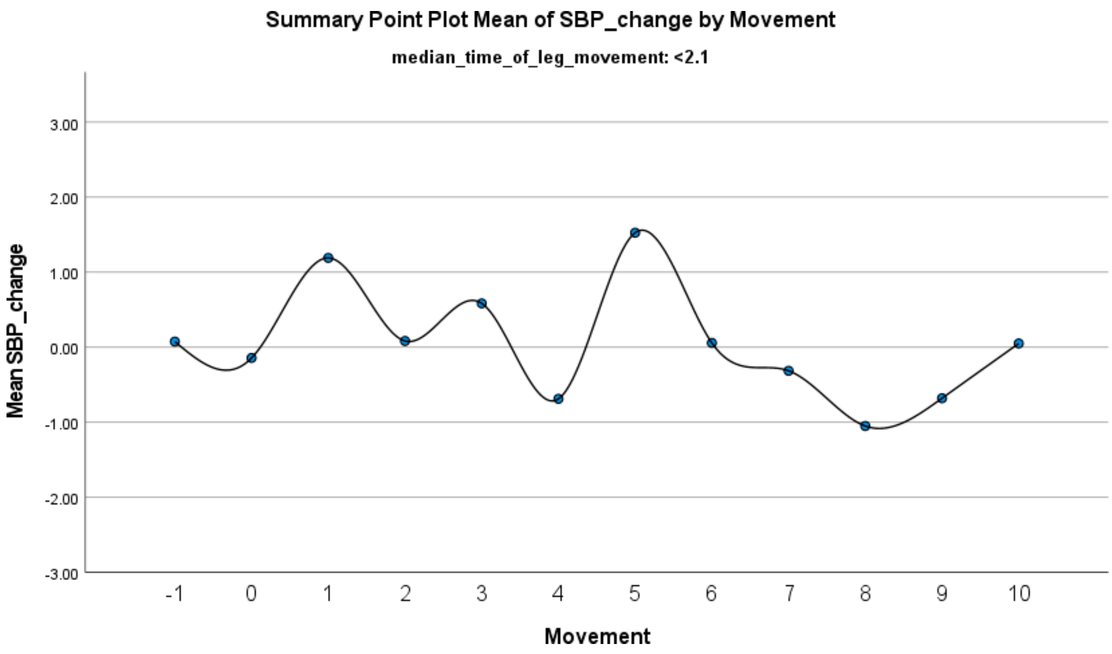

Figure 4. Summary of the mean change in SBP during PLMS with leg movements lasting <2.1 s. The vertical axis represents the mean change in SBP, calculated as the difference between each SBP value and the mean SBP before the limb movement. The horizontal axis indicates the movement series, with '−1' marking the time immediately before the start of the movement and '0' indicating the beginning of the movement. 'Movement' on the *x*-axis refers to leg movement.

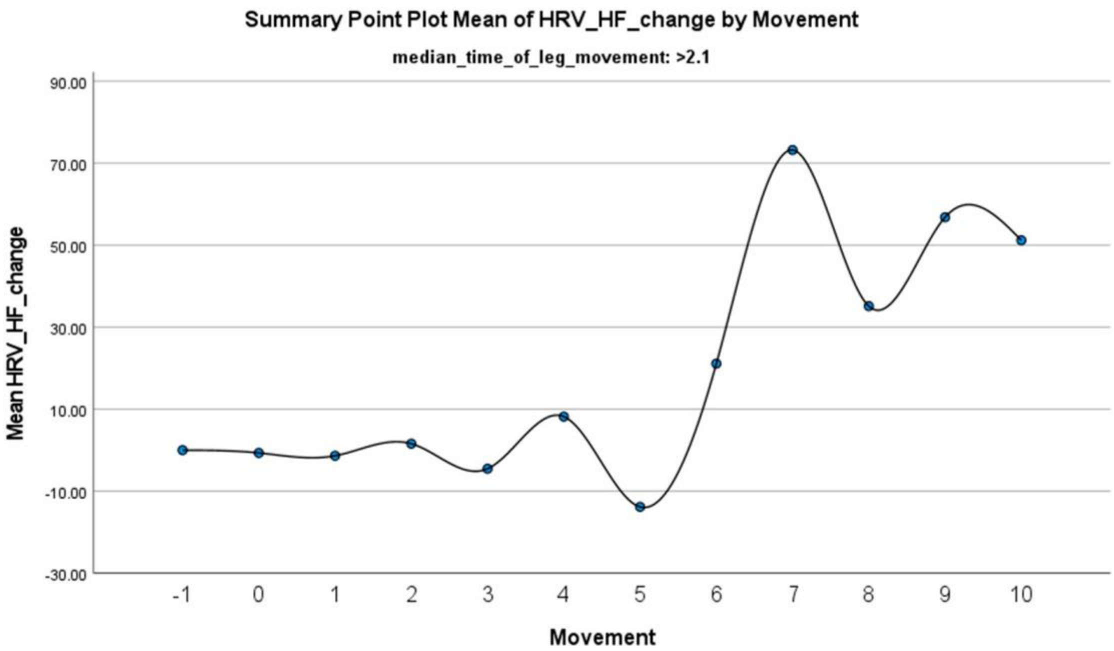

Figure 5. Summary of the mean change in HF-HRV during PLMS with leg movements lasting >2.1 s. The vertical axis represents the mean change in HF-HRV, calculated as the difference between each HRV value and the mean HRV before the limb movement. The horizontal axis indicates the movement series, with '−1' marking the time immediately before the start of the movement and '0' indicating the beginning of the movement. 'Movement' on the *x*-axis refers to leg movement.

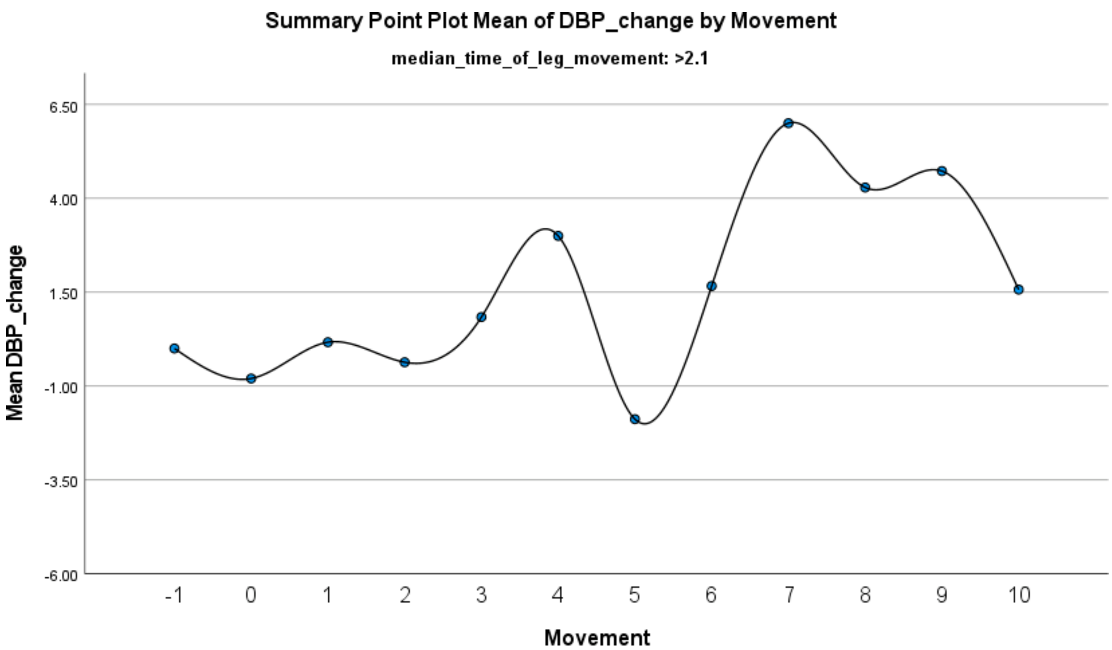

Figure 6. Summary of the mean change in DBP during PLMS with leg movements lasting >2.1 s. The vertical axis represents the mean change in DBP, calculated as the difference between each DBP value and the mean DBP before the limb movement. The horizontal axis indicates the movement series, with '−1' marking the time immediately before the start of the movement and '0' indicating the beginning of the movement. 'Movement' on the *x*-axis refers to leg movement.

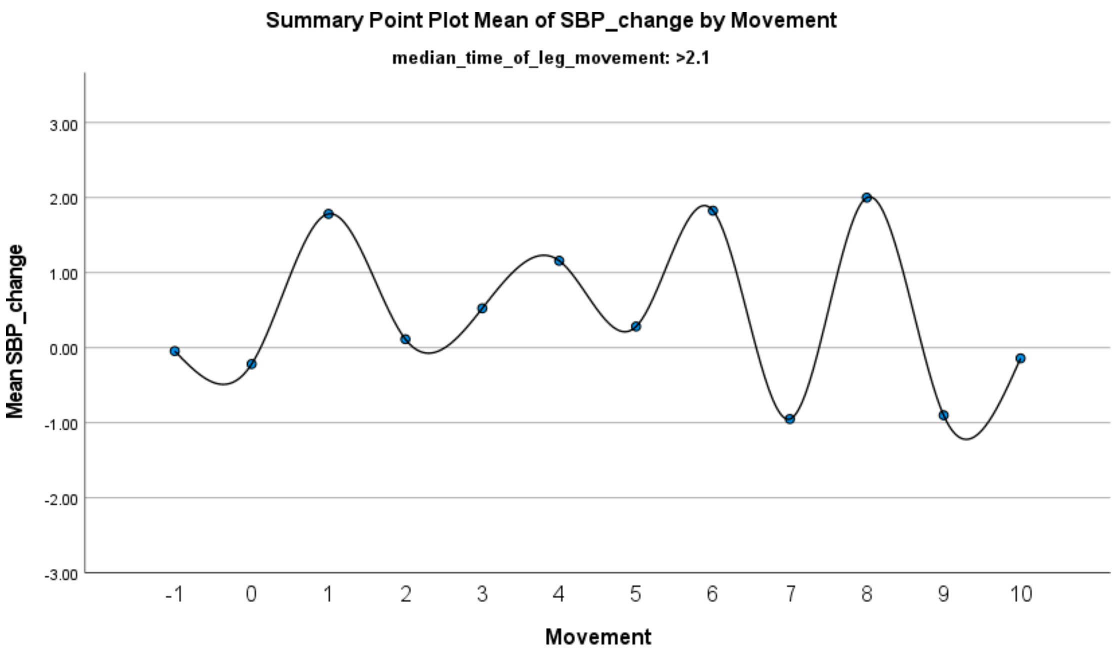

Figure 7. Summary of the mean change in SBP during PLMS with leg movements lasting >2.1 s. The vertical axis represents the mean change in SBP, calculated as the difference between each SBP value and the mean SBP before the limb movement. The horizontal axis indicates the movement series, with '−1' marking the time immediately before the start of the movement and '0' indicating the beginning of the movement. 'Movement' on the x-axis refers to leg movement.

4. Discussion

Our previous study confirmed autonomic co-activation during PLMS; however, the role of PLMS duration in shaping autonomic responses remained unclear. In this study, we examined how the duration of PLMS episodes influences sympathetic and parasympathetic activation. Our findings suggest that longer PLMS events may amplify parasympathetic activity, potentially contributing to autonomic instability and an increased cardiovascular risk.

Scientific evidence indicates that PLMS are associated with significant increases in HR and SBP. Studies have shown that each individual leg movement can lead to an elevation in HR by approximately 7–10 beats per minute [20] and an increase in SBP by approximately 22 mmHg [15]. Given that the interval between limb movements in PLMS ranges from a few to several dozen seconds, these frequent movements can occur hundreds of times per night, potentially affecting overall cardiovascular function [21].

Our study suggests that the duration of PLMS episodes plays a crucial role in autonomic regulation. Prolonged PLMS episodes exceeding 2.1 s elicit stronger parasympathetic responses, providing insight into the relationship between event duration and autonomic regulation.

While previous studies have primarily focused on sympathetic activation during PLMS, our findings highlight that the duration of movements modulates parasympathetic responses. Specifically, longer episodes may elevate parasympathetic tone to a level that exacerbates autonomic conflict, leading to heightened cardiovascular instability. The simultaneous activation of both the sympathetic and parasympathetic branches of the ANS during prolonged PLMS events disrupts autonomic balance, potentially increasing the risk of cardiovascular events, particularly in individuals with pre-existing conditions.

The complexity of autonomic dynamics during prolonged PLMS episodes underscores the critical need to consider movement duration in cardiovascular assessments. Our findings suggest that analysing the duration of PLMS episodes establishes a new standard for understanding their impact on cardiovascular health. This recognition paves the way for further research into the role of movement duration in autonomic co-activation and its potential long-term implications. Acknowledging the importance of timing in autonomic responses, future studies could refine diagnostic and therapeutic strategies for individuals with PLMS, particularly those with cardiovascular vulnerabilities.

Additionally, studies have shown that PLMS are often followed by increases in EEG activity during sleep, suggesting sympathetic activation. PLMS result from nervous system activation associated with microarousals and increases in HR and BP. A high frequency of PLMS throughout the night could be a potential risk factor for nocturnal arrhythmias and hypertension. They may also lead to sleep fragmentation and sleep deprivation, both of which can have negative health consequences [14].

Winkelman et al. discovered that PLMS are associated with cardiac acceleration even in the absence of arousals [22]. These findings highlight the importance of monitoring cardiovascular parameters in individuals with frequent PLMS because repetitive elevations in HR and SBP may have implications for long-term cardiovascular health.

Further supporting our findings, studies reveal that higher low-frequency HRV (LF-HRV)/HF-HRV ratios during sympathetic activity correlate with increased PLMS frequency, shorter intervals between movements, and longer movement durations, which aligns with previous findings in patients with RLS [23]. The LF-HRV/HF-HRV ratio reflects the balance between sympathetic and parasympathetic activity. LF-HRV captures both influences, while HF-HRV represents parasympathetic activity via the vagus nerve. Higher ratios suggest sympathetic dominance, whereas lower ratios indicate parasympathetic dominance. As LF-HRV is influenced by various factors, the ratio requires cautious interpretation within a broader physiological context [24]. In the same study, Guggisberg et al. observed that sympathetic activation begins before movement onset, suggesting it drives PLMS rather than resulting from it. Furthermore, vagal activity following movements was associated with PLMS magnitude, indicating a connection between the networks generating PLMS and vagal centres [24].

The results reported by Winkelman et al. also support these observations, showing that HR begins to accelerate 2–3 cardiac cycles before a PLM, peaks 4–5 cycles after a PLM, and then falls below pre-movement values 8–10 cycles following a PLM [22]. This biphasic HR response underscores the simultaneous engagement of sympathetic and parasympathetic inputs to the heart.

Previous studies have indicated that cardiac sympathetic activity dominates during PLMS; however, our findings suggest that parasympathetic activity also plays a significant role. This suggests that the sympathetic nervous system does not solely regulate HR during PLMS. Instead, both the sympathetic and parasympathetic systems work in tandem, co-activating the heart in response to PLMS.

Our earlier studies using HRV demonstrated the presence of the HF component (which reflects parasympathetic activity) during PLMS, despite no corresponding increase in HR. The simultaneous increase in HF and the lack of HR elevation suggest the co-activation of both sympathetic and parasympathetic cardiac activity.

In homeostatic mechanisms, situations with a dominant branch of the ANS are typical. However, instances of co-activation of both the sympathetic and parasympathetic systems also occur. PLMS most likely represents such a situation. This simultaneous activation, known as autonomic conflict, may be linked to potentially hazardous cardiovascular events.

The clinical significance of autonomic conflict during PLMS is substantial, particularly in individuals with pre-existing cardiovascular conditions or autonomic dysfunction. Similarly to autonomic stress caused by exposure to cold water, concurrent elevations in parasympathetic and sympathetic activity during PLMS episodes might intensify myocardial electrical irregularities, heightening the risk of arrhythmias.

While our study provides valuable insights, several limitations must be acknowledged. The use of brief time windows limited our ability to assess long-term HRV. Another limitation is that although we adhered to AASM guidelines for scoring PSG recordings and incorporated the International Restless Legs Syndrome Study Group (IRLSSG)/World Association of Sleep Medicine (WASM) guidelines for respiratory event-related leg movements to exclude PLMS episodes potentially influenced by respiratory disturbances, this approach may not fully account for subtle respiratory-related influences that could escape standard scoring criteria. Future studies should explore advanced methods to disentangle respiratory and movement-related autonomic effects.

Moreover, although the sample size was small, no PLMS episodes were associated with arousals, which are linked to increased high-frequency EEG activity and sympathetic activation. Consistent HRV changes across all patients and the analysis of 1348 leg movements strengthen the validity of our findings. However, individuals without arousal-associated PLMS episodes may not fully represent the diversity of PLMS phenotypes. Arousal-associated movements often provoke more pronounced autonomic changes, so studies including these episodes could provide a more comprehensive understanding of PLMS-related autonomic dynamics.

Lastly, the absence of longitudinal follow-up precludes an assessment of the long-term cardiovascular implications of PLMS-induced autonomic co-activation. Prospective studies tracking cardiovascular outcomes over time are needed to clarify the clinical significance of our findings and validate the hypothesis that prolonged PLMS episodes increase cardiovascular risk.

Our findings underscore the complexity of autonomic dynamics during prolonged PLMS episodes and suggest that the duration of PLMS is a critical factor influencing autonomic behaviour. The ability to detect and analyse the duration of PLMS episodes establishes a new standard for understanding how PLMS affect cardiovascular health. This paves the way for further research into the role of movement duration in autonomic co-activation and its potential impact on long-term cardiovascular risk. By recognising the importance of timing in autonomic responses, future research may contribute to the development of improved diagnostic and treatment approaches for patients with PLMS, particularly those with pre-existing cardiovascular risks.

5. Clinical Relevance of Autonomic Co-Activation in PLMS

This study highlights two critical findings: the simultaneous activation of the sympathetic and parasympathetic branches of the ANS during PLMS and the significant role of movement duration in modulating these responses. Prolonged PLMS episodes (>2.1 s) amplify autonomic co-activation, potentially disrupting homeostasis and increasing cardiovascular risk, particularly in individuals with pre-existing vulnerabilities.

Notably, parasympathetic activation, indicated by increased HF-HRV components, emerges even without changes in HR or BP. This suggests a nuanced interplay between autonomic branches that is independent of arousal-associated movements, which typically provoke more pronounced sympathetic surges. Such autonomic instability may elevate the risk of arrhythmias and other cardiovascular events.

Additionally, predictive parasympathetic activity—evidenced by elevated HF components preceding PLMS—highlights the importance of timing in ANS responses. These findings align with prior research showing both sympathetic and parasympathetic contributions to autonomic regulation during PLMS.

The method of analysing HRV within short time windows proved effective for capturing dynamic autonomic changes, reinforcing the significance of movement duration in understanding PLMS physiology. Future investigations should prioritise the time-dependent nature of these responses and their implications for cardiovascular health, advancing diagnostic and therapeutic strategies for affected individuals.

Given these findings, evaluating both the frequency and length of PLMS events is critical for identifying individuals prone to autonomic instability. The time-dependent nature of co-activation between the sympathetic and parasympathetic systems may be particularly important in assessing cardiovascular risks. Dysregulation of autonomic HR control in PLMS has been implicated in the development of cardiovascular and cerebrovascular diseases. Understanding these mechanisms and their temporal characteristics could inform clinical strategies aimed at mitigating such risks.

Moreover, the identification of autonomic dysfunction through PLMS could offer valuable insights into the prodromal stages of neurodegenerative diseases, providing an opportunity for early intervention to prevent or slow disease progression. PLMS is frequently observed in conditions such as Parkinson's disease, Alzheimer's disease, and other neurodegenerative disorders, where early detection of ANS dysfunction could be pivotal for improving outcomes.

In summary, this study provides new insights into the autonomic changes associated with PLMS, emphasising the importance of both timing and event duration. While the presence of simultaneous sympathetic and parasympathetic activation during PLMS is increasingly recognised, further research is needed to elucidate the precise mechanisms driving these changes. Future studies should explore the impact of PLMS intensity and timing on cardiovascular outcomes, with the goal of improving patient management and long-term health outcomes. By advancing methodologies for HF-HRV analysis and focusing on time-dependent autonomic dynamics, this research lays the groundwork for a more nuanced understanding of PLMS and its implications for overall health.

Author Contributions: Conceptualization, M.A.M., E.P. and M.P.; methodology, M.A.M. and K.S.M.; software, J.P.; validation, E.P., M.P. and M.W.-W.; formal analysis, M.G. and M.W.-W.; investigation, M.A.M. and K.S.M.; resources, J.P.; data curation, M.A.M.; writing—original draft preparation, M.A.M.; writing—review and editing, all authors; visualisation, M.G.; supervision, M.W.-W.; project administration, J.P.; funding acquisition, M.A.M. All authors have read and agreed to the published version of the manuscript.

Funding: Marta A. Malkiewicz is supported by the Polish National Science Centre (NCN) grant Preludium, number 2019/33/N/NZ5/02815.

Institutional Review Board Statement: The study was approved by the ethics committee of the Independent Bioethics Committee for Scientific Research at the Medical University of Gdansk (NKBBN/388/2022, approval date: 1 July 2022) and all subjects provided written informed consent.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data can be made available on request.

Conflicts of Interest: Markku Partinen reports other income from Bioprojet, other income from Takeda, other income from Idorsia, other income from Umecrine, personal fees and other income from Orion-Pharma, outside the submitted work. The other authors declare no conflicts of interest.

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