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ROZPRAWA DOKTORSKA

OCENA CZYNNOŚCIOWA I STRUKTURALNA NACZYŃ KRWIONOŚNYCH U CHORYCH Z OBTURACYJNYM BEZDECHEM SENNYM

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Lp	Opis bibliograficzny	IF	Punkty
1	**Macek Piotr**, Poręba Rafał, Gać Paweł, Bogunia-Kubik Katarzyna, Dratwa Marta, Więckiewicz Mieszko, Wojakowska Anna, Michałek-Zrąbkowska Monika, Mazur Grzegorz, Martynowicz Helena: Genetic variants of the TERT gene and telomere length in obstructive sleep apnea, Biomedicines, 2022, vol. 10, nr 11, art.2755 [10 s.], DOI:10.3390/biomedicines10112755	4,7*	100
2	**Macek Piotr**, Poręba Małgorzata, Stachurska Aneta, Martynowicz Helena, Mazur Grzegorz, Gać Paweł, Poręba Rafał: Obstructive sleep apnea and sleep structure assessed in polysomnography and right ventricular strain parameters, Brain Sciences, 2022, vol. 12, nr 3, art.331 [11 s.], DOI:10.3390/brainsci12030331	3,3*	100
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WYKAZ SKRÓTÓW

OBS – obturacyjny bezdech senny

RERA – respiratory effort related arousal – wybudzenia związane z nasilonym wysiłkiem oddechowym

AASM– American Academy of Sleep Medicine – Amerykańska Akademii Medycyny Snu

RDI – respiratory distress index – wskaźnik bezdechów, spłyceń oddychania i RERA

AHI – apnea-hypopnea index – wskaźnik bezdechów i spłyceń oddychania

EVA – early vascular aging – przedwczesne starzenie się naczyń

PWV – pulse wave velocity – prędkość fali tętna

CACS – coronary artery calcium score – wskaźnik uwapnienia tętnic wieńcowych

WPROWADZENIE

Obturacyjny bezdech senny (*obstructive sleep apnea,* OBS) jest jednym z najczęstszych zaburzeń układu oddechowego. Częstość jego występowania jest wciąż rosnąca. Dotyczy prawie miliarda osób dorosłych w wieku 30–36 lat na całym świecie [1]. Obturacyjny bezdech senny należy do chorób, które są bardzo słabo rozpoznawane. Szacuje się, iż 82 % mężczyzn i 93 % kobiet w Stanach Zjednoczonych jest niezdiagnozowanych [2]. OBS jest definiowany jako występowanie nawracających epizodów zapadnia się górnych dróg oddechowych w czasie snu, które prowadzą do ograniczenia lub całkowitego zablokowania przepływu powietrza, odpowiednio spłycenia oddechu i bezdechu. Do zdarzeń oddechowych zaliczane się również epizody wybudzeń związanych z nasilonym wysiłkiem oddechowym (*respiratory effort related arousal,* RERA) [3].

Do czynników niemodyfikowalnych zwiększających prawdopodobieństwo wystąpienia obturacyjnego bezdechu sennego zalicza się m.in. płeć męską, wiek, zaburzenia laryngologicznie, takie jak wiotkość podniebienia miękkiego, wady twarzoczaszki, w tym retrognacja i mikrognacja. Z kolei do modyfikowalnych czynników ryzyka obturacyjnego bezdechu sennego zaliczamy: otyłość, powiększenie obwodu szyi, stosowanie leków zwiotczających mięśnie, palenie papierosów, zaburzenia drożności nosa oraz zaburzenia endokrynologicznie, takie jak: niedoczynność tarczycy i zespół policystycznych jajników [4].

Prawidłowy przebieg snu jest niezbędny do prawidłowego funkcjonowania organizmu człowieka. W trakcie bezdechu lub spłycenia oddechu dochodzi do okresowej desaturacji hemoglobiny, która powoduje z kolei hipoksemię. Poza tym w trakcie zdarzeń oddechowych obserwuje się hiperkapnię, zwiększoną aktywność układu współczulnego oraz fragmentację snu. Chorzy z obturacyjnym bezdechem sennym w ciągu dnia zgłaszają nadmierną senność, bóle głowy, zaburzenia pamięci czy suchość w jamie ustnej. W godzinach nocnych dominuje chrapanie, kołatanie serca, nykturia oraz gwałtowne, zauważane najczęściej przez partnerów, występowanie epizodów bezdechu. Obturacyjny bezdech senny jest także niebezpiecznym zaburzeniem, które zwiększa prawdopodobieństwo wystąpienia wypadków w ruchu lądowym [5].

Diagnostyka obturacyjnego bezdechu sennego wykonywana jest w oparciu o wytyczne Amerykańskiej Akademii Medycyny Snu (*American Academy of Sleep Medicine,* AASM).

Polisomnografia jest standardowym badaniem diagnostycznym u dorosłych chorych, u których istnieje podejrzenie obturacyjnego bezdechu sennego na podstawie kompleksowej oceny snu i występowania objawów w ciągu dnia. W oparciu o powyższe kryteria obturacyjny bezdech senny jest definiowany na podstawie wskaźnika zaburzeń oddechowych (*respiratory disturbance index*, RDI), obejmującego liczbę bezdechów, spłyceń oddechów oraz incydentów wybudzeń związanych z wysiłkiem oddechowym w następujący sposób: RDI ≥ 5 zdarzeń/godzinę w połączeniu z objawami charakterystycznymi dla OBS lub RDI ≥ 15 przy braku objawów. Obturacyjny bezdech senny można klasyfikować jako łagodny (RDI ≥ 5 i < 15), umiarkowany (RDI ≥ 15 i < 30) i ciężki (RDI ≥ 30) [6]. W codziennej praktyce klinicznej dopuszcza się wykorzystywanie wskaźnika bezdechów i spłyceń oddechów (apnea-hypopnea index, *AHI*), w którym nie są uwzględnione epizody RERA do diagnostyki OBS [7].

Obturacyjny bezdech senny jest uznanym czynnikiem ryzyka chorób układu krążenia, takich jak: nadciśnienie tętnicze, choroba niedokrwienna serca, zaburzenia rytmu serca, udar mózgu czy cukrzyca typu 2 [8]. Przyjmuje się również, iż OBS znamiennie zwiększa ryzyko rozwoju niewydolności serca [9]. Za główny patomechanizm wpływu obturacyjnego bezdechu sennego na występowanie chorób sercowo-naczyniowych przyjmuje się występowanie hipoksemii, hiperkapnii, zwiększonej aktywność układu współczulnego oraz fragmentację snu [10], [11]. U chorych z obturacyjnym bezdechem sennym wykazywano poza tym zwiększone nasilenie procesu zapalnego, stresu oksydacyjnego, dysfunkcję śródbłonka, zaburzenia procesów hemostazy i aktywacji płytek krwi. Uwzględniając wymienione powyżej mechanizmy wykazano także, iż OBS sprzyja rozwojowi miażdżycy naczyń krwionośnych [12]. Obturacyjny bezdech senny, szczególnie nierozpoznany i nieleczony, jest również czynnikiem wpływającym na wzrost ogólnej śmiertelności [13].

Wraz z wiekiem dochodzi do zmian w ścianie naczyń krwionośnych. Znamienne nasilenie stresu oksydacyjnego oraz procesu zapalnego może prowadzić do wczesnego starzenia się naczyń krwionośnych (*early vascular aging*, EVA). W konsekwencji zwiększona sztywność naczyń krwionośnych, pogrubienie warstwy środkowej tętnic, dysfunkcja śródbłonka naczyniowego i zwiększone centralne ciśnienie tętnicze mogą przyczyniać się do wczesnego powstawania zmian miażdżycowych w naczyniach krwionośnych. W ostatnich latach, oprócz klasycznych czynników ryzyka chorób układu krążenia, negatywnie wpływających na naczynia krwionośne, wskazuje się również na znaczenie długości telomerów w procesie wczesnego starzenia się naczyń krwionośnych [14], [15]. Ocena prędkości fali tętna

(*pulse wave velocity*, PWV) w odniesieniu do wieku i płci jest uznaną metodą wykorzystywaną do oceny sztywności naczyń krwionośnych oraz stwarza możliwość określenia potencjalnego ryzyka wystąpienia chorób układu krążenia oraz ryzyka zgonu z ich powodu [16]. Wskaźnik uwapnienia tętnic wieńcowych (*coronary artery calcium score*, CACS), zgodnie z obowiązującymi zaleceniami towarzystw naukowych, pozwala z dużym prawdopodobieństwem określić ryzyko choroby niedokrwiennej serca [17].

ZAŁOŻENIA I CEL PRACY

Obturacyjny bezdech senny jest niezależnym czynnikiem ryzyka chorób układu krążenia. Dokładna patogeneza oraz wpływ obturacyjnego bezdechu sennego na występowanie chorób sercowo-naczyniowych nie są jednak w pełni poznane. Prawdopodobnie jest to proces złożony i ma charakter wielokierunkowy. W trakcie powtarzających się epizodów bezdechów i/lub spłyceń oddechu dochodzi do zmian ciśnienia w klatce piersiowej, fragmentacji snu, hipoksemii, hiperkapnii oraz nadmiernej aktywności układu współczulnego. W dostępnym piśmiennictwie wykazywano wpływ obturacyjnego bezdechu sennego na zwiększenie procesu zapalnego, nasilenie stresu oksydacyjnego, dysfunkcję śródbłonka naczyniowego oraz powstawanie zmian miażdżycowych w naczyniach krwionośnych. Uwzględniając wieloczynnikowy wpływ obturacyjnego bezdechu sennego na układ krążenia istotną wydaje się być próba poszukiwania w dalszym ciągu nowych mechanizmów oddziaływania obturacyjnego bezdechu sennego na układ sercowo-naczyniowy, a zwłaszcza na naczynia krwionośne w kontekście ich wczesnego starzenia się. Poznanie tych mechanizmów mogłoby bowiem pozwolić na wcześniejszą diagnostykę i leczenie chorób układu krążenia w grupie chorych z zaburzeniami snu.

W ramach rozprawy doktorskiej przeprowadzono badania mające określić zmiany czynnościowe i strukturalne naczyń krwionośnych u chorych z obturacyjnym bezdechem sennym. Z uwagi na częste współistnienie obturacyjnego bezdechu sennego i bruksizmu sennego oceniano zależności pomiędzy wybranymi polimorfizmami genu telomerazy zarówno w grupach chorych z obturacyjnym bezdechem sennym, jak i bruksizmem sennym. Wydaje się to być istotne z tego powodu, iż bruksizm senny jest jednym z najczęściej występujących zaburzeń snu, a jego znaczenie w kontekście patogenezy chorób układu krążenia nie jest dostatecznie poznane i wymaga dalszych badań.

Szczegółowe cele przeprowadzonych badań były następujące:

1. Ocena wpływu obturacyjnego bezdechu sennego na długość telomerów jako potencjalnego wskaźnika wczesnego starzenia się naczyń krwionośnych.
2. Ocena wpływu wybranych polimorfizmów genu telomerazy na ciężkość obturacyjnego bezdechu sennego w kontekście wczesnego starzenia się naczyń krwionośnych.

3. Ocena wpływu wybranych polimorfizmów genu telomerazy na ciężkość bruksizmu sennego jako zaburzenia snu często współwystępującego z obturacyjnym bezdechem sennym oraz określenie jego potencjalnego wpływu na układ krążenia.
4. Ocena wpływu obturacyjnego bezdechu sennego na ryzyko wystąpienia choroby niedokrwiennej serca poprzez określenie wskaźnika uwapnienia tętnic wieńcowych i sztywności naczyń krwionośnych.
5. Ocena wpływu obturacyjnego bezdechu sennego na funkcję prawej komory serca, ocenianej metodą odkształcania podłużnego, która w sposób pośredni może określać zmiany zachodzące w naczyniach krwionośnych krążenia płucnego.

METODYKA

Grupa badana

Do badania zakwalifikowano 366 chorych, średnia wieku 52,69 ± 13,60 lat, z rozpoznanym obturacyjnym bezdechem sennym, hospitalizowanych w Klinice Chorób Wewnętrznych, Zawodowych, Nadciśnienia Tętniczego i Onkologii Klinicznej Uniwersytetu Medycznego we Wrocławiu. Dokładne kryteria włączenia i wyłączenia oraz charakterystyka badanych grup znajdują się w poszczególnych publikacjach, stanowiących cykl rozprawy doktorskiej.

Metodyka badania

Badane osoby z wysokim ryzykiem obturacyjnego bezdechu sennego zostały zakwalifikowane do wykonania pełnego badania polisomnograficznego, nienadzorowanego, typu II, aparatem Nox-A1. Badanie zostało wykonane zgodnie z wytycznymi Amerykańskiej Akademii Medycyny Snu.

Osobom zakwalifikowanym do badania pobrano krew pełną w celu określenia długości telomerów oraz zbadania wybranych polimorfizmów pojedynczego nukleotydu genu telomerazy w kontekście oceny potencjalnego wpływu obturacyjnego bezdechu sennego i bruksizmu sennego na przedwczesne starzenie się naczyń krwionośnych.

Chorzy z niespecyficznymi/nietypowymi bólami w klatce piersiowej, z niskim/umiarkowanym ryzykiem choroby niedokrwiennej serca, zostali zakwalifikowani zgodnie z wytycznymi Europejskiego Towarzystwa Kardiologicznego do wykonania tomografii komputerowej serca, celem oceny prawdopodobieństwa występowania znamiennej choroby niedokrwiennej serca w oparciu o wskaźnik uwapnienia tętnic wieńcowych. Określana także była sztywność naczyń krwionośnych w oparciu o ocenę propagacji fali tętna.

W trakcie hospitalizacji chorzy mieli wykonane również badanie echokardiograficzne wraz z oceną odkształcania podłużnego prawej komory serca, w celu określenia zależności pomiędzy zmianami zachodzącymi w płucnych naczyniach krwionośnych a funkcją prawej komory serca.

Wszystkie osoby zakwalifikowane do badania wyraziły świadomą zgodę na udział w nim. Projekt badawczy był zatwierdzony przez Komisję Bioetyczną Uniwersytetu Medycznego we Wrocławiu (nr KB 525/2020) i został przeprowadzony zgodnie z Deklaracją Helsińską.

Otrzymane wyniki badań poddane były analizie statystycznej, która została szczegółowo opisana w metodyce poszczególnych publikacji włączonych do rozprawy doktorskiej.

WYNIKI

W przeprowadzonych badaniach nie wykazano znamiennej zależności pomiędzy polimorfizmami rs2853669 i rs2736100 genu telomerazy a ciężkością obturacyjnego bezdechu sennego. Nie zaobserwowano także istotnej zależności pomiędzy długością telomerów i ciężkością obturacyjnego bezdechu sennego. Obecność allelu G w locus rs2736100 genu telomerazy w badanej grupie chorych była związana z występowaniem nadciśnienia tętniczego i obserwowana była znamiennie częściej u chorych z nadciśnieniem tętniczym w porównaniu do chorych bez nadciśnienia tętniczego (46,00% *vs.* 24,49%; $p < 0,05$). Częstość występowania nadciśnienia tętniczego była istotnie większa u chorych z allelem C w locus rs2853669 genu telomerazy w porównaniu do chorych bez tego allelu (50,79% *vs.* 30,23%; $p < 0,05$). Ponadto zaobserwowano w badanej grupie chorych znamiennie mniejszą częstość występowania cukrzycy typu 2 u homozygot rs2736100 genu telomerazy niż u heterozygot rs2736100 genu telomerazy (5,63% *vs.* 15,38%; $p < 0,05$).

W przeprowadzonych badaniach nie stwierdzono znamiennego związku pomiędzy polimorfizmem rs2853669 genu telomerazy a nasileniem bruksizmu sennego. Wykazano natomiast, iż w badanej grupie chorzy z allelem T w locus rs2736100 genu telomerazy charakteryzowali się niższą wartością wskaźnika epizodów fazowych bruksizmu (2,06 *vs.* 3,97; $p < 0,05$). W oparciu o analizę krzywej ROC stwierdzono, iż wartość wynosząca 0,8 wskaźnika epizodów fazowych bruksizmu może być wykorzystana do różnicowania obecności allelu T w locus. Czułość i swoistość wynosiły odpowiednio 0,328 i 0,893. Analiza regresji wykazała, iż brak allelu T genu telomerazy rs2736100, płeć męska i nadciśnienie tętnicze są czynnikami ryzyka dla wyższej wartości wskaźnika epizodów fazowych bruksizmu.

Chorzy z rozpoznanym OBS charakteryzowali się istotnie wyższym CACS niż grupa bez OBS (550,25 ± 817,76 *vs.* 92,59 ± 164,56; $p < 0,05$). Wysokie ryzyko istotnej choroby niedokrwiennej serca występowało znamiennie częściej w grupie z rozpoznanym OBS niż w grupie bez OBS (40,3% *vs.* 4,8%; $p < 0,05$). Chorzy z ciężkim i umiarkowanym OBS mieli istotnie wyższy CACS niż chorzy z łagodnym OBS (910,04 ± 746,31 *vs.* 833,35 ± 1129,87 *vs.* 201,66 ± 192,04; $p < 0,05$). Stwierdzono znamienną dodatnią zależność pomiędzy AHI i CACS ($r = 0,34$; $p < 0,05$). Analiza regresji pozwoliła stwierdzić, iż choroba tętnic obwodowych definiowana zwiększoną sztywnością naczyń krwionośnych, była niezależnym czynnikiem ryzyka wyższych wartości AHI. Poza tym analiza regresji wykazała, iż obturacyjny bezdech

senny, płeć męska, starszy wiek, cukrzyca typu 2, choroba tętnic obwodowych i palenie papierosów były niezależnymi czynnikami ryzyka dla wyższych wartości CACS. Wykazano, iż AHI ≥ 14,9 jest wskaźnikiem wysokiego ryzyka istotnej choroby niedokrwiennej serca z czułością i swoistością odpowiednio 62,2% i 80,0%.

W przeprowadzonych badaniach dotyczących związku obturacyjnego bezdechu sennego i funkcji prawej komory serca wykazano znamienne różnice pomiędzy grupami chorych z OBS i bez OBS, biorąc pod uwagę średnie odkształcanie wolnej ściany prawej komory (−32,64 *vs.* −27,17; $p < 0,05$), odkształcanie wolnej ściany prawej komory w segmencie środkowym (−33,71 *vs.* −28,30; $p < 0,05$), średnie odkształcanie przegrody międzykomorowej (−20,24 *vs.* −15,93; $p < 0,05$), średnie odkształcania segmentu podstawnego przegrody międzykomorowej (−20,14 *vs.* −16,06; $p < 0,05$), średnie odkształcanie segmentu środkowego przegrody międzykomorowej (−20,57 *vs.* −16,48; $p < 0,05$), a także segmentu koniuszkowego przegrody międzykomorowej (−20,00 *vs.* −15,24; $p < 0,05$). Nie stwierdzono znamiennej zależności pomiędzy AHI a badanymi parametrami odkształcenia prawej komory. Zaobserwowano istotną dodatnią zależność pomiędzy epizodami bezdechu sennego i średnim odkształceniem wolnej ściany prawej komory ($r = 0,37$; $p < 0,05$), chrapaniem i średnim odkształceniem wolnej ściany w segmencie środkowym ($r = 0,34$; $p < 0,05$), średnim tętnem i odkształceniem wolnej ściany prawej komory w segmencie podstawnym ($r = 0,34$; $p < 0,05$). Poza tym występowała znamienna dodatnia zależność pomiędzy oddechami Cheyne'a-Stokesa i odkształceniem przegrody międzykomorowej w segmencie podstawnym i środkowym (odpowiednio $r = 0,36$; $p < 0,05$ i $r = 0,42$; $p < 0,05$).

OMÓWIENIE

W badaniach dotyczących oceny związku pomiędzy wybranymi polimorfizmami pojedynczego nukleotydu genu telomerazy i obturacyjnym bezdechem sennym nie wykazano znamiennych różnic. Nie wykazano również znamiennej zależności pomiędzy obturacyjnym bezdechem sennym i długością telomerów. W badanej grupie chorych stwierdzono występowanie znamiennej ujemnej zależności pomiędzy długością telomerów i wiekiem badanych chorych. Obecność allelu G w locus rs2736100 genu telomerazy była związana z częstszym występowaniem nadciśnienia tętniczego. Częstość występowania nadciśnienia tętniczego była większa wśród chorych posiadających allel C w locus rs2853669 w porównaniu do chorych bez tego allelu. Poza tym obserwowano niższą częstość występowania cukrzycy typu 2 u chorych z homozygotycznym układem nukleotydów rs2736100 genu telomerazy niż u chorych z heteorozygotycznym układem. Pomimo braku występowania znamiennej zależności pomiędzy obturacyjnym bezdechem sennym i wybranymi polimorfizmami genu telomerazy oraz obturacyjnym bezdechem sennym i długością telomerów, stwierdzono z kolei występowanie zależności pomiędzy wybranymi polimorfizmami genu telomerazy i występowaniem nadciśnienia tętniczego oraz cukrzycy typu 2, czyli chorób często współistniejących z zaburzeniami snu. Może to wskazywać, iż szczególny układ nukleotydów genu telomerazy w badanej grupie chorych z nadciśnieniem tętniczym i cukrzycą typu 2 może predysponować do niekorzystnej przebudowy i wczesnego starzenia się naczyń krwionośnych.

W przeprowadzonych badaniach dotyczących związku pomiędzy wybranymi polimorfizmami pojedynczego nukleotydu genu telomerazy i bruksizmem sennym nie wykazano związku między polimorfizmem rs2853669 genu telomerazy i nasileniem bruksizmu sennego. Stwierdzono jednak, iż chorzy posiadający allel T w locus rs2736100 genu telomerazy prezentowali niższy wskaźnik epizodów fazowych bruksizmu. Analiza regresji wykazała, iż brak allelu T w locus rs2736100 genu telomerazy, płeć męska i nadciśnienie tętnicze są czynnikami ryzyka zwiększenia wartości wskaźnika epizodów fazowych bruksizmu. Uzyskane wyniki badań mogą być podstawą do prowadzenia dalszych badań dotyczących oceny związku pomiędzy bruksizmem sennym, jednym z najczęstszych zaburzeń snu, często współwystępującym z obturacyjnym bezdechem sennym, a chorobami układu krążenia i próby określenia jego potencjalnego wpływu na naczynia krwionośne.

W przeprowadzonych badaniach oceniano występowanie zależności pomiędzy obturacyjnym bezdechem sennym a ryzykiem znamiennej choroby niedokrwiennej serca, określanym w oparciu o wskaźnik uwapnienia tętnic wieńcowych i sztywność naczyń krwionośnych. Wykazano, iż chorzy z obturacyjnym bezdechem sennym mieli znacząco wyższe CACS w porównaniu z chorymi bez OBS, zarówno pod względem całkowitej wartości wskaźnika, jak i wskaźnika dla poszczególnych tętnic wieńcowych. Chorzy z ciężkim OBS i umiarkowanym OBS prezentowali znamiennie wyższe wartości CACS w porównaniu do chorych z łagodnym OBS. Poza tym stwierdzono występowanie znamiennej dodatniej zależności pomiędzy wskaźnikiem bezdechów oraz spłyceń oddechów i wskaźnikiem uwapnienia tętnic wieńcowych. Na podstawie przeprowadzonej analizy regresji wykazano, iż obturacyjny bezdech senny, płeć męska, starszy wiek, cukrzyca typu 2, choroba tętnic obwodowych i palenie papierosów były niezależnymi czynnikami ryzyka wyższych wartości wskaźnika uwapnienia tętnic wieńcowych. AHI ≥ 14,9 przewidywał wysokie ryzyko istotnej choroby niedokrwiennej serca. Przeprowadzone badania pozostają w zgodzie z innymi badaniami wskazującymi, iż obturacyjny bezdech senny może znamienne wpływać na przyspieszenie procesu miażdżycowego tętnic wieńcowych i tym samym zwiększać ryzyko wystąpienia istotnej choroby niedokrwiennej serca [17]. W związku z tym chorzy z rozpoznanym obturacyjnym bezdechem sennym powinni być poddawani rutynowej ocenie w kierunku choroby niedokrwiennej serca.

Na podstawie przeprowadzonych badań dotyczących zależności pomiędzy obturacyjnym bezdechem sennym a funkcją prawej komory serca ocenianą w oparciu o określenie odkształcania podłużnego w badaniu echokardiograficznym wykazano znamienne różnice. Zmiany zachodzące podczas bezdechów i spłyceń oddechu mogą negatywnie wpływać na naczynia krwionośne. Epizody hipoksemii i hiperkapnii mogą być potencjalną przyczyną wzrostu ciśnienia w krążeniu płucnym w mechanizmie skurczu tętnic płucnych. Mechanizm ten zapobiega mieszaniu się krwi z gorzej utlenowanych części płuc [18]. Ponadto obserwowane u chorych z obturacyjnym bezdechem sennym nasilenie procesu zapalnego, stresu oksydacyjnego i dysfunkcja śródbłonka mogą negatywnie wpływać na naczynia krwionośne [19]. Na podstawie przeprowadzonych badań stwierdzono, iż chorzy z obturacyjnym bezdechem sennym mają gorszą funkcję skurczową prawej komory serca, co może pośrednio świadczyć o negatywnym wpływie obturacyjnego bezdechu sennego na naczynia krwionośne krążenia płucnego.

WNIOSKI

1. Nie występują zależności pomiędzy wybranymi polimorfizmami genu telomerazy, długością telomerów i stopniem nasilenia obturacyjnego bezdechu sennego.
2. Występują zależności pomiędzy wybranymi polimorfizmami genu telomerazy a cukrzycą typu 2 i nadciśnieniem tętniczym.
3. Istnieje powiązanie pomiędzy wybranymi polimorfizmami genu telomerazy i stopniem nasilenia bruksizmu sennego.
4. Chorzy z obturacyjnym bezdechem sennym mają zwiększone ryzyko istotnej choroby niedokrwiennej serca i charakteryzują się zwiększoną sztywnością naczyń krwionośnych.
5. Chorzy z obturacyjnym bezdechem sennym charakteryzują się gorszą funkcją prawej komory serca, co może przemawiać za niekorzystnym wpływem zaburzeń oddychania na płucne naczynia krwionośne.

STRESZCZENIE

Obturacyjny bezdech senny jest rosnącym problemem społecznym bieżących lat. Ponad miliard osób na świecie jest dotkniętych tą chorobą. Dla obturacyjnego bezdechu sennego charakterystyczne jest występowanie w trakcie nocy powtarzających się epizodów zapadania górnych dróg oddechowych, prowadzących do bezdechów i/lub spłyceń oddechu. Podstawowe objawy obturacyjnego bezdechu sennego w nocy to chrapanie, epizody bezdechów, wybudzenia, fragmentacja snu czy nykturia. Natomiast w ciągu dnia dominują bóle głowy, senność oraz zmęczenie. Nieleczona choroba wpływa na zwiększenie ryzyka wypadków w ruchu lądowym. Głównymi czynnikami ryzyka obturacyjnego bezdechu sennego są: otyłość, krótka szyja, płeć męska, starszy wiek, palenie papierosów, nadciśnienie tętnicze, nieprawidłowości w budowie twarzoczaszki.

Obturacyjny bezdech senny jest istotnym czynnikiem ryzyka chorób układu krążenia. W przebiegu obturacyjnego bezdechu sennego obserwuje się epizody hipoksemii, hiperkapnii, fragmentację snu, nadmierną aktywność układu współczulnego, nasilenie procesu zapalnego, stresu oksydacyjnego oraz dysfunkcję śródbłonka. Wymienione procesy negatywnie wpływają na układ krążenia, w tym na naczynia krwionośne. U chorych z obturacyjnym bezdechem sennym obserwuje się częstsze występowanie nadciśnienia tętniczego, choroby niedokrwiennej serca, zaburzeń rytmu serca, niewydolności serca czy udarów mózgu. Obturacyjny bezdech senny jest także przyczyną zwiększonej śmiertelności z powodu chorób układu krążenia. W związku z tym poszukiwanie nowych, potencjalnych mechanizmów niekorzystnego wpływu obturacyjnego bezdechu sennego na układ krążenia, a zwłaszcza na naczynia krwionośne jest jak najbardziej uzasadnione.

Celem niniejszej rozprawy doktorskiej była ocena zmian czynnościowych i strukturalnych naczyń krwionośnych u chorych z rozpoznanym obturacyjnym bezdechem sennym.

W przeprowadzonych badaniach wykazano, iż obturacyjny bezdech senny może zwiększać ryzyko wystąpienia istotnej choroby niedokrwiennej serca, wpływać negatywnie na wskaźniki określające sztywność naczyń krwionośnych oraz wywierać niekorzystny wpływ na naczynia krążenia płucnego. Stwierdzono, iż chorzy cierpiący na obturacyjny bezdech senny charakteryzowali się znamiennie mniejszym odkształceniem podłużnym prawej komory serca

niż osoby bez obturacyjnego bezdechu sennego. Nie wykazano istotnej zależności pomiędzy polimorfizmami pojedynczego nukleotydu genu telomerazy, długością telomerów i stopniem nasilenia obturacyjnego bezdechu sennego. Udowodniono jednak, iż obecność poszczególnych nukleotydów w badanych locus genu telomerazy może wpływać na częstość występowania cukrzycy typu 2 i nadciśnienia tętniczego. Stwierdzono, iż brak allelu T w locus rs2736100 genu telomerazy, płeć męska i nadciśnienie tętnicze są czynnikami ryzyka większego nasilenia bruksizmu sennego.

Uzyskane wyniki badań poszerzają wiedzę na temat niekorzystnego wpływu obturacyjnego bezdechu sennego na układ krążenia, zwłaszcza w kontekście zmian czynnościowych i strukturalnych naczyń krwionośnych. Poczynione obserwacje mogą przekładać się w sposób bezpośredni na codzienną praktykę kliniczną. Adekwatna ocena ryzyka sercowo-naczyniowego wśród chorych z obturacyjnym bezdechem sennym, może mieć wpływ na intensywność leczenia oraz wczesne wdrożenie odpowiedniej profilaktyki chorób układu krążenia.

SUMMARY

Obstructive sleep apnoea has been a growing social problem in recent years. More than one billion people worldwide are affected by the disease. A characteristic feature of obstructive sleep apnoea is the occurrence of repeated episodes of upper airway collapse during the night, leading to apnoea and/or shortness of breath. The primary symptoms of obstructive sleep apnoea at night are snoring, apnoeic episodes, awakenings, sleep fragmentation and nycturia. Whereas the main symptoms during the day are headaches, drowsiness and fatigue. If left untreated, the disease increases the risk of traffic accidents. The main risk factors for obstructive sleep apnoea are obesity, short neck, male gender, older age, smoking, hypertension, abnormalities in the craniofacial structure.

Obstructive sleep apnoea is a significant risk factor for cardiovascular disease. In the course of obstructive sleep apnoea, episodes of hypoxaemia, hypercapnia, sleep fragmentation, excessive sympathetic nervous system activity, increased inflammation, oxidative stress and endothelial dysfunction are observed. These processes negatively affect the cardiovascular system, including the blood vessels. Patients with obstructive sleep apnoea have a higher incidence of hypertension, ischaemic heart disease, cardiac arrhythmias, heart failure and strokes. Obstructive sleep apnoea is also a cause of increased mortality from cardiovascular disease. Therefore, the search for new potential mechanisms for the harmful effects of obstructive sleep apnoea on the cardiovascular system and especially on the blood vessels is highly justified.

The aim of the brief doctoral dissertation was to evaluate functional and structural changes in blood vessels in patients diagnosed with obstructive sleep apnoea.

The research has shown that obstructive sleep apnoea can increase the risk of significant ischaemic heart disease, adversely affect vascular stiffness indices and have adverse effects on the pulmonary circulation vessels. It was found that patients with obstructive sleep apnoea had significantly less right ventricular longitudinal strain than those without obstructive sleep apnoea. No significant relationship was found between single nucleotide polymorphisms of the telomerase gene, telomere length and severity of obstructive sleep apnoea. However, it has been shown that the presence of particular nucleotides at the telomerase gene locus studied can influence the incidence of type 2 diabetes and hypertension. The absence of the T allele at the

rs2736100 locus of the telomerase gene, male gender and hypertension were found to be risk factors for greater severity of sleep bruxism.

The results of the study supplement the knowledge of the harmful effects of obstructive sleep apnoea on the cardiovascular system, especially in the context of functional and structural changes in blood vessels. The observations can translate directly into everyday clinical practice. Adequate cardiovascular risk assessment among patients with obstructive sleep apnoea can influence treatment intensity and early implementation of appropriate cardiovascular disease prevention.

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Article

Genetic Variants of the TERT Gene and Telomere Length in Obstructive Sleep Apnea

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Abstract: Introduction: Obstructive sleep apnea (OSA) is a worldwide breathing disorder that has been diagnosed globally in almost 1 billion individuals aged 30–69 years. It is characterized by repeated upper airway collapses during sleep. Telomerase reverse transcriptase (TERT) is involved in the prevention of telomere shortening. This prospective, observational study aimed to investigate the relationship between single nucleotide polymorphisms (SNPs) of TERT and the severity of OSA, taking into account hypertension and diabetes prevalence. Methods: A total of 149 patients with OSA were diagnosed using one-night video-polysomnography based on the American Academy of Sleep Medicine guidelines. The TERT SNPs and telomere length (TL) were detected using real-time quantitative polymerase chain reaction. Results: Statistical analysis showed that there is no relationship between the rs2853669 and rs2736100 polymorphisms of TERT, and the severity of OSA ($p > 0.05$). Moreover, no relationship between TL and the severity of OSA was observed. The G allele in the locus of rs2736100 TERT was associated with hypertension prevalence and was more prevalent in hypertensives patients (46.00% vs. 24.49%, $p = 0.011$). The prevalence of hypertension was higher in patients with the C allele in the locus of rs2853669 than in patients without this allele (50.79% vs. 30.23%, $p = 0.010$). Moreover, a lower prevalence of diabetes was observed in homozygotes of rs2736100 TERT than in heterozygotes (5.63% vs. 15.38%, $p = 0.039$). Conclusion: This study showed no relationship between OSA and TERT SNPs. However, SNPs of the TERT gene (rs2736100 and rs2853669) were found to affect arterial hypertension and diabetes prevalence.

Keywords: TERT; single nucleotide polymorphism; telomerase; obstructive sleep apnea; diabetes; hypertension

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1. Introduction

Obstructive sleep apnea (OSA) is one of the most common respiratory system diseases. Its prevalence is continuously increasing, affecting nearly 1 billion adults aged 30–69 years worldwide [1]. OSA patients encounter repeated upper airway collapses, leading to oxygen desaturation, numerous arousals, and sleep fragmentation, which may influence the aging process [2]. The number of apnea and hypopnea episodes, arousals, and time during the night spent with an oxygen saturation level of less than 90% contribute to the alteration of cellular communication, deregulation of nutrient sensing, mitochondrial dysfunction, and genomic instability in OSA patients [3]. Snoring, apneas, and sleepiness are the main symptoms of OSA although fatigue, shortness of breath and choking, erectile dysfunction,

trouble concentrating, and even insomnia are reported in some patients [4]. OSA leads to cardiovascular conditions such as arterial hypertension, stroke, coronary artery disease, heart failure, and arrhythmias [5]. About 40% of OSA patients also suffer from hypertension. However, about 50% of hypertensive patients [6] and 72–80% of patients with resistant hypertension meet the criteria for OSA (apnea–hypopnea index, AHI > 5) [7]. Endothelium dysfunction, systemic inflammation, and oxidative stress are common in both OSA and hypertension, promoting biological aging as well [8]. Diabetes also commonly co-occurs with OSA [9]. Intermittent hypoxia, which is a central feature of OSA, elicits a proinflammatory response in visceral adipose tissue and contributes to insulin resistance [10]. Therefore, OSA has been shown to cause or worsen metabolic syndrome [11].

Telomerase reverse transcriptase (TERT), encoded by the TERT gene, is a specialized reverse transcriptase composed of a catalytic protein (reverse transcriptase, TERT) and telomerase RNA components (TERC) [12]. It plays a vital role in maintaining telomere and chromosomal integrity and stability [13]. Several studies showed that single nucleotide functional polymorphisms (SNPs) in the TERT gene may affect its expression and telomerase activity [14]. SNPs at loci encoding TERT and TERC have been shown to be correlated with telomere length (TL) and an increased risk of age-related diseases and mortality [15–18]. TERT rs2736100 and TERC rs12696304 are two well-researched SNPs affecting telomerase expression and TL [19–22].

However, data on the relationship between SNPs of TERT and OSA are scarce in the literature. Therefore, this study aimed to evaluate the role of TERT SNPs (rs2736100 and rs2853669) in OSA, taking into account hypertension and diabetes prevalence. The null hypothesis was that the genetic variant of TERT varies between OSA patients and healthy controls, as well as between hypertensive and normotensive patients and between diabetic and nondiabetic patients.

2. Materials and Methods

2.1. The Study Design

This prospective, observational study was carried out on patients admitted to the Department and Clinic of Internal, Occupational Diseases, Hypertension, and Clinical Oncology of Wroclaw Medical University. One-night video-polysomnography was conducted in the Sleep Laboratory of Wroclaw Medical University using Nox-A1 (Nox Medical, Reykjavik, Iceland).

A total of 149 patients were enrolled in this study (44.67% male and 55.33% female). Average age and body mass index (BMI) was 49.00 ± 15.07 and 28.96 ± 5.05, respectively. Overweight (BMI > 25), diabetes mellitus, arterial hypertension, and ischemic heart disease were diagnosed in 46.30%, 11.40%, 39.59%, and 5.37% of individuals, respectively.

The group size was determined using a sample size calculator. The selection conditions were as follows: population size 3 million, fraction size 0.1, maximum error 5%, significance level 0.05. The required minimum size of the study group was 139. During the analyzed period, 149 patients at Sleep Lab were examined, hence the final size of the study group.

Patients who met the following inclusion criteria were included in this study: willingness to participate, clinically suspected OSA, and age > 18 years old. The exclusion criteria were as follows: severe mental disorders, which prevent them from undergoing polysomnography, intake of drugs that can affect the breathing and/or neuromuscular activity, active malignancy, respiratory and/or cardiac insufficiency, and active inflammation.

All participants provided informed consent to participate in the study, and the study was approved by the Ethics Committee of Wroclaw Medical University (ID KB 525/2020) and conducted following the Declaration of Helsinki.

Diagnosis of OSA was made based on the American Academy of Sleep Medicine (AASM) standards. All participants underwent one-night polysomnography. The following parameters were recorded: sleep and respiratory data such as sleep latency, wake after sleep onset, rapid eye movement (REM) latency, sleep efficiency, total sleep time, and the ratio of N1 (sleep stage 1), N2 (sleep stage 2), N3 (sleep stage 3), and REM (REM sleep stage), along

with the video and audio recording of the sleep episode. Respiratory events were recorded using a nasal pressure transducer, and oxygen saturation was measured using a finger pulse oximeter. Following the one-night polysomnography, a certified polysomnographist assessed automatic 30-s epochs of polysomnograms, and the epochs were classified based on the standard criteria for sleep by the AASM 2013 Task Force. Respiratory events were documented as follows: the absence of airflow (>90%) for ≥10 s was scored as an apneic event, whereas a reduction in the amplitude of breathing by ≥30% for ≥10 s with a ≥3% decline in the blood oxygen saturation level or arousal was scored as a hypopnea. The respiratory effort was assessed using respiratory inductance plethysmography belts around the thorax and abdomen. A single modified electrocardiogram lead II was used to assess the ECG. On the day after polysomnography, blood samples of the patients were collected at 7.00 a.m. by venipuncture.

Arterial hypertension, ischemic heart disease, and diabetes mellitus were recorded based on medical history. All patients were weighed and measured on admission to the ward.

2.2. DNA Extraction

Genomic DNA was isolated from 200 µL of peripheral blood taken on EDTA using the NucleoSpin Blood (MACHEREY-NAGEL GmbH & Co. KG, Dueren, Germany) based on the manufacturer's instructions. DNA concentration and purity were quantified using a DeNovix (DeNovix Inc., Wilmington, DE, USA). The isolated DNA was subjected to TERT genotyping and the evaluation of TL.

2.3. TL Quantification

The average TL was measured in the DNA samples of 149 patients. The DNA samples were diluted with nuclease-free water to a concentration of 5 ng/µL, and the TL was measured using a real-time quantitative polymerase chain reaction (qPCR) on a LightCycler480 II Real-Time PCR system (Roche Diagnostics International, Rotkreuz, Switzerland) using qPCR assay kits (ScienCell's Absolute Human Telomere Length Quantification qPCR Assay Kit, Carlsbad, CA, USA), according to the manufacturer's instructions. Two consecutive reactions were performed for each of the DNA samples: the first for amplification of the single-copy reference (SCR) gene and the second for the telomeric sequence. The SCR primer set is used to recognize and amplify the 100-bp region on human chromosome 17 and serves as a reference for data normalization. The qPCR conditions were as follows: 95 °C for 10 min, followed by 32 cycles of 95 °C for 20 s, 52 °C for 20 s, and 72 °C for 45 s. Data were analyzed according to the manufacturer's instructions. All reactions were run in duplicate.

2.4. Genotyping of TERT Gene Polymorphisms

The SNPs within the TERT gene were chosen based on results from the SNP Function Prediction tool of the National Institute of Environmental Health Sciences (NCBI Database) website and other auxiliary databases (https://snpinfo.niehs.nih.gov/snpinfo/snpfunc.html; https://www.ncbi.nlm.nih.gov/snp/; https://www.ensembl.org/index.html). The following criteria were used: change in RNA and/or amino acid chain, potential splicing site and/or miRNA binding site, and minor allele frequency in Caucasians above 10%.

Based on the above criteria, two SNPs were selected for the study: TERT rs2736100 (G > T), located in intron 2, and TERT rs2853669 (T > C), located at −245 bp (Ets2 binding site) in the promoter region. These two SNPs were determined using LightSNiP typing assays (TIB MOLBIOL, Berlin, Germany). Both assays were based on qPCR. Amplifications were performed on a LightCycler480 II Real-Time PCR system (Roche Diagnostics International AG, Rotkreuz, Switzerland) according to the manufacturer's instructions. The PCR conditions were as follows: 95 °C for 10 min, followed by 45 cycles of 95 °C for 10 s, 60 °C for 10 s, and 72 °C for 15 s. The PCR was followed by one cycle of 95 °C for 30 s, 40 °C for 2 min, and gradual melting from 75 °C to 40 °C.

The two TERT polymorphic variants were detected in patients and controls using LightSNiP typing assays (TIB MOLBIOL, Berlin, Germany) by real-time PCR amplifications

with melting curve analysis. The reactions were performed on a LightCycler 480 II Real-Time PCR system (Roche Diagnostics International, Rotkreuz, Switzerland) following the manufacturer's instructions.

2.5. Statistical Analysis

Statistical analysis was carried out using the statistical package "Dell Statistica 13.1" (Dell Inc., Round Rock, TX, USA). The arithmetic means and SDs of the estimated parameters were calculated for the quantitative variables. The distribution of the variables was evaluated using Lilliefors and Shapiro–Wilk W tests. For independent quantitative variables with normal and nonnormal distribution, Student's t-test and Mann–Whitney U test were used, respectively. Based on these results, qualitative variables were expressed as percentages. The results at $p < 0.05$ were considered statistically significant.

3. Results

The participants were classified into two groups: the study group (patients with OSA) and the control group (patients without OSA). OSA was diagnosed in 100 patients (67.11%). Mild ($5 \leq$ AHI < 15), moderate ($15 \leq$ AHI < 30), and severe OSA (AHI ≥ 30) were diagnosed in 35 (23.48%), 29 (19.46%), and 36 (24.16%) patients, respectively. In 49 (32.89%) participants, OSA was excluded (AHI < 5). The average TL was 2.98 $\pm$ 1.07 kB. All parameters observed using polysomnography are presented in Table 1.

Table 1. Polysomnographic data of the study sample and telomere length.

Parameter	Mean	Minimum	Maximum	SD
AHI (n/h)	18.50	0.2	100	20.54
ODI (n/h)	17.56	0.1	88.40	19.28
SL (min)	21.86	1	112.60	20.23
WASO (min)	52.29	1.00	195.50	44.75
SE (%)	82.69	52.40	98.30	10.28
NREM 1 (%of TST)	4.75	0.1	36.10	4.79
NREM 2 (% of TST)	46.73	4.30	78.70	11.43
NREM 3 (% of TST)	26.00	2.60	54.90	10.82
REM (% of TST)	22.23	4.10	41.30	7.57
MEAN SpO2 (%)	93.08	83.30	97.30	2.43

SD—standard deviation; AHI—apnea–hypopnea index; ODI—oxygen desaturation index; SL—sleep latency; WASO—wake after sleep onset; SE—sleep efficiency; NREM– sleep stage 1; NREM2—sleep stage 2; NREM3—sleep stage 3; REM—rapid eye movement sleep stage; MEAN SpO2—mean oxygen saturation.

A negative linear correlation was observed between TL and age ($r = -0.18$, $p = 0.028$); however, no statistically significant correlation was found between TL and polysomnography parameters. Moreover, no statistically significant correlation or differences were found between TL and the diagnosis and severity of OSA.

Then, the relationship between the SNPs of TERT and OSA was evaluated. The prevalence of the TERT SNPs among the study participants is presented in Table 2.

Table 2. The prevalence of TERT SNP in the entire study group.

TERT rs2736100			**TERT rs2853669**		
Genotype	*n*	%	Genotype	*n*	%
TG	78	52.34	TT	86	57.72
TT	49	32.89	TC	52	34.90
GG	22	14.77	CC	11	7.38
Allele			Allele		
T	127	85.23	C	63	42.28
G	100	67.11	T	138	92.62

No statistically significant differences between the TERT SNPs and more frequent OSA diagnoses were observed among the study participants. The prevalence of the TERT SNPs with the respect to the AHI value (patients with confirmed vs. excluded OSA) is presented in Table 3. Whether the TERT SNPs affect the severity of OSA was also evaluated. No relationship was observed between the nucleotide system of both polymorphisms and the incidence of mild, moderate, and severe OSA. The effect of TERT SNPs on TL was not found.

Table 3. The prevalence of the TERT SNP's in patients with and without OSA. Statistically significant differences are indicated by boldface ($p < 0.05$).

TERT rs2736100				**TERT rs2853669**			
Genotype	AHI ≥ 5	AHI < 5	Average telomere length [kB]	Genotype	AHI ≥ 5	AHI < 5	Average telomere length [kB]
TG	55 (70.51%)	23 (29.49%)	2.97 ± 1.03	TT	58 (68.24%)	27 (31.76%)	3.01 ± 1.10
TT	28 (58.33%)	20 (41.67%)	2.93 ± 1.14	TC	36 (69.23%)	16 (30.77%)	2.97 ± 1.10
GG	16 (72.73%)	6 (27.27%)	3.08 ± 1.09	CC	5 (45.45%)	6 (54.55%)	2.70 ± 0.68

The relationship between arterial hypertension, diabetes mellitus and ischemic diseases, and TERT SNPs were studied. The information about these disorders was obtained based on medical history. In addition, the mean BMI values in patients with the studied polymorphisms were compared.

First, the patients were compared based on the rs2736100 SNP, in which significant differences between the TERT SNP and arterial hypertension diagnoses were observed. However, no statistical differences between polymorphisms and other diseases were found. All details are presented in Table 4.

Table 4. The prevalence of arterial hypertension in the rs2736100 SNPs of the TERT gene. Statistically significant differences are indicated by boldface ($p < 0.05$).

Allele	**Hypertensives**	**Normotensives**	**Diabetics**	**Non-Diabetics**	**BMI Value**	**Ischemic Disease**	**Non-Ischemic Disease**
TG	**37 (47.44%)**	**41 (52.56%)**	12 (15.38%)	66 (84.62%)	28.69 ± 4.36	6 (7.69%)	72 (92.31%)
TT	**12 (24.49%)**	**37 (75.51%)**	3 (6.12%)	46 (93.88%)	30.47 ± 6.99	2 (4.08%)	47 (95.92%)
GG	**9 (40.91%)**	**13 (59.09%)**	1 (4.55%)	21 (95.45%)	27.38 ± 3.45	0 (0.00%)	22 (100%)

Moreover, the results showed that patients with the G allele more commonly suffer from arterial hypertension than patients without the G allele (Table 5). Other alleles were not found to influence the prevalence of disorders. While analyzing the differences between patients based on homozygotes and heterozygotes of rs2736100, a homozygous nucleotide system was found to decrease the prevalence of arterial hypertension and diabetes mellitus. All details are presented in Table 6.

Table 5. The prevalence of arterial hypertension among patients carrying the G allele in the locus of rs2736100.

	Hypertensives	**Normotensives**	***p* Value**
G allele −	12 (24.49%)	37 (75.51%)	$p = 0.011$
G allele +	46 (46.00%)	54 (54.00%)	

Table 6. The prevalence of the disorders in patients with the rs2736100 SNP of the TERT gene, taking into account the presence of homozygotes. Statistically significant differences are indicated by boldface ($p < 0.05$).

	Hypertensives	**Normotensives**	**Diabetics**	**Non-Diabetics**	**BMI Value**	**Ischemic Disease**	**Non-Ischemic Disease**
Homozygous (+)	**21 (29.58%)**	**50 (70.42%)**	**4 (5.63%)**	**67 (94.37%)**	29.29 ± 6.02	2 (2.82%)	69 (97.18%)
Homozygous (−)	**37 (47.44%)**	**41 (52.56%)**	**12 (15.38%)**	**66 (84.62%)**	28.69 ± 4.37	6 (7.69%)	72 (92.31%)

Then, the prevalence of the studied disorders was compared based on the rs2853669 SNP. Statistically significant differences were observed between the rs2853669 SNP and arterial hypertension alone. No relationship was found between other disorders and the rs2854669 SNP. All details are presented in Table 7.

Table 7. The prevalence of arterial hypertension in the rs2853669 SNPs of the TERT gene. Statistically significant differences are indicated by boldface ($p < 0.05$).

Allele	Hypertensives	Normotensives	Diabetics	Non-Diabetics	BMI Value	Ischemic Disease	Non-Ischemic Disease
TT	**26 (30.23%)**	**60 (69.77%)**	8 (9.30%)	78 (90.70%)	29.40 ± 5.87	3 (3.49%)	83 (96.51%)
TC	**27 (51.92%)**	**25 (48.08%)**	8 (15.38%)	44 (84.62%)	28.47 ± 4.11	5 (9.62%)	47 (90.38%)
CC	**5 (45.45%)**	**6 (54.55%)**	0 (0.00%)	11 (100%)	27.80 ± 2.68	0 (0.00%)	11 (100%)

Patients with the C allele in the rs2853669 SNP were more commonly diagnosed with arterial hypertension than those without it (Table 8). No relationships between other alleles, homozygotes, and the prevalence of the other studied disorders were observed.

Table 8. The prevalence of arterial hypertension among patients with the C allele in the locus of rs 2853669.

	Hypertensives	Normotensives	*p* Value
C allele −	26 (30.23%)	60 (69.77%)	$p = 0.010$
C allele +	32 (50.79%)	31 (49.21%)	

Finally, no relationship was observed between the mean values of BMI and the TERT SNPs.

4. Discussion

Located on chromosome locus 5p15.33, TERT plays a role in the lengthening and preservation of telomeres. In the present study, two well-studied SNPs—rs2853669 in the TERT promoter and rs2736100 located within intron 2 of TERT—were investigated in a group of patients with high OSA risk. OSA is considered an aging disease, especially related to accelerated vascular aging. In the course of OSA, the accumulation of functional and structural changes in vessels, including arterial stiffening, increased carotid intima–media thickness, as well as carotid diameter enlargement, is an important contributor to cardiovascular diseases. The primary mechanism of accelerated vascular aging in OSA is complex and includes intermittent hypoxia, sympathetic activation, and systemic inflammation [23]. Yagihara et al. classified participants in their study into a group of patients treated with CPAP (continuous positive airway pressure) and a control group treated with a nasal dilator and reported that the age of patients with OSA judged by appearance was lower in the group treated with CPAP compared with the control group [24].

Previous studies reported that the TERT variant rs2736100 is associated with TL and multiple disease risks, including colorectal cancer, myeloproliferative neoplasms [21], primary glomerulonephritis/end-stage renal disease [25], decreased idiopathic pulmonary fibrosis, combined pulmonary fibrosis, and emphysema syndrome [26]. The presence of the C allele in the locus of the rs2736100 SNP of the TERT gene is associated with longer telomeres, whereas the presence of the A allele is associated with shorter telomeres. The meta-analysis showed that cancer was positively associated with the C allele and that noncancerous diseases were negatively associated with the C allele [27].

To the best of our knowledge, this is the first study investigating the role of rs2736100 and rs2853669 genetic variants in OSA. Although no relationships were observed between OSA and the TERT SNPs, an association between hypertension and TERT gene polymorphism was observed, as well as an association between diabetes and TERT gene polymorphism. Hypertension is a common age-related disease that increases the risk of cardiovascular diseases, including atherosclerosis, coronary heart disease, stroke, and chronic kidney disease [8]. In patients with essential hypertension, a shorter leukocyte TL

coupled with a lower expression of telomerase genes was reported previously. However, no differences in the genotype of rs2736100 and rs12696304 SNPs were reported between normotensive and hypertensive patients [28]. Feng showed that homozygous GG was associated with atherosclerosis risk [29]. Hypertension and diabetes are risk factors for atherosclerosis development. Thus, the findings of the present study are in agreement with these observations. The results of the present study showed that the G allele of the rs2736100 SNP was associated with hypertension and diabetes prevalence and that it was more prevalent in hypertensive patients; however, no statistical differences were observed in the T allele. In addition, differences were found in the rs2853669 SNP, taking into account the presence of the C allele in its locus. (50.79% vs. 30.23%, $p = 0.010$).

OSA is commonly associated with diabetes, with prevalence ranging from 23% to 86% [30]. However, comorbid OSA is observed between 30% [31] and 80% [32] of people with diabetes. Other common comorbidities of diabetes include heart disease, stroke, cancers, dementia, kidney disease, and depression [33]. The aging process in diabetes is associated with alterations in glucose metabolism, including both relative insulin resistance and islet cell dysfunction, thus leading to impaired glucose intolerance and/or postprandial hyperglycemia [34]. A previous study demonstrated that the incidence of type 2 diabetes was increased in carriers of the CC SNP (rs2853669) of the TERT gene [35]. Goswami showed that the TC genotype plays a protective role against the development of type 2 diabetes [36]. The present study showed a decreased prevalence of diabetes in homozygotes of the rs2736100 SNP of the TERT gene (5.63% vs. 94.37%, $p = 0.039$). Thus, the results of the present study are in agreement with those of previous studies.

TL was also evaluated in a patient with OSA. Telomeres are DNA regions of variable length at the end of chromosomes that protect the chromosome and prevent DNA from degradation [37,38]. A part of telomeric DNA is lost during cell division. Therefore, TL is an indicator of biological aging [38,39]. Goglin et al. [40] reported the correlation between mortality rate and TL. Telomeres are often referred to as a "molecular clock of aging" because of their progressive shortening due to aging [41]. TL may be affected by various factors, such as gender [42], psychological stress [43], nutritional factors [44,45], physical activity, and TERT activity. Individuals with a short TL were at an increased risk of cardiovascular diseases, myocardial infarction, heart failure, and stroke [46–50]. Intermittent hypoxia also directly affects TL [51]. The activity of HIF-1 (hypoxia-inducible factor, a heterodimer composed of subunits α and β) is found to be increased in OSA patients [52–55]. The overactivation of HIF-1 leads to overexpression of TERT, an increased level of telomerase, and telomere stabilization [56–58]. The data on the association between TL and OSA are contradictory. Many studies have reported LTL shortening in OSA [59–63]; however, a few studies have reported telomere lengthening [64–66].

In this study, no significant relationship between the TERT gene polymorphisms and average BMI values was observed. Shen et al. [67] reported no effect modifications between the variant alleles and breast cancer risk in subgroups stratified by cigarette smoking, BMI status, and family history.

No correlation between TL and OSA, hypertension, diabetes, or ischemic heart disease was observed in the present study; however, a positive linear correlation between TL and age was found. These observations may be attributable to the bidirectional effect of OSA on telomeres depending on the disease's onset, severity, and duration. Initially, an increase in the HIF-1 telomerase activity protects telomeres, but when the oxidative stress and the inflammatory state reach the threshold level, telomere shortening begins. However, this hypothesis needs further research. The following are the limitations of the present study: the subgroup of diabetes was small, and ambulatory blood pressure monitoring was not conducted; however, this is beyond the scope of the study.

5. Conclusions

1. No association between OSA and TERT SNPs was observed.
2. The SNPs of the TERT gene (rs2736100 and rs2853669) were found to affect arterial hypertension prevalence.
3. The prevalence of type 2 diabetes was decreased in homozygotes of the rs2736100 SNP of the TERT gene.

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Assessment of Telomerase Reverse Transcriptase Single Nucleotide Polymorphism in Sleep Bruxism

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Abstract: Introduction: Sleep bruxism (SB) is a widespread masticatory muscle activity during sleep and affects approximately 13.2% of the general population. Telomerase reverse transcriptase (TERT) plays a role in preventing the shortening of the telomere. This prospective, observational study aimed to investigate the relationship between single nucleotide polymorphism (SNP) of TERT and the severity of SB and to identify the independent risk factors for SB. Methods: A total of 112 patients were diagnosed by performing one-night polysomnography based on the guidelines of the American Academy of Sleep Medicine. TERT SNP was detected by real-time quantitative polymerase chain reaction (qPCR). Results: Statistical analysis showed the lack of relationship between the rs2853669 polymorphism of TERT and severity of SB ($p > 0.05$). However, the study showed that patients with allele T in the 2736100 polymorphism of TERT had a lower score on the phasic bruxism episode index (BEI). Based on the receiver operating characteristic (ROC) curve, the value of phasic BEI was 0.8 for the differential prediction for the presence of allele T in the locus. The sensitivity and specificity were 0.328 and 0.893, respectively. The regression analysis showed that lack of TERT rs2736100 T allele, male gender, and arterial hypertension are the risk factors for the higher value of phasic BEI. Conclusion: The SNP of the TERT gene affects phasic SB intensity. The absence of TERT rs2736100 T allele, male sex, and arterial hypertension are independent risk factors for phasic SB.

Keywords: sleep bruxism; telomerase reverse transcriptase; single nucleotide polymorphism

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1. Introduction

The widely accepted international consensus by Lobbezoo et al. defines sleep bruxism (SB) as a "masticatory muscle activity during sleep that is characterized as rhythmic (phasic) or nonrhythmic (tonic) and is not a movement disorder or a sleep disorder in otherwise healthy individuals" [1]. The prevalence of SB is estimated to be 13.2% in the general population [2]. The pathogenesis of SB is complex and not fully understood. Age, chronic stress, sensitivity to emotional stress [3] or anxiety disorders, insomnia, caffeine consumption, gastroesophageal reflux disease [4], smoking, alcohol intake, and drug use are considered as relevant risk factors for SB [5]. Polymorphism of dopamine and serotonin receptor genes, dysfunction of the autonomic nervous system [6,7], hypertension [8], and airway obstruction [9] are also associated with the pathogenesis of SB [10].

A recent study showed that SB is associated with systemic inflammation [11], which has been shown to affect telomere length [12]. Telomerase reverse transcriptase (TERT)

prevents the shortening of telomeres by synthesizing telomeric repeats onto the end of the 3′ G-rich strand. Telomerase consists of a catalytic subunit TERT, a template ribonucleic acid (RNA), telomerase RNA component (TERC), and several other proteins [13]. Telomeres protect the ends of chromosomes from degradation and end-to-end fusion, thereby providing genomic stability [14,15]. Telomere shortening is associated with loss of proliferative activity and cell aging [16]. When telomeres are damaged or become critically short, DNA damage signaling is triggered, leading to various diseases of aging [17], such as loss of immune function, leukemias, myelodysplastic syndrome, squamous cell skin and gastrointestinal cancers, pulmonary fibrosis, gastrointestinal disorders, liver cirrhosis, and neuropsychiatric conditions [18,19]. Accelerated aging may be usually accompanied by diabetes, hypertension, atherosclerosis, myocardial infarction, graying of hair, and skin pigmentation [20]. Sleep deprivation, delayed circadian rhythm [21], insomnia, and sleep breathing disorder have also been associated with shorter telomeres and alteration in TERT activity [22]. However, there are no data on the relationship between masticatory muscle activity during sleep and TERT gene polymorphism. TERT rs2736100 and TERC rs12696304 are two well-studied single nucleotide polymorphisms (SNPs) that affecting telomere length and/or telomerase expression [23–26]. Therefore, the present study explored genotypes for the SNPs rs2736100 and rs2853669 of the TERT gene in patients with SB. The present study aimed to investigate the relationship between SNPs of the TERT gene and the severity of SB and to identify the independent risk factors for SB. We hypothesize that the polymorphism of the TERT gene may affect the intensity of SB and that it will be a new and unknown link in the pathogenesis of sleep bruxism.

2. Materials and Methods

2.1. Participants

The prospective, observational study was conducted in the Department and Clinic of Internal, Occupational Diseases, Hypertension, and Clinical Oncology at the Wroclaw Medical University in Poland. This study was carried out as a part of a project titled "Assessment of telomerase gene polymorphism in patients with obstructive sleep apnea" conducted in Wroclaw Medical University. One-night video polysomnography (PSG) was performed in the Sleep Laboratory of the Wroclaw Medical University by using Nox-A1 (Nox Medical, Reykjavik, Iceland). A total of 112 patients, 55 men and 57 women, were enrolled in the study. The number of patients participating in the study was estimated on the basis of the sample size calculator assuming the following calculation conditions: population size 3 million, fraction size 0.5, confidence level 95%, maximum error 10%. The number of patients recruited for the study exceeded the minimum value of 96 people. Diabetes, hypertension and ischemic heart disease were diagnosed in 9 (8.03%), 35 (31.25%), and 5 (4.46%) participants, respectively. The group characteristic and mean polysomnographic indices are presented in Table 1.

The study was approved by the Ethics Committee of the Wroclaw Medical University (ID KB—525/2020) and was conducted following the Declaration of Helsinki. All the participants provided informed consent to participate in the study. The participants were qualified to enter our study based on the following inclusion criteria: willingness to participate, age > 18 years, and clinically suspected SB and/or obstructive sleep apnea (OSA).The exclusion criteria were as follows: secondary bruxism associated with neurological conditions; intake of drugs that affect neuromuscular functioning, presence of severe mental disorders that cause inability to undergo PSG; active malignancy, respiratory and/or cardiac insufficiency, and active inflammation. The enrolled patients were diagnosed with possible or probable SB according to international concensus by Lobbezoo [1]. There were no patients with definite sleep bruxism diagnosed prior to psg examination.

Table 1. Group characteristics and mean values of polysomnographic indices.

Parameter	Mean	Median	Minimum	Maximum	SD
BMI	28.54	28.00	20.00	54.00	5.44
Age	46.27	45.50	20.00	78.00	15.49
AHI (n/h)	16.48	8.75	0.00	100.10	19.48
SL (min)	22.06	15.40	0.00	112.60	21.04
WASO (min)	48.93	33.80	1.00	195.50	41.35
SE (%)	82.90	85.40	52.40	98.30	10.31
N1 (% of TST)	4.94	3.30	0.10	36.10	5.15
N2 (% of TST)	46.68	48.20	15.20	75.80	10.09
N3 (% of TST)	25.98	25.60	2.60	54.90	10.47
REM (% of TST)	22.42	23.10	4.10	38.40	7.65
Arousals (n/h)	5.80	3.30	0.00	51.00	8.01
Obstructive apneas (n/h)	5.77	0.40	0.00	76.90	13.31
Mixed apneas (n/h)	0.31	0.00	0.00	25.20	2.40
Central apneas (n/h)	0.56	0.10	0.00	15.10	1.79
Cheyne-Stokes breathing (% of TST)	0.56	0.00	0.00	15.80	1.93
ODI (n/h)	16.31	9.30	0.00	83.40	18.77
Mean SpO_2 (%)	93.39	93.75	83.30	97.30	2.42
Minimal SpO_2 (%)	84.22	85.00	54.00	95.00	7.94
Average Desat Drop (% of TST)	4.31	3.65	2.10	19.80	2.23
BEI (n/h)	4.18	2.35	0.00	24.70	4.58
Phasic BEI (n/h)	2.35	0.75	0.00	19.30	3.39
Tonic BEI (n/h)	1.05	0.70	0.00	6.40	1.17
Mixed BEI (n/h)	0.64	0.45	0.00	4.00	0.70

AHI, apnea–hypopnea index; BMI, body mass index; ODI, oxygen desaturation index; TST, total sleep time (min); SL, sleep latency; REML, REM latency; WASO, wake after sleep onset; SE, sleep efficiency; N1, sleep stage 1; N2, sleep stage 2; N3, sleep stage 3; REM, rapid eye movement sleep stage; mean SpO_2, mean oxygen saturation; minimal SpO_2, minimal oxygen saturation; BEI, bruxism episode index; SD, standard deviation.

2.2. PSG

The American Academy of Sleep Medicine (AASM) standards were used to diagnose SB. Electromyographic (EMG) recordings were obtained from the masseter muscle region bilaterally. The EMG phenotypes of SB were qualified as phasic, tonic, or mixed. Audio and video recordings were obtained and assessed. Bruxism episode index (BEI) indicates the total number of SB (phasic, tonic, and mixed) episodes per hour. According to the AASM standards, the peak of the EMG amplitude during a bruxism episode must be at least twice the amplitude of the background EMG. If the interruption between episodes was less than 3 s, such interruptions were considered to be part of the same episode [27]. The phasic episode was scored if it lasted at least 2 s with three or more bursts. The episode was qualified as a tonic episode if it lasted for more than 2 s with sustained bursts; a mixed episode was considered if the episode could not be scored as tonic or phasic. SB is diagnosed if the value of BEI is at least 2. We assessed SB's severity as follows: BEI = 2–4, mild/moderate SB; BEI > 4, severe SB [27]. All patients underwent full-night PSG. Electroencephalogram (EEG) of the patients was recorded using the AASM recommended EEG montages during the PSG. The respiratory effort was assessed based on respiratory inductance plethysmography (RIP) belts circulating the thorax and abdomen. A single modified electrocardiogram Lead II was used to assess ECG. A nasal pressure transducer was used to measure respiratory episodes. Polysomnograms were scored in 30-s epochs. An automatic analysis was conducted, followed by a manual analysis by a certified polysomnographist. Epochs were classified based on the standard criteria for sleep by the AASM 2013 Task Force [28]. The PSG outcomes included the following: sleep latency (SL); wake after sleep onset (WASO); rapid eye movement (REM) latency; total sleep time; sleep efficiency; and the ratio of N1 (sleep stage 1), N2 (sleep stage 2), N3 (sleep stage 3), and REM (REM sleep stage).

Blood samples were collected from the participants by venipuncture at 7.00 AM on the day after PSG.

2.3. DNA Extraction

Genomic DNA was isolated from 200 µL of peripheral blood collected in EDTA tubes using the NucleoSpin Blood (MACHEREY-NAGEL GmbH & Co. KG, Dueren, Germany) according to the manufacturer's instructions. DNA concentration and purity were quantified on a DeNovix spectrophotometer (DeNovix Inc., Wilmington, DE, USA). Isolated DNA was used for TERT genotyping in patients with SB.

2.4. Genotyping of TERT Gene Polymorphisms

The selection of the investigated SNPs in the TERT gene was based on the results from the SNP Function Prediction tool of the National Institute of Environmental Health Sciences (NCBI Database) website and other auxiliary databases (https://snpinfo.niehs.nih.gov/snpinfo/snpfunc.html (last accessed on 1 June 2021); https://www.ncbi.nlm.nih.gov/snp/ (last accessed on 1 June 2021); https://www.ensembl.org/index.html (last accessed on 5 July 2021)). The following criteria were used: minor allele frequency in Caucasians above 10% and change in RNA and/or amino acid chain, potential splicing site, and/or miRNA binding site.

Based on the above criteria, 2 SNPs were selected for the study: TERT rs2736100 (G > T) located in intron 2, and TERT rs2853669 (T > C), located at −245 bp (Ets2 binding site) in the promoter region. Both TERT rs2736100 and rs2853669 SNPs were determined using LightSNiP typing assays (TIB MOLBIOL, Berlin, Germany). Both assays are based on qPCR. Amplifications were performed on a LightCycler 480 II Real-Time PCR system (Roche Diagnostics International AG) according to the manufacturer's protocol. The PCR conditions were as follows: 95 °C for 10 min followed by 45 cycles of 95 °C for 10 s, 60 °C for 10 s, and 72 °C for 15 s. PCR was followed by one cycle of 95 °C for 30 s, 40 °C for 2 min, and gradual melting from 75 °C to 40 °C.

2.5. Statistical Analysis

The statistical package "Dell Statistica 13.1" (Dell Inc., Round Rock, TX, USA) was used to perform statistical analysis. The arithmetic means and SDs of the estimated parameters were calculated for the quantitative variables. The distribution of variables was examined using Lilliefors test and W-Shapiro–Wilk test. For the independent quantitative variables with normal and non-normal distribution, we used Student's *t*-test and Mann–Whitney U test, respectively. The results for qualitative variables were expressed as percentages. McNemar's or Cochran's test was used for statistical analysis of dependent qualitative variables. To determine the relationship between the analyzed variables, a regression analysis was performed. Parameters of the model obtained in the multivariate regression analysis were estimated using the least squares method. Moreover, the test accuracy was assessed based on ROC (receiver operating characteristic) analysis. The results were considered to be statistically significant at 2-sided $p < 0.05$.

3. Results

SB (BEI > 2) was diagnosed in 62 (55.35%) participants. Mild/moderate (2 ≤ BEI < 4) and severe SB (BEI ≥ 4) were confirmed in 22 (19.64%) and 40 (35.71%) subjects, respectively.

Mild (5 ≤ AHI < 15), moderate (15 ≤ AHI < 30), and severe OSA (AHI ≥ 30) were diagnosed in 24 (21.42%), 20 (17.85%), and 24 (21.42%) subjects, respectively. OSA was excluded (AHI < 5) in 44 (39.28%) participants.

The prevalence of TERT SNPs is presented in Table 2.

In our study, we did not find statistically significant differences between patients with SB (BEI > 2) and without SB (BEI < 2) for SNPs in the TERT gene.

Our study indicated significant differences between phasic BEI among patients with rs2736100 TERT polymorphism carrying allele T. Phasic BEI (2.06 vs. 3.97, $p < 0.05$) was higher in patients without allele T. We did not observe similar differences in participants with rs2853669 polymorphism of the TERT gene.

Table 2. Prevalence of TERT SNPs in the entire study group.

TERT rs2736100			TERT rs2853669		
Genotype	*n*	%	Genotype	*n*	%
TG	54	48.65	TT	63	56.76
TT	39	35.14	TC	41	39.94
GG	18	16.21	CC	7	6.3
Allele			Allele		
T	93	83.78	C	48	43.24
G	72	64.86	T	104	93.69

The parameters of BEI and phasic, tonic, and mixed episodes in participants carrying allele T and allele G of rs2736100 TERT polymorphism are shown in Table 3.

Table 3. Polysomnographic parameters of patients carrying allele T and allele G of rs2736100 TERT polymorphism.

SB Parameter	T Allele −	T Allele +	*p*	G Allele −	G Allele +	*p*
BEI (n/h)	6.57 ± 7.2	4.13 ± 6.44	0.15	4.54 ± 8.99	4.52 ± 4.90	0.99
Phasic BEI (n/h)	3.97 ± 5.53	2.06 ± 2.75	**0.02**	2.25 ± 3.33	2.44 ± 3.46	0.78
Tonic BEI (n/h)	1.30 ± 1.64	1.00 ± 1.08	0.33	0.79 ± 0.68	1.19 ± 1.35	**0.08**
Mixed BEI (n/h)	0.87 ± 0.98	0.59 ± 0.63	0.11	0.57 ± 0.54	0.67 ± 0.77	0.48

BEI, bruxism episode index; values are shown as mean ± SD; statistically significant differences ($p < 0.05$) marked as bold.

Because of the significant difference between phasic BEI (2.06 vs. 3.97) in patients for the presence of T allele in the locus of the TERT gene, the receiver operating characteristic (ROC) curve was generated. Based on the ROC curve, the value of PhE/h = 0.8 was determined as the differentiating value for the prediction of the presence of T allele in the studied locus (Figure 1).

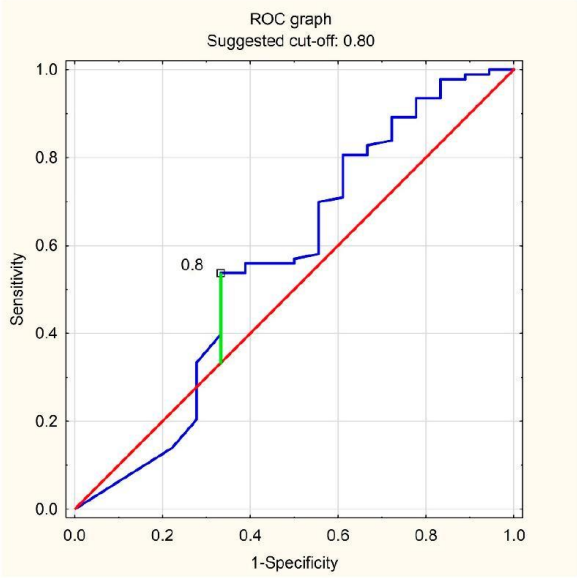

Figure 1. ROC graph.

In the subgroup of patients with T allele in the locus of the TERT gene, more participants showed phasic BEI below 0.8 than those without T allele (Table 4).

Table 4. Frequency of phasic BEI values depends on the presence of T allele in the studied locus.

	T Allele +	T Allele −
Phasic BEI $\leq$ 0.8	50 (67%)	6 (33%)
Phasic BEI $\geq$ 0.8	43 (46%)	12 (67%)

In the subgroup, the value of BEI below 0.8 indicated the presence of T allele in the locus of the TERT gene with sensitivity and specificity of 0.328 and 0.893, respectively, which gives a prediction accuracy of 0.659.

A regression analysis was performed to determine the independent factors associated with phasic BEI value. In the univariate regression analysis, the relationships between potential independent variables, i.e., anthropometric parameters, comorbidities, polysomnographic parameters and SNP polymorphisms of telomerase reverse transcriptase, and the dependent variable, i.e., phasic BEI, were determined. Then, by means of backward multivariate regression analysis, the final estimation of the relationship between the variables significant in the univariate analyzes and the phasic BEI was made. The following statistically significant estimation model was obtained: phasic BEI = 5.35 − 2.53 alleles T + 1.63 male gender + 1.23 AH ± 3.37. On the basis of this model, it can be stated that the absence of T allele in the locus, male gender, and arterial hypertension were independent predictors for the increased phasic BEI value in the studied patients.

4. Discussion

The most important result of the present study is the association of phasic bruxism episodes and TERT gene polymorphism. The TERT gene is located on chromosome 5p15.33 [29] and encodes the catalytic subunit of telomerase [30–33]. We investigated two SNPs: rs2853669 in the TERT promoter and rs2736100 located within intron 2 of TERT [34]. The selection of the investigated SNPs in the TERT gene was based on the results from the SNP Function Prediction tool of the National Institute of Environmental Health Sciences. We considered the following criteria: minor allele frequency in Caucasians above 10% and change in RNA and/or amino acid chain, potential splicing site, and/or miRNA binding site.

TERT rs2736100 C allele has been previously shown to be associated with shorter telomere [35], lung cancer [36,37], and sporadic idiopathic pulmonary fibrosis [38–40]. Multiple oncogenic roles of TERT in cancer development and progression have been established. However, recently, there is evidence on the protective role of TERT in neurons. TERT may activate autophagy for toxic neuronal proteins and ameliorate the effects of amyloid-β, pathological tau, and α-synuclein involved in neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease [41–44]. TERT is expressed in several regions of the brain, such as the olfactory bulb, cortex [45], hippocampus [46], and subventricular zone and in Purkinje neurons of the cerebellum [47]. Interestingly, caffeine, a known risk factor for SB, may promote TERT expression [48]. It is worth noting that overexpression of TERT in experimental models induces repetitive behaviors and other autism spectrum disorder (ASD)-like behavioral symptoms as well as synaptic deficits [49]. A recent study in an animal model showed that TERT overexpression distorts the balance between excitation and inhibition, impairs hippocampal synaptic plasticity, and reduces the expression of learning-related molecules in the hippocampus [50]. Therefore, we propose that the activity of TERT may affect the neurotransmission and, thus, induce sleep rhythmic masseter movement activity. However, this hypothesis requires further investigation.

We also demonstrated that male gender and arterial hypertension are independent risk factors for phasic SB. Male gender and hypertension were previously reported as risk factors for increased BEI [8]. Thus, the present study is in agreement with these results.

Our study did not indicate the association between tonic or mixed bruxism and SNP of the TERT gene. Firstly, there is very modest information regarding EMG subtypes of SB. It is worth noting that phasic bruxism is the most common SB subtype [51,52]. Tonic bruxism episodes are the rarest; however, in healthy subjects, tonic bruxism is more common [53]. Increased severity of phasic bruxism was observed in hypertensives, while the tonic activity was similar in hypertensives and normotensives [54]. Michalek–Zrabkowska et al. recently showed that snoring intensity correlates with phasic bruxism, but not with tonic bruxism [52]. Thus, phasic bruxism activity seems to be not only the most common, but is also associated with systemic diseases. We demonstrated an association between phasic bruxism and SNP of the TERT gene. Therefore, our result suggests that the pathogenesis of phasic episodes may differ from that of the tonic ones. However, further polysomnographic studies are required to confirm this assumption.

The last, but not least, issue to discuss is whether TERT polymorphism affects cell aging in patients with SB. TERT rs2736100 affects telomere length and/or telomerase expression [54]; therefore, this SNP of the TERT gene may influence the process of aging. Moreover, the phenomenon of telomere shortening in short-term sleepers or those with low sleep quality has been reported. Based on data from a Lebanese population, Zgheib et al. assessed whether the relative telomere length could act as a potential biomarker for age-related diseases. A total of 497 subjects participated in their study. Regression analysis showed that people with sleep difficulty have shorter telomeres than those with normal sleep [55]. Tempaku et al. indicated in their study the association between short telomere length with long sleep duration and insomnia [56]. The increased number of arousals and altered sleep architecture in subjects with SB have been reported previously [57]. Thus, we can hypothesize that the aging process may be altered in sleep bruxers. However, further studies on telomere length and telomerase activity in SB are required to verify this hypothesis.

Summarizing, we have confirmed the hypothesis that polymorphism of TERT may affect SB intensity. However, we have observed the effect on the most common phasic bruxism, but not mixed or tonic.

The main limitation of our study is one-night PSG. It is known that the addition of a second night provides more valuable information; however, because of the Polish national health service regulations, we could not conduct two-night PSG.

Moreover, the studied group was heterogeneous; many of the participants suffered from sleep apnea. It has been repeatedly demonstrated that OSA is a risk factor for SB and that these sleep conditions co-occur frequently. However, through regression analysis, we have shown that TERT polymorphism is a risk factor for phasic bruxism independent of the AHI value.

5. Conclusions

(1) The SNP of the TERT gene affects phasic SB intensity.
(2) The absence of TERT rs2736100 T allele, male sex, and arterial hypertension are independent risk factors for phasic SB.
(3) Further studies are needed to assess the role of SNP of the TERT gene and TERT activity in SB pathogenesis.

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Obstructive Sleep Apnea as a Predictor of a Higher Risk of Significant Coronary Artery Disease Assessed Non-Invasively Using the Calcium Score

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Abstract: The aim of this study was to assess the coronary artery calcium score in patients with obstructive sleep apnea (OSA). The study group (group A) consisted of 62 patients with diagnosed obstructive sleep apnea (mean age: 59.12 ± 9.09 years, mean AHI index in polysomnography: 20.44 ± 13.22/h), and 62 people without diagnosed obstructive sleep apnea (mean age 59.50 ± 10.74 years) constituted the control group (group B). The risk of significant coronary artery disease was assessed in all patients, based on the measurement of the coronary artery calcium score (CACS) using computed tomography. The following cut-off points were used to assess the risk of significant coronary artery disease: CACS = 0—no risk, CACS 1–10—minimal risk, CACS 11–100—low risk, CACS 101–400—moderate risk, and CACS > 400—high risk. Group A was characterized by statistically significantly higher CACS than group B (550.25 ± 817.76 vs. 92.59 ± 164.56, $p < 0.05$). No risk of significant coronary artery disease was statistically significantly less frequent in group A than in group B (0.0% vs. 51.6%, $p < 0.05$). A high risk of significant coronary artery disease was statistically significantly more frequent in group A than in group B (40.3% vs. 4.8%, $p < 0.05$). In group A, patients with severe OSA and patients with moderate OSA had statistically significantly higher CACS than patients with mild OSA (910.04 ± 746.31, 833.35 ± 1129.87, 201.66 ± 192.04, $p < 0.05$). A statistically significant positive correlation was found between the AHI and CACS (r = 0.34, $p < 0.05$). The regression analysis showed that OSA, male gender, older age, type 2 diabetes, peripheral arterial disease, and smoking were independent risk factors for higher CACS values. AHI ≥ 14.9 was shown to be a predictor of a high risk of significant coronary artery disease with a sensitivity and specificity of 62.2% and 80.0%, respectively. In summary, obstructive sleep apnea should be considered an independent predictive factor of a high risk of significant coronary artery disease (based on the coronary artery calcium score).

Keywords: coronary artery calcium score; coronary artery disease risk; obstructive sleep apnea

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1. Introduction

Coronary artery disease (CAD) is defined as the presence of atherosclerosis in coronary arteries [1]. The formation of atherosclerotic plaque is a complex process that depends on many factors affecting the intimal layer of the coronary artery wall. Endothelial dysfunction, oxidized serum lipids, inflammation, and thrombosis, with secondary effects of angiogenesis and calcification, are involved in the pathogenesis of plaque formation and progression [2]. Coronary heart disease includes the diagnosis of stable angina, acute coronary syndrome, and silent myocardial ischemia [3]. The main symptom of this disorder is

chest pain or discomfort, which may radiate to the shoulder and arm. Typically, symptoms are exacerbated by physical exertion or emotional stress and decrease during rest [4].

CAD is the most common reason for a single cause of mortality and loss of disability-adjusted life years globally. In 2015, the CAD caused 8.9 million deaths and 164 million DALYs [5].

The main risk factors of CAD are type 2 diabetes mellitus [6], cigarette smoking [7], sedentary lifestyle [8], high cholesterol level [9], arterial hypertension [10], and obstructive sleep apnea [11].

Coronarography is the primary method used to diagnose significant coronary artery stenosis [12]. Its disadvantages are its cost and risk of vessel damage, and the physiological effect of the stenosis on myocardial function cannot be clearly assessed. To assess the physiological significance of coronary artery stenosis, the FFR (fractional flow reserve) is measured during coronary angiography [13]. During the measurement, it is necessary to insert a coronary pressure guidewire and administer a vasodilator. There is a low risk of damage to the coronary artery during the measurement [14]. However, the relevance of computed tomography angiography (CCTA), which may be used to assess significant coronary artery diseases, is growing [15]. CCTA is a non-invasive, fast, reliable, and reproducible method that assesses the coronary artery calcium (CAC) score based on the presence of calcium in the coronary artery [16]. CAC is a mathematically estimated, quantitative, unit-free parameter characterizing the amount of calcium within atherosclerotic plaques in coronary walls [17]. The following cut-off points were used to assess the risk of significant coronary artery disease: CACS = 0—no risk, CACS 1–10—minimal risk, CACS 11–100—low risk, CACS 101–400—moderate risk, and CACS > 400—high risk. According to recent guidelines, CCTA is increasingly recommended for screening in asymptomatic individuals to identify those at high risk of developing coronary artery disease and cardiac events, as well as for assessing coronary artery obstruction in symptomatic individuals [18].

Obstructive sleep apnea (OSA) is one of the most common respiratory disorders that is characterized by recurrent complete (apneas) and partial (hypopneas) upper airway collapse events [19]. The event can cause intermittent hypoxemia, autonomic fluctuation, and sleep fragmentation [20]. Snoring, apnea, and sleepiness are the main symptoms of OSA, although fatigue, breathlessness and choking, erectile dysfunction, concentration problems, and even insomnia have been reported in some patients [21]. Notably, 40–80% of patients with hypertension, heart failure, atrial fibrillation, and ischemic heart disease suffer from OSA [11]. Sympathetic activation, low-grade inflammation, oxidative stress, and endoplasmic reticulum stress are induced by intermittent hypoxia and play a role in cardiometabolic dysfunction [20]. Approximately 34% and 17% of middle-aged men and women suffer from OSA [22]; generally, approximately one billion people meet the criteria for OSA [23].

This study aimed to evaluate the coronary artery calcium score in patients with obstructive sleep apnea, specifically assessing the relationship between CACS and diagnosed OSA and between OSA severity and CACS.

2. Materials and Methods

A total of 124 patients were included in this study. The inclusion criteria included age > 18 years and coronary artery computed tomography indications and willingness to participate. Patients with previously diagnosed myocardial ischemic disease, chronic renal failure, history of stroke, and hyper- and hypothyroidism, and patients with insufficient coronary CT, severe mental disorders that prevent polysomnography, drug intake that can affect the breathing and/or neuromuscular activity, active malignancy, and active inflammation were excluded from the study.

All participants provided informed consent to participate in the study, and the study was approved by the Ethics Committee of Wroclaw Medical University (ID KB 369/2020) and conducted following the Declaration of Helsinki.

The clinical examination methodology included a medical history, measurement of total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, fasting glucose, and coronary computed tomography angiography. Full-night polysomnography was performed in patients with a high clinical probability of OSA. Blood pressure values were measured using the Korothov method. Hypertension and assessment of its degree were performed based on the European Society of Cardiology guidelines. Standard methods determined blood cholesterols, triglycerides, and glucose concentration according to the manufacturer's instructions for the used reagent kits. The clinical characteristics of the studied group of patients are presented in Table 1.

Table 1. Clinical characteristics of the study groups: group A—patients with obstructive sleep apnea; group B—patients without obstructive sleep apnea.

	Group A (n = 62)	**Group B (n = 62)**	***p***
Age (years)	59.12 ± 9.09	59.50 ± 10.74	ns
BMI (kg/m^2)	31.09 ± 3.05	24.21 ± 3.46	0.001
overweight (%)	35.5	27.4	ns
obesity (%)	62.9	6.4	0.001
Gender (%)			
men	40.3	43.5	ns
women	59.7	56.5	
Arterial hypertension (%)	56.4	53.2	ns
sBP (mmHg)	142.66 ± 7.98	144.52 ± 7.50	ns
dBP (mmHg)	88.39 ± 5.56	88.63 ± 5.52	ns
Diabetes mellitus type 2 (%)	21.0	19.3	ns
Glucose (mg/dL)	111.53 ± 36.47	120.71 ± 42.43	ns
Hypercholesterolemia (%)	66.1	56.4	ns
Lower-limb arteriosclerosis (%)	21.0	22.6	ns
Total cholesterol (mg/dL)	198.35 ± 41.06	203.95 ± 44.08	ns
Triglycerides (mg/dL)	190.13 ± 123.32	173.44 ± 83.60	ns
Cigarette smoking (%)	30.6	37.1	ns
Obstructive sleep apnea (%)	100.0	0.0	-
Mild	46.8	0.0	
Moderate	37.1	0.0	
Severe	16.1	0.0	
AHI (/h)	20.44 ± 13.22	-	-

AHI—apnea–hypopnea index; BMI—body mass index; dBP—diastolic blood pressure; sBP—systolic blood pressure; ns—non-significant.

Diagnosis of OSA was made based on the American Academy of Sleep Medicine (AASM) standards. Patients with a clinical probability of OSA were admitted to the Department of Internal Medicine, Occupational Diseases, Hypertension, and Clinical Oncology, where they underwent one-night polysomnography. Afterward, a certified polysomnographist assessed automatic 30 s epochs of polysomnograms, and the epochs were classified based on the standard criteria for sleep using the AASM 2013 Task Force. Respiratory events were documented as follows: no airflow (>90%) for ≥10 s was scored as apnea, while a ≥30% reduction in respiratory amplitude for ≥10 s with a ≥3% drop in blood oxygen saturation or arousal was scored as hypopnea. The total number of apneas and hypopneas per hour, defined as the AHI (apnea–hypopnea index) was used to assess the severity of OSA. Taking into account the value of the AHI, mild ($5 \leq AHI < 15$), moderate ($15 \leq AHI < 30$), and severe OSA ($AHI \geq 30$) was diagnosed [24].

A 128-slice SOMATOM Definition Dual-Source CT scanner (Siemens Healthineers, Erlangen, Germany) was used to perform coronary computed tomography angiography. The

study protocol included the following phases: topogram, a phase without an intravenous contrast agent to estimate the coronary artery calcium index (CACS), bolus tracking, nitroglycerin administration, and a phase with an intravenous contrast agent to assess the heart and coronary arteries properly. Iodine-based non-ionic contrast agent iomeprol (Iomeron 400, Bracco UK Ltd., Wycombe, UK) was administered intravenously using an automatic syringe through the ulnar fossa veins. The CACS was calculated using the syngo.CT CaScoring application (Siemens Healthineers, Erlangen, Germany). The software automatically classified any lesion ≥ 1 mm^2 and density ≥ 130 Hounsfield units (HUs) as calcification. Each lesion classified as calcification was then classified as a lesion in the corresponding coronary arteries, namely the left main (LM), left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA). Based on Agatston's algorithm, the application calculated the CACS for each coronary artery as well as the total CACS. Two experienced radiologists verified the calculated values. The risk of significant coronary artery disease was determined based on the CACS value. The following criteria were used: CACS = 0, practically no risk of significant CAD; CACS 1–10, minimal risk of significant CAD; CACS 11–100, mild risk of significant CAD; CACS 101–400, moderate risk of significant CAD; and CACS ≥ 400, high risk of significant CAD. The result of each patient undergoing a CT scan of the coronary arteries was prepared using the Coronary Artery Calcium Data and Reporting System (CAC-DRS). This system indicates the result of the total calcium score, the calcium score of individual coronary arteries, and the number of vessels involved in the atherosclerotic process. Based on the result, the system provides suggestions for further management for the primary and secondary prevention of cardiovascular incidents [25].

Statistical analysis was performed using Dell Statistica 13 software (Dell Inc., Tulsa, OK, USA). Mean, median, interquartile range, and standard deviation were calculated for quantitative variables. The normal distribution of variables was verified using Lilliefors and Shapiro–Wilk tests. The quantitative independent variables with a normal distribution were analyzed using the *t*-test for independent variables. Variables with a non-normal distribution were analyzed using the Mann–Whitney U test for the quantitative independent variables. A chi-square test with the highest reliability was used for the analysis of independent quantitative variables. Correlation and regression analysis were conducted to determine the relationship between the study variables. Due to the lack of normal distribution of the analyzed variables, non-parametric Spearman correlation coefficients were determined. Backward stepwise multiple regression analysis was performed. In addition, accuracy was tested by proposing cut-off points for the tests estimated from receiver operating characteristic (ROC) curves. The level of statistical significance was set at $p < 0.05$.

3. Results

The patients included in this study were divided into a group of individuals with OSA (group A) and a group without diagnosed OSA (group B). The mean age was 59.12 $\pm$ 9.09 and 59.50 $\pm$ 10.74, respectively. The mean AHI index in the subgroup with OSA was 20.44 $\pm$ 13.22/h. The clinical characteristics are shown in Table 1.

Group A had a significantly higher CACS than group B (550.25 $\pm$ 817.76 vs. 92.59 $\pm$ 164.56, $p < 0.05$). The calcium score of individual coronary arteries (LM, LAD, LCX, and RCA) was significantly higher in the group of patients with OSA than in those without diagnosed OSA. Considering the cardiovascular risk estimated based on the CACS, there were statistically significant differences between groups A and B in the categories of no risk of significant coronary artery disease (0.0% vs. 51.6%) and a high risk of significant coronary artery disease (40.3% vs. 4.8%). Patients without OSA were significantly more likely to have no atherosclerotic lesions in the coronary arteries than those with OSA. All details can be found in Table 2.

Table 2. Coronary artery calcification score parameters in the study groups: group A—patients with obstructive sleep apnea; group B—patients without obstructive sleep apnea.

	Group A (n = 62)	**Group B (n = 62)**	*p*
CA_{CS}	550.25 ± 817.76	92.59 ± 164.56	0.001
LM_{CS}	31.37 ± 85.62	1.06 ± 4.95	0.006
LAD_{CS}	235.25 ± 244.77	57.38 ± 102.22	0.001
LCX_{CS}	84.97 ± 201.75	11.51 ± 30.58	0.005
RCA_{CS}	196.98 ± 512.29	22.61 ± 71.34	0.009
Risk of significant CAD			
practically no risk	0.0	51.6	0.001
minimal	1.6	11.3	ns
mild risk	29.0	8.1	ns
moderate	29.0	24.2	ns
high	40.3	4.8	0.001
CAC-DRS A			
A0	0.0	53.2	0.001
A1	30.6	17.7	ns
A2	24.2	21.0	ns
A3	45.2	8.1	0.001
CAC-DRS N			
N0	0.0	53.2	0.001
N1	21.0	12.9	ns
N2	14.5	8.1	ns
N3	37.1	22.6	ns
N4	27.4	3.2	0.001

CACS—coronary artery calcium score; CAC-DRS A—Agatston scoring in Coronary Artery Calcium Data and Reporting System; CAC-DRS N—number of vessels in Coronary Artery Calcium Data and Reporting System CAD—coronary artery disease; LAD_{CS}—left anterior descending calcium score; LCX_{CS}—left circumflex calcium score; LM_{CS}—left main calcium score; RCA_{CS}—right coronary artery calcium score; ns—non-significant.

In the next step, we checked whether there were statistically significant differences in the OSA group, considering disease severity as a differentiating factor. In group A, patients with severe OSA and moderate OSA had a significantly higher CACS than patients with mild OSA (910.04 ± 746.31, 833.35 ± 1129.87, 201.66 ± 192.04, $p < 0.05$). All the details are shown in Table 3.

Table 3. Coronary artery calcium score assessment in the study subgroups: subgroup A1—patients with mild obstructive sleep apnea; subgroup A2—patients with moderate obstructive sleep apnea; subgroup A3—patients with severe obstructive sleep apnea.

	Subgroup A1 (n = 29)	**Subgroup A2 (n = 23)**	**Subgroup A3 (n = 10)**	*p*
CA_{CS}	201.66 ± 192.04	833.35 ± 1129.87	910.04 ± 746.31	A1-A2: 0.004 A1-A3: 0.014
LM_{CS}	9.58 ± 21.79	49.74 ± 128.84	52.32 ± 68.94	ns
LAD_{CS}	124.58 ± 114.79	308.30 ± 294.83	388.18 ± 271.09	A1-A2: 0.004 A1-A3: 0.002
LCX_{CS}	24.49 ± 38.90	166.20 ± 309.02	73.58 ± 94.57	ns
RCA_{CS}	42.21 ± 81.15	305.38 ± 737.27	396.46 ± 527.36	ns

CA_{CS}—coronary artery calcium score; LAD_{CS}—left anterior descending calcium score; LCX_{CS}—left circumflex calcium score; LM_{CS}—left main calcium score; RCA_{CS}—right coronary artery calcium score; ns—non-significant.

A statistically significant positive correlation was found between the AHI and CACS ($r = 0.34$, $p < 0.05$). Furthermore, a statistically significant correlation was observed between the CACS and age, BMI, and triglyceride levels. All details are presented in Table 4 and Figure 1.

Table 4. Results of correlation analysis in the study group of patients.

	CA_{CS}	
	r	***p***
Age (years)	0.40	0.001
BMI (kg/m^2)	0.31	0.001
sBP (mmhg)	−0.03	ns
dBP (mmhg)	−0.01	ns
Glucose (mg/dL)	0.09	ns
Total cholesterol (mg/dL)	0.08	ns
Triglycerides (mg/dL)	0.23	0.008
AHI (/h)	0.34	0.006

AHI—apnea–hypopnea index; BMI—body mass index; CA_{CS}—coronary artery calcium score; dBP—diastolic blood pressure; r—correlation coefficient; sBP—systolic blood pressure; ns—non-significant.

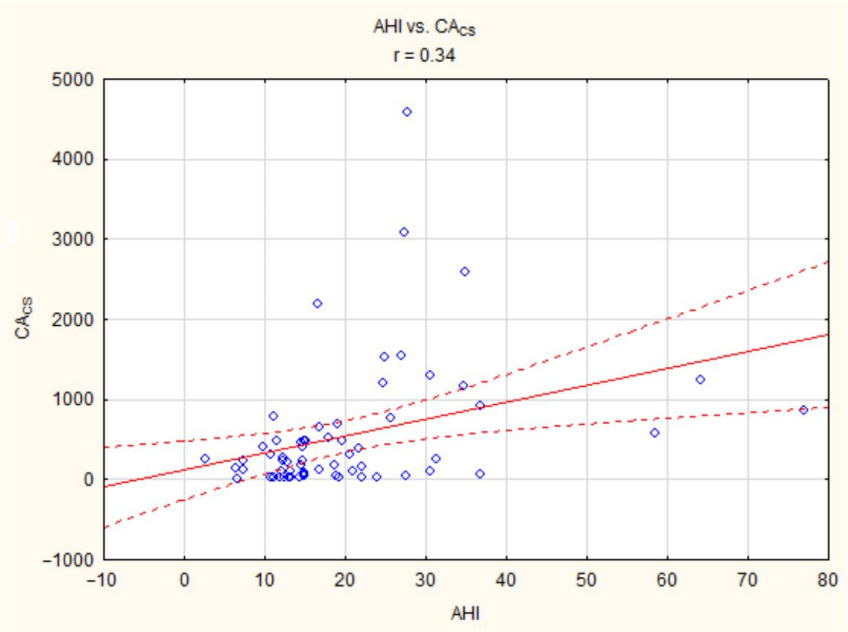

Figure 1. Linear relationship between AHI (/h) and CA_{cs} in patients with obstructive sleep apnea study group.

To verify the independence of the obtained relationships between the basic body parameters (age, gender, and BMI), blood pressure (systolic and diastolic blood pressure), the basic biochemical parameters (total cholesterol concentration, triglycerides concentration, and glucose concentration), history of concomitant cardiovascular diseases (arterial hypertension, type 2 diabetes, hypercholesterolemia, and peripheral artery diseases), smoking, obstructive sleep apnea, and the CACS, backward stepwise multiple regression analysis was performed, obtaining the model presented in Table 5. The regression analysis showed that OSA, male gender, older age, type 2 diabetes, peripheral arterial disease, and smoking were independent risk factors for higher CACS values.

Table 5. Backward stepwise multiple regression model for the dependent variable CACS.

	Model for: CA_{cs} Regression Coefficient	SEM of RC	*p*
Intercept	−159.972	62.463	0.047
Men	180.852	86.480	0.042
Age (years)	10.473	4.941	0.037
Type 2 diabetes mellitus	253.977	111.207	0.024
Peripheral arterial disease	453.292	112.049	0.001
Smoking	337.100	111.359	0.003
Obstructive sleep apnea	241.330	107.825	0.027

CA_{cs}—coronary artery calcium score; SEM of RC—standard error of the mean of the regression coefficient.

ROC analysis identified the optimal AHI values that were predictive factors for a specific risk of significant CAD. Based on the ROC curve analysis, an AHI ≥ 14.9 was detected as a predictor of at least moderate risk of significant coronary artery disease with a sensitivity and specificity of 63.2% and 62.8%, respectively. AHI ≥ 14.9 predicted a high risk of significant coronary artery disease with a sensitivity and specificity of 62.2% and 80.0%, respectively. All details are presented in Table 6 and Figures 2 and 3.

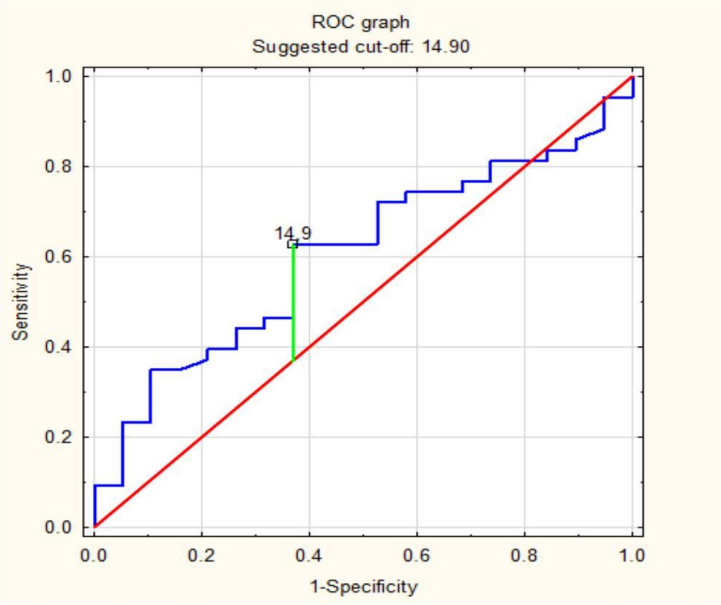

Figure 2. ROC curve of prediction of at least moderate risk of significant coronary artery disease based on AHI (/h) values in a group of patients with obstructive sleep apnea.

Table 6. Results of sensitivity and specificity analysis of AHI as a predictor of the risk of significant coronary artery disease assessed with coronary artery calcium score values in a group of patients with obstructive sleep apnea.

	Prediction of ≥ Moderate Risk of Significant Coronary Artery Disease	Prediction of Significant Risk of Significant Coronary Artery Disease
AHI (/h) cut-off for predicting the risk of significant coronary artery disease	≥14.9	≥14.9

Table 6. *Cont.*

	Prediction of ≥ Moderate Risk of Significant Coronary Artery Disease	Prediction of Significant Risk of Significant Coronary Artery Disease
Sensitivity	0.632	0.622
Specificity	0.628	0.800
Accuracy	0.629	0.694
Positive predictive values	0.429	0.821
Negative predictive values	0.794	0.588
Likelihood ratios (positive)	1.697	3.108
Likelihood ratios (negative)	0.587	0.473

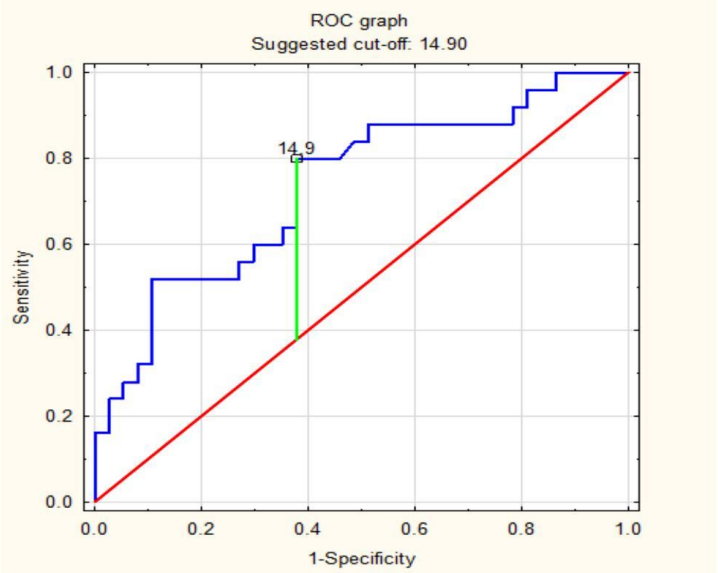

Figure 3. ROC curve of prediction of significant risk of significant coronary artery disease based on AHI (/h) values in a group of patients with obstructive sleep apnea.

4. Discussion

Patients who underwent coronary artery tomography were eligible for the study. Patients with a high probability of OSA underwent polysomnography. The results of this study showed that patients with OSA had significantly higher CACS than patients without OSA, in terms of both their global and individual coronary artery scores. Based on the CACS, the risk of significant CAD was calculated. Statistically significant differences between groups A and B were shown in patients with practically no risk and high risk of CAD. In the next step of the analysis, patients with diagnosed OSA were compared among themselves, considering the severity of the disease. In our study, group A patients with severe OSA and moderate OSA had statistically significantly higher CACS than patients with mild OSA. Moreover, a statistically significant positive correlation was found between the AHI and CACS in our group of patients. The regression analysis showed that OSA, male gender, older age, type 2 diabetes, peripheral arterial disease, and smoking were independent risk factors for higher CACS values. AHI ≥ 14.9 predicted a high risk of significant coronary artery disease.

There are few studies in the available literature on the association of OSA with the CACS. Sea et al., conducted a study involving 461 patients who underwent polysomnog-

raphy and coronary artery tomography. Their analysis, after excluding the confounding factors, showed that lower saturation was independently associated with the CACS. There was no association of other parameters measured during polysomnography with the CACS [26]. In addition, in a subsequent study, the authors decided to assess the progression of subclinical CAD using the CACS. Patients underwent polysomnography and computed tomography of the coronary arteries. A follow-up CT scan was performed at any time. Total sleep time of SaO2 < 90%, the percentage of time of SaO2 < 90%, and the degree of mean oxygen desaturation were significantly correlated with CACS progression, even after excluding the confounding factors. The above study indicates that a lack of OSA treatment is associated with CAD progression [27].

Medeiros et al., evaluated the hypothesis of an association between OSA and the presence of atherosclerotic coronary lesions. They analyzed women aged 45–65 years without known cardiovascular disease. In contrast to our study, cardiovascular risk was not differentiated by the CACS value; CACS > 100 Agatston scores were used as the cut-off point. Based on the regression analysis, moderate or severe OSA was indicated as an independent risk factor for the presence of atherosclerotic lesions in the coronary arteries, which is consistent with the results of our study [28]. In contrast, in another study, Arik et al., showed that the AHI was weakly correlated with the CACS. In univariate analysis, age, AHI, basal oxygen desaturation, and oxygen desaturation index were associated with the CACS. However, in regression analysis, only the AHI and age were independent predictors of atherosclerotic lesions in the coronary arteries, which partly coincides with the results of our study, in which the regression analysis revealed that OSA, sex (male), type 2 diabetes mellitus, age, and smoking were independent predictors of significant CAD [29]. Bikov et al., investigated the association between OSA and CAD, showing that segment involvement and segment stenosis scores were higher in patients with OSA than in the control group. Furthermore, these indices significantly correlated with the severity of OSA. However, no significant correlation was shown between the CACS and OSA [30].

In a meta-analysis, Hao et al., showed an association between OSA and the presence of atherosclerotic lesions in patients without symptoms of heart disease. Furthermore, in a pairwise comparison, they indicated that the CACS might depend on the severity of OSA, which corresponds to our results [31].

CACS is a good method for detecting calcified atherosclerotic plaques and determining the risk of significant CAD. However, non-calcified plaques are identified in approximately 10% of patients with CACS = 0 [32]. A study is available in which the authors investigated the association between coronary non-calcified plaques and the severity of stenosis in patients with OSA. They showed that non-calcified plaques were significantly more common in patients with OSA than in patients without OSA. Patients with OSA also had more severe stenosis and a greater number of involved vessels than those without OSA. [33] Similar observations have also been reported in other studies [34–37]. Criqui et al., showed that higher coronary artery calcium density was associated with a lower cardiovascular disorder risk, affecting plaque stabilization [17].

Obstructive sleep apnea is a common sleep-breathing disorder affecting an increasing number of patients [38]. OSA is associated with a higher incidence of hypertension [39], coronary artery disease [5], stroke and cardiac arrhythmias [40], and type 2 diabetes mellitus [41]. The pathogenesis of the disease includes intermittent hypoxia, oxidative stress, and endothelial dysfunction, which are involved in the progression of the atherosclerotic process [20].

Coronary artery calcium is a highly specific feature of atherosclerosis in the coronary arteries, and the CACS is one of the best-studied and available tests in cardiovascular risk assessment. The development of CAC is understood as an active pathogenic process that can be stopped by controlling cardiovascular risk factors [42]. However, a different prevalence of coronary artery calcium was shown between Caucasians and the other three ethnic groups. In addition, it was revealed that the scores of all four ethnic groups with

similar strength coronary artery calcium can be used to assess the probability of significant CAD [43].

The assessment of coronary artery calcium allows for the assessment of the likelihood of significant CAD and the implementation of primary prevention. CACS = 0 is the best predictive marker of practically no risk of significant CAD. In contrast, patients with CACS > 0, who are more likely to have significant CAD than having practically no risk, will benefit from pharmacotherapy [25]. However, CACS = 0 cannot be used alone to exclude significant CAD in patients with symptoms of CAD. In a study involving 2088 patients with symptoms of coronary artery disease, Kim et al., found CACS = 0 in 1114 patients, 48 of whom were diagnosed with significant CAD in the next step [44]. In another study, Aslan et al., revealed that age >50 years, male sex, and diabetes were independently associated with non-calcified coronary plaques, and in these patient groups, coronary computed tomography angiography is more recommended [45].

In our study, based on the ROC curve analysis, a cut-off point of AHI $\geq$ 14.9 was found to be a possible predictor of significant CAD. Therefore, a global assessment of the coronary arteries based on computed tomography angiography should be considered to exclude coronary artery disease even in asymptomatic patients with OSA.

Obstructive sleep apnea is associated with CAD. It is important to select patients at risk based on the presence of the risk factors of OSA to perform an appropriate diagnosis and, if OSA is confirmed, to implement treatment as soon as possible. In patients with higher AHI values, it is advisable to diagnose CAD by evaluating the CACS, but, as shown in the study cited above, there is a risk that even with CACS = 0, CAD cannot be ruled out unequivocally. Therefore, contrast-enhanced CT angiography should be considered in this case to detect non-calcified atherosclerotic plaques.

The limitations of our study include the relatively small size of the groups and their heterogeneity. It should be noted, however, that the studied groups with and without OSA did not differ in the incidence of cardiovascular risk factors and the incidence of coexisting cardiovascular diseases. In addition, the regression analysis was used in our statistical analysis, which made it possible to assess the impact of the potential modifying factors on the assessed relationship between OSA vs. CACS. This approach was used to demonstrate the independence of this relationship from other co-occurring factors. The main methodology limitation of our study is the lack of polysomnography in patients at low risk of OSA. Unfortunately, even a low risk does not exclude OSA. Another major problem is the non-simultaneous performance of polysomnography and coronary computed tomography. Only the AHI was included in the analysis performed. As a next step, the relationship between hypoxemia, sleep fragmentation, arousal, and CAD severity would have to be investigated. A review of the literature showed that the above parameters have a particular association with oxidative stress, inflammation, and endothelial dysfunction, which may be related to atherosclerosis. Other parameters available in polysomnography were not included, which requires further research. In addition, the relationship between the use of appropriate treatment and the severity of atherosclerotic lesions, as assessed with the CACS, should be investigated in the next step. In our study, we investigated the association of OSA with the CACS, so we did not check the association of OSA with non-calcified atherosclerotic plaques, which also needs to be explored in the future. Other quantitative parameters of cardiac morphology and function, which can be assessed in coronary computed tomography angiography images, should also be verified in terms of their dependence on the occurrence and severity of OSA.

5. Conclusions

1. Obstructive sleep apnea should be considered an independent predictor of a high risk of significant coronary artery disease (based on the coronary artery calcium score);
2. OSA, male gender, older age, type 2 diabetes, peripheral arterial disease, and smoking should be considered as independent risk factors for higher CACS values;

3. AHI $\geq$ 14.9 was detected as a potential predictor of at least a moderate risk of significant coronary artery disease;
4. The CACS may depend on the severity of OSA.

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Obstructive Sleep Apnea and Sleep Structure Assessed in Polysomnography and Right Ventricular Strain Parameters

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Abstract: Our study aimed to assess functional, structural changes of the right ventricular using strain parameters and sleep structure using polysomnography in patients with obstructive sleep apnea (OSA). Our study group consisted of 43 patients, 29 men, 14 women. The mean age was 56.36 ± 14.77. All patients underwent full night polysomnography and transthoracic echocardiography. The right ventricular global longitudinal strain was measured by 2D speckle-tracking echocardiography. The prevalence of OSA (AHI ≥ 5) was 76.7% in the studied group. We observed a significant positive correlation between OAH and average free wall strain (r = 0.37), snore and mid-free wall strain (r = 0.34), average HR, and basal free wall strain (r = 0.34). Moreover, CSB was positively correlated with basal septal strain and mid septal strain (r = 0.36 and 0.42). In summary, among patients with sleep disorders, functional disorders of the right ventricle, assessed using the strain method, are partly observed.

Keywords: obstructive sleep apnea; right ventricle; sleep structure; strain

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1. Introduction

Obstructive sleep apnea (OSA) is a chronic sleep breathing disorder characterized by frequent episodes of collapsing of the upper airway during sleep [1]. It leads to an acute desaturation of arterial blood and arousal due to reopening of the airway and continued breathing. Clinically, the patients who suffer from OSA can complain of daytime sleeping, snoring, impaired concentration, morning headaches, and insomnia [2]. Moreover, OSA in some cases can cause arrythmias. There are few mechanisms including nervous system fluctuations, intermittent hypoxia [3]. Pollicina et al. indicated in their study the relationship between obstructive sleep apnea and neurodegenerative diseases with low cognitive performance and low memory. It has been indicated that CPAP treatment seems to improve cognitive defects [4].

The recurrent hypoxia and hypercapnia increase the risk of cardiovascular and cerebrovascular disorders caused by oxidative stress due to inadequate arterial blood oxygenation and metabolic demand [5].

OSA frequency in the general population affects at least 9–15% of middle-aged adults, and significantly, it is more common among men. Many factors increase OSA's risk and severity, such as age, overweight, alcohol use and self-reported previous cardiovascular disorders [6]. One study indicated a higher risk of OSA in patients with rhinitis as

Pace et al. showed that patients with non-allergic rhinitis with eosinophilia syndrome were at increased risk of OSA with respect to allergic rhinitis and healthy individuals [7].

Based on the American Academy of Sleep Medicine the sleep-related breathing disorders may be divided into obstructive sleep apnoea, central sleep apnoea with or without Cheyne-Strokes breathing pattern and sleep-related hypoventilation. These states can lead to increase pulmonary arterial pressure. The most common association of chronic obstructive pulmonary disease and OSA can cause pulmonary hypertension. The patients with OSA and pulmonary hypertension should be treated using CPAP [8].

Pulmonary hypertension is a hemodynamic and pathophysiological state that can be found among patients with OSA [9]. This disorder occurs among 20–40% of patients [10]. Moreover, 27–30% of individuals without left ventricular dysfunction or hypoxemic lung disease have PH [11]. The people with OSA and PH have a lower quality of life and higher mortality than those without PH [12]. There are two main reasons for PH. Pulmonary hypertension can be caused by dysfunction of the left ventricular. In this case, increasing pressure in the left atrium causes a destructive effect on the pulmonary vessels. Its consequences are remodelling of vessels and the presence of PH [13]. The other reason is the decreasing level of oxygen in the airway, which results in the contraction of the pulmonary vessels. For patients with OSA, episodes of oxygen desaturation during the night are characterized. The cumulative effect of hypoxia can lead to PH [14].

Furthermore, pulmonary hypertension in patients with OSA can lead to the development of right ventricular hypertrophy and dysfunction in more severe cases. Junfang et al. indicated in their studies that right ventricular diastolic dysfunction begins before developing heart failure and pulmonary hypertension in patients with OSA [15].

Echocardiography is a suitable, non-invasive method for structural and functional assessment of the heart. A few studies concerning echocardiographic changes in the right ventricular of patients with OSA were published in recent years [16–18].

Imaging techniques based on strain have been shown increasing clinical utility in assessing the heart chambers, especially for visualization of the right ventricular [19].

Our study aimed to assess functional, structural changes of the right ventricular using strain parameters and sleep structure using polysomnography in patients with obstructive sleep apnea.

2. Materials and Methods

The study was performed in the Sleep Laboratory in the Department of Internal Medicine, Occupational Diseases, Hypertension, and Clinical Oncology at Wroclaw Medical University, Poland.

The patients were admitted to our Clinic due to arterial hypertension or obstructive sleep apnea diagnostics. Our study group consisted of 43 patients, 29 men, 14 women. The mean age was 56.36 $\pm$ 14.77.

Our study included individuals who declared their willingness to participate and fulfilled the following criteria: age above 18 years and clinical suspicion of obstructive sleep apnea or resistant arterial hypertension. Exclusion criteria were as follows: immature patients, inability to undergo polysomnography or echocardiography, intake of medicines affecting neuromuscular functioning or breath function, the presence of severe mental disorders, active malignancy, neurological disorders, and/or neuropathic pain, the coexistence of respiratory insufficiency or active inflammation.

The study was approved by the Ethics Committee of the Wroclaw Medical University in principles of the Declaration of Helsinki. The study was designed and described in accordance with the STROBE guidelines. The participants received all information about the study.

Full night polysomnography using Nox-A1 (Nox Medical, Reykjavik, Iceland) was performed among all patients in the Sleep Laboratory of the Department of Internal Medicine, Occupational Diseases, Hypertension and Clinical Oncology at the Wroclaw Medical University, Poland. Polysomnograms (PSGs) were scored in 30-s epochs and were classified

based on standard criteria for sleep by the American Academy of Sleep Medicine 2013 Task Force. PSG outcomes included as follows: sleep latency, REM (rapid eye movement) latency, total sleep time, sleep efficiency, the ratio of N1 (sleep stage 1), N2 (sleep stage 2), N3 (sleep stage 3), and the stage of REM (rapid eye movement sleep stage) [20].

The day after polysomnography, echocardiography was performed. All patients underwent transthoracic echocardiography conducted by a single cardiologist. The echocardiogram was obtained in all precordial positions using 2-dimensional, M-mode, conventional, and tissue Doppler examination according to the American Echocardiography Association guidelines. Apical 4-chamber left parasternal long-axis (PLAX) and parasternal short-axis (PSAX), left parasternal RV inflow can provide images for the assessment of RV systolic and diastolic function and RV systolic pressure (RVSP). The right ventricular (RV) dimension is measured at end-diastole from a right ventricle–focused apical 4-chamber view. The right atrium dimension was also estimated in apical view. The left PSAX (left parasternal short axis) view demonstrates RVOT (RV outflow tract) at the pulmonic valve level. In contrast, the left PLAX (left parasternal long axis) view allows for the measurement of the proximal portion of the RVOT.

The right ventricular systolic function was calculated using several parameters, such as RIMP (right ventricular index of myocardial performance), TAPSE (tricuspid annular plane systolic excursion), and tissue Doppler-derived tricuspid lateral annular systolic velocity.

Assessment of RV diastolic function was performed using the pulsed Doppler of the tricuspid inflow, tissue Doppler of the lateral tricuspid annulus, and measurements of IVC size and collapsibility.

A strain is defined as a percentage change in myocardial deformation. The right ventricular global longitudinal strain (RVGLS) was measured by 2D speckle-tracking echocardiography, in which deformation of the right ventricular is determined by tracking speckles from frame to frame. It was calculated in the four-chamber view by speckle-tracking analysis. The RVGLS was obtained as a mean value of three segments of the RV free wall (basal, mid, and apical) and the intraventricular septum (basal, mid, and apical).

Statistical analyses were performed using the statistical package "Dell Statistica 13.1" (Dell Inc., Tulsa, OK, USA). The distribution of variables was checked by Lilliefors and W-Shapiro–Wilk tests. The *t*-test was used for the independent quantitative variables with the normal distribution. For variables with a distribution other than normal, the Mann–Whitney U-test was used for quantitative independent variables. For independent qualitative variables, the quadrate-square test of the highest reliability was used. Correlation and regression analysis was performed to determine the relationships between the variables studied. Parameters of the model obtained in the regression analysis were estimated using the least-squares method. The results on the level of $p < 0.05$ were assumed to be statistically significant.

3. Results

The mean age of all participants was 56.36 ± 14.77 years. Women constituted 32.7% (n = 14) of all the participants. The mean BMI was 26.71 ± 25.75 kg/m^2. Diabetes and coronary artery diseases were diagnosed in 11.6% (n = 5) and 9.3% (n = 4) of the study patients, respectively. Hypertension was diagnosed in 60.5% (n = 26) patients. All clinical characteristics in the study group are included in Table 1.

Table 1. Clinical characteristics of the study group.

	X	Me	SD	Min	Max
Age [years]	56.36	59.50	14.77	23.00	81.00
Height [cm]	172.67	173.00	8.96	158.00	188.00
Body mass [kg]	80.27	82.00	19.04	53.00	125.00
Body mass index [kg/m^2]	26.71	25.75	4.90	19.95	36.13

Table 1. *Cont.*

	X	Me	SD	Min	Max
	n			%	
Age < 60	21			48.8	
Age ≥ 60	22			51.2	
Men	29			67.4	
Women	14			32.5	
Normal body mass	26			60.5	
Overweight/obesity	17			39.5	
Arterial hypertension	26			60.5	
Coronary artery diseases	4			9.3	
Type 2 diabetes	5			11.6	

The mean AHI was 27.09 ± 19.76. The prevalence of OSA (AHI ≥ 5) was 76.7% (n = 33) in the studied group. All polysomnography parameters are presented in Table 2.

Table 2. Polysomnography parameters in the study group.

	X	Me	SD	Min	Max
AHI [events/hours]	27.09	23.05	19.76	0.20	71.30
ODI [events/hours]	27.44	26.30	19.74	0.20	73.70
Snore [events/hours]	23.43	11.40	24.93	0.00	81.60
OAH [events/hours]	6.84	1.70	10.30	0.00	38.40
CAH [events/hours]	0.80	0.15	1.66	0.00	9.10
CSB [events/hours]	1.60	0.00	4.09	0.00	19.90
Average SpO2 [%]	91.42	92.20	4.75	65.50	96.10
Minimal SpO2 [%]	80.90	82.00	7.45	64.00	94.00
% SpO2 < 90 [%]	14.75	5.30	21.29	0.00	91.00
Average desaturation [%]	6.48	4.50	11.51	2.00	77.00
Average HR [bpm]	61.63	61.85	8.16	45.80	80.00
Minimal HR [bpm]	49.33	50.00	9.31	24.00	69.00
Maximal HR [bpm]	89.85	89.50	15.65	62.00	141.00
Sleep efficiency [%]	78.16	81.25	14.55	25.30	93.60
TST N1 [% sleep time]	8.52	4.50	8.24	0.60	33.90
TST N2 [% sleep time]	54.94	51.60	27.62	24.40	98.00
TST N3 [% sleep time]	21.74	19.35	13.31	1.20	61.50
TST REM [% sleep time]	25.35	21.40	19.28	2.90	98.50
	n			%	
AHI < 5 (without OSA)	10			23.3	
AHI ≥ 5 (OSA)	33			76.7	
AHI: 5–15 (mild OSA)	4			9.3	
AHI: 15–30 (moderate OSA)	15			34.9	
AHI ≥ 30 (severe OSA)	14			32.5	

AHI, apnea–hypopnea index; ODI, oxygen desaturation index; OAH, obstructive apneas events; CAH, central apneas events; CSB, Cheyne-Stokes breathing; SpO2, saturation; HR, heart rate; TST, total sleep time (min); N1, sleep stage 1; N2, sleep stage 2; N3, sleep stage 3; REM, rapid eye movement sleep stage; OSA, obstructive sleep apnea.

Right ventricular echocardiography and right ventricular strain parameters are included in Tables 3 and 4.

Table 3. Right ventricular echocardiography parameters in the study group.

	X	Me	SD	Min	Max
RAA [cm^2]	25.02	24.75	1.13	24.00	26.70
RA major dimension [mm]	49.40	44.00	17.64	24.00	92.00

Table 3. *Cont.*

	X	Me	SD	Min	Max
RA minor dimension [mm]	47.60	43.00	15.93	23.00	84.00
RVOT p [mm]	31.58	32.00	4.33	18.00	40.00
RVOT m [mm]	32.86	33.50	4.45	22.00	41.00
RVOT d [mm]	27.80	27.00	4.03	21.00	37.00
MPA [mm]	26.11	25.00	1.90	24.00	29.00
RVD [mm]	36.95	37.00	4.26	29.00	51.00
s'RV [cm/s]	13.63	13.00	2.46	10.00	20.00
TAPSE [mm]	24.51	24.00	3.60	19.00	34.00
RV E [cm/s]	60.58	60.50	11.67	39.00	92.00
RV A [cm/s]	51.79	47.50	15.74	28.00	109.00
RV E/A	1.00	0.91	0.30	0.71	1.68
RVEDt [ms]	254.42	242.00	64.75	118.00	405.00
RV E' [cm/s]	10.00	9.00	3.70	4.00	24.00
RV A' [cm/s]	12.90	13.00	3.45	5.00	21.00
TCO [ms]	393.40	377.00	47.05	319.00	494.00
RVET [ms]	300.93	303.00	27.84	247.00	354.00
RIMP	0.71	0.71	0.15	0.60	0.81
PAV [cm/s]	74.35	73.00	9.88	55.00	104.00
PAAT [ms]	140.93	145.00	26.12	88.00	198.00

RAA, right atrial area; RA, right atrial; RVOT p, proximal right ventricular outflow diameter; RVOT m, mid right ventricular outflow diameter; RVOT d, distal right ventricular outflow diameter; MPA, main pulmonary artery diameter; RVD, basal right ventricle diameter; s'RV, peak systolic velocity of tricuspid annulus by pulsed wave Tissue Doppler Imaging; TAPSE, tricuspid annular plane systolic excursion; RV E, early peak transtricuspid diastolic flow; RV A, late peak transtricuspidal diastolic flow; RV E/A, ratio of early to late peak transtricuspid diastolic flow; RVEDt, deceleration time of early peak transtricuspid diastolic flow; RV E', early peak diastolic velocity of tricuspid annulus by pulsed wave Tissue Doppler Imaging; RV A', late peak diastolic velocity of tricuspid annulus by pulsed wave Tissue Doppler Imaging; TCO, tricuspid valve closure opening time; RVET, right ventricular ejection time; RIMP, right ventricular myocardial performance index; PAFV, peak of pulmonary artery flow velocity; PAAT, pulmonary artery acceleration time

Table 4. Right ventricular strain parameters in the study group.

	X	Me	SD	Min	Max
Average free wall strain [%]	−27.83	−27.00	5.81	−42.00	−17.50
Basal free wall strain [%]	−27.19	−26.00	6.10	−45.00	−15.00
Mid free wall strain [%]	−28.88	−28.00	5.67	−44.00	−20.00
Apex free wall strain [%]	−23.67	−23.00	6.56	−36.00	−8.00
Average septal strain [%]	−16.58	−17.00	4.41	−25.00	−6.67
Basal septal strain [%]	−16.47	−17.00	4.73	−26.00	−5.00
Mid septal strain [%]	−17.02	−17.00	4.72	−26.00	−4.00
Apex septal strain [%]	−16.26	−15.00	5.60	−29.00	−4.00

We observed statistically significant differences between patients with OBS (AHI $\geq$ 5) and without OBS considering average free wall strain (−32.64 vs. −27.17 p = 0.023), mild free wall strain (−33.71 vs. −28.30 p = 0.020), average septal strain (−20.24 vs. −15.93 p = 0.015), basal septal strain (−20.14 vs. −16.06 p = 0.030), mid septal strain (−20.57 vs. −16.48 p = 0.030), and apex septal strain (−20 vs. −15.24 p = 0.037), as shown in Table 5.

Table 5. Right ventricular strain parameters in subgroups separated based on OSA (statistically significant differences between the groups were bolded).

	AHI < 5 (without OSA)		**AHI ≥ 5 (OSA)**		***p* Value**
	X	**SD**	**X**	**SD**	
Average free wall strain [%]	**−32.64**	**5.40**	**−27.17**	**5.60**	**0.023**
Basal free wall strain [%]	−31.57	7.46	−26.58	5.67	0.052
Mid free wall strain [%]	**−33.71**	**3.50**	**−28.30**	**5.65**	**0.020**

Table 5. *Cont.*

	AHI < 5 (without OSA)		AHI ≥ 5 (OSA)		*p* Value
	X	SD	X	SD	
Apex free wall strain [%]	−26.71	8.73	−23.03	6.23	0.194
Average septal strain [%]	**−20.24**	**3.25**	**−15.93**	**4.21**	**0.015**
Basal septal strain [%]	**−20.14**	**3.02**	**−16.06**	**4.55**	**0.030**
Mid septal strain [%]	**−20.57**	**2.64**	**−16.48**	**4.74**	**0.034**
Apex septal strain [%]	**−20.00**	**5.42**	**−15.24**	**5.26**	**0.037**

No statistically significant correlation was found between AHI and all right ventricular strain parameters. We observed a significant positive correlation between OAH and average free wall strain (r = 0.37), snore and mid-free wall strain (r = 0.34), average HR, and basal free wall strain (r = 0.34). Moreover, CSB was positively correlated with basal septal strain and mid septal strain, r = 0.36 and 0.42, respectively. The correlation between polysomnography and right ventricular parameters are included in Table 6.

Table 6. Correlations between polysomnography parameters and right ventricular strain parameters in whole study group (the statistically significant correlation coefficients were bolded).

	Average Free Wall Strain	Basal Free Wall Strain	Mid Free Wall Strain	Apex Free Wall Strain	Average Septal Strain	Basal Septal Strain	Mid Septal Strain	Apex Septal Strain
AHI [events/hours]	0.20	0.08	0.26	0.07	−0.01	0.02	−0.01	−0.04
ODI [events/hours]	0.16	0.04	0.22	0.07	0.05	0.10	0.06	−0.02
Snore [events/hours]	0.19	0.09	**0.34**	0.15	0.03	0.12	0.00	−0.03
OAH [events/hours]	**0.37**	0.21	0.30	0.11	−0.06	−0.17	−0.07	0.05
CAH [events/hours]	0.17	0.18	0.15	−0.01	0.14	0.26	0.24	−0.08
CSB [events/hours]	−0.01	−0.09	0.07	0.11	0.33	**0.36**	**0.42**	0.15
Average SpO2 [%]	−0.28	−0.23	−0.22	−0.14	0.07	0.10	0.11	0.00
Minimal SpO2 [%]	−0.08	−0.01	−0.16	−0.20	−0.14	−0.12	−0.12	−0.12
% SpO2 < 90 [%]	0.17	0.08	0.24	0.19	0.12	0.15	0.12	0.06
Average desaturation [%]	0.11	0.10	0.12	−0.06	−0.07	−0.07	−0.01	−0.11
Average HR [bpm]	0.26	**0.34**	0.20	−0.10	0.17	0.22	0.16	0.09
Minimal HR [bpm]	0.08	0.13	0.02	−0.18	0.02	0.06	0.01	−0.00
Maximal HR [bpm]	0.25	0.24	0.10	0.03	0.19	0.12	0.17	0.20
Sleep efficiency [%]	−0.22	−0.21	−0.25	−0.14	−0.09	−0.07	−0.01	−0.15
TST N1 [% sleep time]	0.20	0.19	0.16	0.07	0.02	−0.07	0.01	0.10
TST N2 [% sleep time]	−0.01	0.02	−0.02	−0.04	0.01	0.05	0.02	−0.03
TST N3 [% sleep time]	0.02	−0.01	0.10	0.11	−0.00	0.05	−0.02	−0.03
TST REM [% sleep time]	0.21	0.07	0.02	−0.07	0.07	0.12	0.12	−0.01

AHI, apnea–hypopnea index; ODI, oxygen desaturation index; OAH, obstructive apneas events; CAH, central apneas events; CSB, Cheyne-Stokes breathing; SpO2, saturation; HR, heart rate; TST, total sleep time (min); N1, sleep stage 1; N2, sleep stage 2; N3, sleep stage 3; REM, rapid eye movement sleep stage; OSA, obstructive sleep apnea.

In the study subgroup with age below 60 years, a positive correlation was observed between AHI and mid free wall strain (Figure 1).

Moreover, we found a statistically significant correlation between AHI and basal septal strain (r = 0.56) only in the women subgroup (Figure 2).

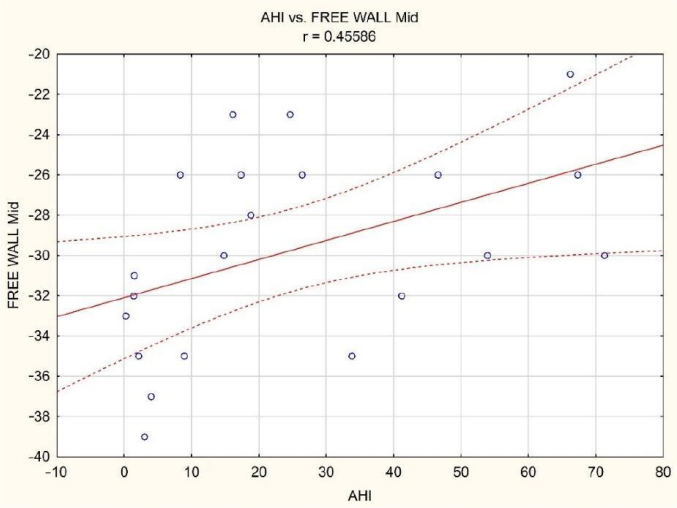

Figure 1. Correlation between AHI and RV mid free wall strain in the study subgroup with age below 60 years (red solid line—estimation curve, dashed lines—95% confidence interval of the estimation curve, small blue circles—individual cases).

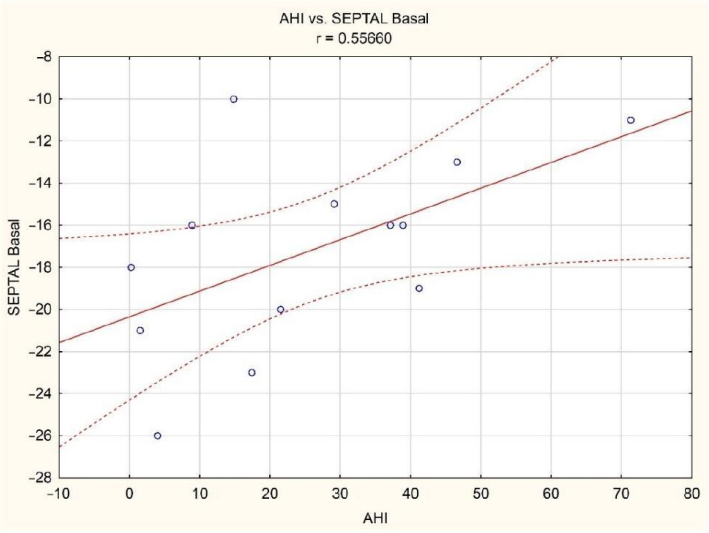

Figure 2. Correlation between AHI and RV basal septal strain in women subgroup (red solid line—estimation curve, dashed lines—95% confidence interval of the estimation curve, small blue circles—individual cases).

4. Discussion

In our study, we showed statistically significant differences considering the severity of obstructive sleep apnea and average free wall strain, mid free wall strain, average, basal, mid, and apex septal strain. Based on correlation analysis, we have indicated that snore

and mild free wall strain, OAH and average free wall strain, average hr and basal free wall strain, CSB and basal septal, and mid septal strain are correlated respectively.

Obstructive sleep apnea harms the cardiovascular system by mechanical, neurohumoral, and inflammatory mechanisms. Obturation of the respiratory tract cause during inspiration: decreased intrathoracic pressure, hypoxia, and arousal. The drop in intrathoracic increases left ventricular transmural pressure, which caused increased afterload and consequently venous return. The other effect contains right ventricular distention, a leftward shift of the interventricular septum, and decreased LV filling. The reduction in minute capacity results from the mechanism described [2]. Obstructive sleep apnea also causes repeated elevations in systemic blood pressure due to sleep arousal and the sympathetic nervous system's hyperactivity [21]. Combining these two mechanisms may lead to insufficient oxygenation of the heart and predisposing the patient to coronary artery disease, arrhythmias, left ventricular hypertrophy, and sometimes heart failure [22–24]. The prevalence of PH in OSA depending on the methodology of the studies. The most recent research agrees on a prevalence of 15–20%. PH is rarely observed without hypoxia during the day. Kessel et al. indicated that the severity of the parameters of the nocturnal event does not affect the presence of PH but showed that a combination of OSA with chronic obstructive pulmonary disease increased the probability of PH. A good method for the treatment of PH in patients with OSA is CPAP, but when it is not enough to correct sleep related hypoxaemia, oxygen supplementary is necessary [25].

Some publications suggest that patients who suffer from obstructive sleep apnea exhibit pulmonary hypertension, which may cause damage, primarily to the right ventricular [26–28]. Moreover, patients can present symptoms of right ventricular failure without pulmonary hypertension in some cases. Pulmonary artery pressure may increase during apneas, but the mechanism of disturbances in the right ventricular work is still under discussion.

Hypoxemia is the most likely cause of the increases in pressure in the pulmonary circulation. It is known that pulmonary vasoconstriction is the consequence of acute hypoxia to maintain an appropriate level of alveolar ventilation. It is a physiological reaction. Intermittent hypoxia is characterized for people with OBS. This state causing pulmonary vasoconstriction may lead to pulmonary hypertension and increases right ventricular afterload.

Patel et al. checked in their research the relationship between diffuse right ventricular fibrosis and heart failure with preserved ejection fraction. The researchers enrolled 14 patients with PH-HFpEF, 13 with pulmonary arterial hypertension, and a control group (eight people). All participants underwent magnetic resonance of the heart to assess myocardial fibrosis. They indicated that the patients with PAH and PH-HFpEF had similar myocardial fibrosis levels, but RV ECV among patients with PH-HFpEF was associated with worse RV function indices-RV free wall strain [29].

Chu et al. assess in their study right ventricular performance and the impact of continuous positive airway pressure therapy in patients with obstructive sleep apnea. Thus, 80 patients with OBS were recruited for the clinical trials. Using 2-dimensional speckle tracking echocardiography and real-time 3-dimensional echocardiography, the researcher assessed the right ventricular function. The obstructive sleep apnea was diagnosed using full night polysomnography. They indicated that patients with diagnosed OBS had significantly decreased global and longitudinal strain, like our study. In their research did not consider the severity of the disease. We also compared the RV free wall (basal, mid, and apical) and the intraventricular septum (basal, mid, and apical) with other polysomnography parameters, and we found a significant positive correlation between OAH and average free wall strain (r = 0.37), snore and mid-free wall strain (r = 0.34), average HR, and basal free wall strain (r = 0.34). Moreover, CSB was positively correlated with basal septal strain and mid septal strain, with r = 0.36 and 0.42, respectively. Chu et al. showed that six-month CPAP therapy caused a significant increase of global and longitudinal strain. Moreover, they observed a decrease of AHI and duration of desaturation <90% [30].

Similar observations were made in research by D'Andrea et al. They indicated that non-invasive ventilation positively affects the function of the right ventricular [31].

Our research showed significant differences between some parameters of right ventricular strain in patients with and without OSA. The strain parameters in patients with OSA were decreased, except for basal free wall strain and apex free wall strain. A similar observation is found in the research Byonauro et al. The study group contained 29 patients with OSA and without heart failure. All participants underwear 3D echocardiography of the right ventricular. The authors showed that patients with OSA like our research had differences in the strain parameters. They did not find differences considering parameters such as TAPSE and the right ventricular fraction between groups with OSA and control [32].

In the next part of the statistical analysis, the correlation between the polysomnographic and echocardiography parameters was checked. The correlation between AHI and the strains was not found in the general study group. AHI was correlated with mild free wall strain only among patients younger than 60 years old. Moreover, the basal septal strain was correlated with AHI only in women.

Altekin et al. contained other conclusions in their publication. The study contained 21 without OSA and 58 individuals with OSA. They used the speckle tracking echocardiography method to check the presence of right ventricular dysfunction before the advent of RV failure and pulmonary hypertension in patients with OSA. They found significant differences between the severity of OSA and the right ventricular strain and systolic strain rate. Moreover, they showed the correlation between strain parameters and the severity of OSA. They indicated like our research that the strain could be a valuable method to detect subclinical right ventricular dysfunction among patients with OSA, even in the absence of pulmonary hypertension [33].

The strength of our study is the use of full night polysomnography in the diagnosis of obstructive sleep apnea. Our research showed a positive correlation between the snore events and mild free wall strain, OAH and average free wall strain, CSB and basal septal strain, average HR, and basal free wall strain.

There are not many publications containing the relationship between polysomnographic and echocardiographic parameters. Kepez et al. indicated AHI, nocturnal mean SO2, and nocturnal deep desaturation index to be significantly correlated with apical right ventricular peak systolic strain and SR values. Moreover, regression analysis was performed and AHI was an independent predictor of apical right ventricular peak systolic strain. As in our research, there are no correlations between weight, age, and strain parameters [34].

The limitations of our study are the lack of left ventricular strain assessment, lack of information about the coexistence of other respiratory diseases, and no direct assessment of pulmonary artery pressure.

In the future, similar studies should be considered in subgroups of different sex, age, coexistence of risk factors for cardiovascular diseases, as well as coexistence of other cardiovascular, respiratory, and nervous system diseases.

In summary, among patients with sleep disorders, functional disorders of the right ventricle, assessed using the strain method, are partly observed. Detection of right ventricular dysfunction is critical among patients with OBS in the prevention of heart failure [35].

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Wroclaw Medical University.

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

Data Availability Statement: The data presented in this study are available upon request from the corresponding author. The data are not publicly available.

Conflicts of Interest: The authors declare no conflict of interest.

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OŚWIADCZENIA O WSPÓŁAUTORSTWIE

Wrocław, 22.06.2023

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Oświadczam, że w pracy:

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2. Macek Piotr, Więckiewicz Mieszko, Poręba Rafał, Gać Paweł, Bogunia-Kubik Katarzyna, Dratwa Marta, Wojakowska Anna, Mazur Grzegorz, Martynowicz Helena: Assessment of telomerase reverse transcriptase single nucleotide polymorphism in sleep bruxism, Journal of Clinical Medicine, 2022, vol. 11, nr 3, art.525 [11 s.], DOI:10.3390/jcm11030525
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4. Macek Piotr, Poręba Małgorzata, Stachurska Aneta, Martynowicz Helena, Mazur Grzegorz, Gać Paweł, Poręba Rafał: Obstructive sleep apnea and sleep structure

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Laboratorium Immunogenetyki Klinicznej i Farmakogenetyki
Instytut Immunologii i Terapii Doświadczalnej
ul. Rudolfa Weigla 12
53-114 Wrocław

OŚWIADCZENIE O WSPÓŁAUTOSTWIE

Oświadczam, że w pracy:

1. **Macek Piotr**, Więckiewicz Mieszko, Poręba Rafał, Gać Paweł, Bogunia-Kubik Katarzyna, Dratwa Marta, Wojakowska Anna, Mazur Grzegorz, Martynowicz Helena: Assessment of telomerase reverse transcriptase single nucleotide polymorphism in sleep bruxism, Journal of Clinical Medicine, 2022, vol. 11, nr 3, art.525 [11 s.], DOI:10.3390/jcm11030525
   Mój udział poległ na planowaniu i nadzorowaniu wykonania badań immunogenetycznych, interpretacji uzyskanych wyników oraz współredagowaniu merytorycznym publikacji.

2. **Macek Piotr**, Poręba Rafał, Gać Paweł, Bogunia-Kubik Katarzyna, Dratwa Marta, Więckiewicz Mieszko, Wojakowska Anna, Michałek-Zrąbkowska Monika, Mazur Grzegorz, Martynowicz Helena: Genetic variants of the TERT gene and telomere length in obstructive sleep apnea, Biomedicines, 2022, vol. 10, nr 11, art.2755 [10 s.], DOI:10.3390/biomedicines10112755
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Prof. dr hab. med. Rafał Poręba
specjalista chorób wewnętrznych
kardiolog, diabetolog, angiolog
4190345

Kierownik
Laboratorium Immunogenetyki
Klinicznej i Farmakogenetyki
prof. dr hab. Katarzyna Bogunia-Kubik

Wrocław, 22.06.2023

mgr Marta Dratwa

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Marta Dratwa

Prof. dr hab. med. Rafał Poręba
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R. Poręba

ZGODA KOMISJI BIOETYCZNEJ

KOMISJA BIOETYCZNA
przy
Uniwersytecie Medycznym
we Wrocławiu
ul. Pasteura 1; 50-367 WROCŁAW

OPINIA KOMISJI BIOETYCZNEJ Nr KB – 525 /2020

Komisja Bioetyczna przy Uniwersytecie Medycznym we Wrocławiu, powołana zarządzeniem Rektora Uniwersytetu Medycznego we Wrocławiu nr 133/XV R/2017 z dnia 21 grudnia 2017 r. oraz działająca w trybie przewidzianym rozporządzeniem Ministra Zdrowia i Opieki Społecznej z dnia 11 maja 1999 r. (Dz.U. nr 47, poz. 480) na podstawie ustawy o zawodzie lekarza z dnia 5 grudnia 1996 r. (Dz.U. nr 28 z 1997 r. poz. 152 z późniejszymi zmianami) w składzie:

prof. dr hab. Jacek Daroszewski (choroby wewnętrzne, endokrynologia, diabetologia)
prof. dr hab. Krzysztof Grabowski (chirurgia)
dr Henryk Kaczkowski (chirurgia szczękowa, chirurgia stomatologiczna)
mgr Irena Knabel-Krzyszowska (farmacja)
prof. dr hab. Jerzy Liebhart (choroby wewnętrzne, alergologia)
ks. dr hab. Piotr Mrzygłód, prof. nadzw. (duchowny)
mgr prawa Luiza Műller (prawo)
dr hab. Sławomir Sidorowicz (psychiatria)
prof. dr hab. Leszek Szenborn, (pediatria, choroby zakaźne)
Danuta Tarkowska (pielęgniarstwo)
prof. dr hab. Anna Wiela-Hojeńska (farmakologia kliniczna)
dr hab. Andrzej Wojnar, prof. nadzw. (histopatologia, dermatologia) przedstawiciel Dolnośląskiej Izby Lekarskiej)
dr hab. Jacek Zieliński (filozofia)

pod przewodnictwem
prof. dr hab. Jana Kornafela (ginekologia i położnictwo, onkologia)

Przestrzegając w działalności zasad Good Clinical Practice oraz zasad Deklaracji Helsińskiej, po zapoznaniu się z projektem badawczym pt.:

„Ocena czynnościowa i strukturalna naczyń krwionośnych u chorych z obturacyjnym bezdechem sennym"

zgłoszonym przez **lek. Piotra Macka** doktoranta Szkoły Doktorskiej w Katedrze i Klinice Chorób Wewnętrznych, Zawodowych Nadciśnienia Tętniczego i Onkologii Klinicznej Uniwersytetu Medycznego im. Piastów Śląskich we Wrocławiu oraz złożonymi wraz z wnioskiem dokumentami, w tajnym głosowaniu postanowiła **wyrazić zgodę** na przeprowadzenie badania w Klinice Chorób Wewnętrznych, Zawodowych Nadciśnienia Tętniczego i Onkologii Klinicznej USK pod nadzorem prof. dr hab. Rafała Poręby **pod warunkiem zachowania anonimowości uzyskanych danych**.

Uwaga: Badanie to zostało objęte ubezpieczeniem odpowiedzialności cywilnej Uniwersytetu Medycznego we Wrocławiu z tytułu prowadzonej działalności.

Pouczenie: W ciągu 14 dni od otrzymania decyzji wnioskodawcy przysługuje prawo odwołania do Komisji Odwoławczej za pośrednictwem Komisji Bioetycznej UM we Wrocławiu.

Opinia powyższa dotyczy projektu badawczego będącego podstawą rozprawy doktorskiej.

Wrocław, dnia 14 września 2020 r.

Uniwersytet Medyczny we Wrocławiu
KOMISJA BIOETYCZNA
przewodniczący
prof. dr hab. Jan Kornafel