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Ocena przydatności pomiaru prędkości fali tętna do oceny czynników ryzyka chorób sercowo naczyniowych oraz cywilizacyjnych - cykl publikacji

Rozprawa doktorska

Promotor:
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Niniejszą pracę dedykuję Moim Ukochanym Rodzicom

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WYKAZ PUBLIKACJI STANOWIĄCYCH ROZPRAWĘ DOKTORSKĄ

1. Validation of a new device for photoplethysmographic measurement of multi-site arterial pulse wave velocity.
   Tadeusz Sondej, **Iwona Jannasz**, Krzysztof Sieczkowski, Andrzej Dobrowolski, Karolina Obiała, Tomasz Targowski, Robert Olszewski.
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2. Relationship between the Central and Regional Pulse Wave Velocity in the Assessment of Arterial Stiffness Depending on Gender in the Geriatric Population.
   Jannasz Iwona, Sondej Tadeusz, Targowski Tomasz, Mańczak Małgorzata, Obiała Karolina, Dobrowolski Andrzej Piotr, Olszewski Robert.
   Sensors (Basel). 2023 Jun 22;23(13):5823. doi: 10.3390/s23135823. PMID: 37447671; PMCID: PMC10347145.
   IF 3,4 punktacja MNiSW: 100

3. The Impact of COVID-19 on Carotid-Femoral Pulse Wave Velocity: A Systematic Review and Meta-Analysis.
   Jannasz Iwona, Pruc Michał, Rahnama-Hezavah Mansur, Targowski Tomasz, Olszewski Robert, Feduniw Stepan, Petryka Karolina, Szarpak Łukasz.
   J Clin Med. 2023 Sep 4;12(17):5747. doi: 10.3390/jcm12175747. PMID: 37685813; PMCID: PMC10488425.
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4. Is the association between pulse wave velocity and bone mineral density the same for men and women? - A systematic review and meta-analysis.
   Jannasz Iwona, Brzeziński Jakub, Mańczak Małgorzata, Sondej Tadeusz, Targowski Tomasz, Rysz Jacek, Olszewski Robert.
   Arch Gerontol Geriatr. 2024 Apr; 119:105309. doi: 10.1016/j.archger.2023.105309. Epub 2023 Dec 11. PMID: 38171030.
   IF 3,5 punktacja MNiSW: 70

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Spis treści

1. Wykaz stosowanych skrótów

AASI – Ambulatory Arterial Stiffness Index (pośredni pomiar sztywności tętnic uzyskany podczas ambulatoryjnego całodobowego automatycznego pomiaru ciśnienia tętniczego)

AHA – American Heart Association (Amerykańskie Towarzystwo Kardiologiczne)

aDBP – aortic Diastolic Blood Pressure (rozkurczowe ciśnienie krwi estymowane w aorcie)

aMAP – aortic Mean Arterial Pressure (średnie ciśnienie tętnicze estymowane w aorcie)

aPP – aortic Pulse Pressure (ciśnienie tętna estymowane w aorcie)

aPWV – aortic Pulse Wave Velocity (prędkość fali tętna estymowana w aorcie)

aSBP – aortic Systolic Blood Pressure (skurczowe ciśnienie krwi estymowane w aorcie)

BMD – Bone Mineral Density (gęstość mineralna kości)

baPWV – Brachial-Ankle Pulse Wave Velocity (prędkość fali tętna mierzona między tętnicą ramienną a kostkową)

bDBP – Brachial Diastolic Blood Pressure (rozkurczowe ciśnienie krwi mierzone w tętnicy ramiennej)

bSBP – Brachial Systolic Blood Pressure (skurczowe ciśnienie krwi mierzone w tętnicy ramiennej)

cfPWV – carotid-femoral Pulse Wave Velocity (prędkość fali tętna mierzona między tętnicą szyjną a udową)

COVID-19 – Coronavirus Disease 2019 (Choroba koronawirusowa 2019)

CVD – Cardiovascular Diseases (Choroby sercowo-naczyniowe)

DBP – Diastolic Blood Pressure (ciśnienie rozkurczowe)

DXA – Dual-Energy X-ray Absorptiometry (densytometria rentgenowska z użyciem podwójnej wiązki promieniowania X)

ESC – European Society of Cardiology (Europejskie Towarzystwo Kardiologiczne)

ESH -European Society of Hypertension (Europejskie Towarzystwo Nadciśnienia Tętniczego)

HDL-C – High-Density Lipoprotein Cholesterol (lipoproteina o wysokiej gęstości)

IR – infrared (światło podczerwone)

LDL-C – Low-Density Lipoprotein Cholesterol (lipoproteina o niskiej gęstości)

MAP – Mean Arterial Pressure (średnie ciśnienie tętnicze)

MPPT –custom for Multi-Site arterial pulse wave velocity measurements (urządzenie do wielomiejscowego pomiaru prędkości fali tętna)

NIGRiR – Narodowy Instytut Geriatrii, Reumatologii i Rehabilitacji

NOS – Newcastle-Ottawa Scale (Skala Newcastle-Ottawa)

NTproBNP – N-terminal pro B-type Natriuretic Peptide (N-końcowy propeptyd natriuretyczny typu B)

PPG – Photoplethysmography (Fotopletyzmografia)

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Preferowane elementy raportowania dla przeglądów systematycznych i metaanaliz)

PTT – Pulse Transit Time (czas przejścia fali tętna)

PWV – Pulse Wave Velocity (prędkość fali tętna)

SARS-CoV-2 – Severe Acute Respiratory Syndrome Coronavirus 2 (drugi koronawirus ciężkiego ostrego zespołu oddechowego)

SBP – Systolic Blood Pressure (ciśnienie skurczowe)

rPWV – radial Pulse Wave Velocity (prędkość fali tętna mierzona w tętnicy promieniowej)

2. Streszczenie w języku polskim

Sztywność tętnic jest uznawana za istotny wskaźnik ryzyka chorób układu sercowo-naczyniowego (CVD). Sztywność tętnic jest określana pośrednio poprzez pomiar prędkości fali tętna (Pulse Wave Velocity - PWV). Istnieje kilka rodzajów pomiarów PWV, jednakże złoty standard w ocenie sztywności tętnic stanowi pomiar prędkości fali tętna między tętnicą szyjną a udową (cfPWV - carotid-femoral PWV). Zwiększenie sztywności tętnic jest główną przyczyną wzrostu ciśnienia tętna w procesie starzenia się organizmu. Nasilenie zmniejszenia podatności tętnic w przebiegu sztywności dotyczy głównie aorty i proksymalnych, elastycznych tętnic oraz w mniejszym stopniu obwodowych tętnic mięśniowych. Istnieje jednak potrzeba szerszego badania relacji między centralnymi i regionalnymi pomiarami PWV, ponieważ regionalne PWV bada mniejsze obszary tętnic, co może dawać dodatkowe informacje na temat zdrowia naczyń. Należy także przeanalizować wpływ takich czynników jak płeć czy wiek na tę zmienną.

Istotną kwestią jest ocena możliwego związku sztywności tętnic oraz gęstości mineralnej kości (BMD), które są kluczowymi wskaźnikami stanu zdrowia sercowo-naczyniowego i siły kości. Parametry te mają istotne znaczenie w ocenie czynników ryzyka związanego z chorobami CVD oraz osteoporozą. Choroba cywilizacyjna, jaką jest osteoporoza, prowadzi do zmniejszenia gęstości kości, która często występuje równolegle z miażdżycą, co sugeruje istnienie wspólnych mechanizmów patofizjologicznych tych schorzeń. Niniejsze badania miały na celu ocenę sztywności tętnic w różnych grupach populacyjnych oraz zbadanie związku między sztywnością tętnic a BMD, jak również ocenę wpływu płci oraz wieku na te parametry w populacji geriatrycznej.

Celem pracy jest ocena przydatności pomiaru prędkości fali tętna do oceny czynników ryzyka chorób sercowo naczyniowych oraz cywilizacyjnych .

Niniejsza rozprawa doktorska została oparta o cztery oryginalne artykuły naukowe, opublikowane w recenzowanych czasopismach (dwa badania własne oraz dwie metaanalizy).

Cykl publikacji:

1. Validation of a new device for photoplethysmographic measurement of multi-site arterial pulse wave velocity. Tadeusz Sondej, Iwona Jannasz, Krzysztof Sieczkowski, Andrzej Dobrowolski, Karolina Obiała, Tomasz Targowski, Robert Olszewski.

Biocybernetics and Biomedical Engineering. Volume 41, Issue 4,2021, Pages 1664 - 1684, ISSN 0208-5216. https://doi.org/10.1016/j.bbe.2021.11.001.

2. Relationship between the Central and Regional Pulse Wave Velocity in the Assessment of Arterial Stiffness Depending on Gender in the Geriatric Population. Jannasz Iwona, Sondej Tadeusz, Targowski Tomasz, Mańczak Małgorzata, Obiała Karolina, Dobrowolski Andrzej Piotr, Olszewski Robert. Sensors (Basel). 2023 Jun 22;23(13):5823. doi: 10.3390/s23135823. PMID: 37447671; PMCID: PMC10347145.

3. The Impact of COVID-19 on Carotid-Femoral Pulse Wave Velocity: A Systematic Review and Meta-Analysis. Jannasz Iwona, Pruc Michał, Rahnama-Hezavah Mansur, Targowski Tomasz, Olszewski Robert, Feduniw Stepan, Petryka Karolina, Szarpak Łukasz. J Clin Med. 2023 Sep 4;12(17):5747. doi: 10.3390/jcm12175747. PMID: 37685813; PMCID: PMC10488425.

4. Is the association between pulse wave velocity and bone mineral density the same for men and women? - A systematic review and meta-analysis. Jannasz Iwona, Brzeziński Jakub, Mańczak Małgorzata, Sondej Tadeusz, Targowski Tomasz, Rysz Jacek, Olszewski Robert.Arch Gerontol Geriatr. 2024 Apr; 119:105309. doi: 10.1016/j.archger.2023.105309. Epub 2023 Dec 11. PMID: 38171030.

Artykuł 1 pt. „Validation of a new device for photoplethysmographic measurement of multi-site arterial pulse wave velocity" dotyczy walidacji nowego urządzenia do pomiaru prędkości fali tętna (PWV), wykorzystującego wielomiejscową fotopletyzmografię (PPG). Jest to metoda wygodna, tania i pozwalająca na długoterminowy pomiar PWV w trybie ciągłym, tj. wynik pomiaru PWV może być uzyskiwany dla każdego uderzenia serca (beat-to-beat) w czasie od kilkunastu sekund do nawet kilku godzin lub dłużej. W zaproponowanym rozwiązaniu, oprócz pomiaru ciągłego PWV, zastosowano pomiar wielomiejscowy. Polegał on na tym, że czujniki PPG (które mierzyły przepływ krwi w miejscu pomiaru), zostały umieszczone w kilku miejscach, tj. na czole, płatkach uszu, palcach rąk i stóp. Razem było to 7 miejsc pomiarowych. Dzięki temu możliwy był pomiar PWV, w odniesieniu do różnych lokalizacji czujnika PPG, a tym samym w różnych miejscach układu sercowo-naczyniowego. Zastosowana aparatura pomiarowa oznaczona jako MPPT (nowe urządzenie

do wielomiejscowego pomiaru prędkości fali tętna) jest dedykowanym i pionierskim urządzeniem, skonstruowanym przez ekspertów z Wydziału Elektroniki Wojskowej Akademii Technicznej (WAT) w Warszawie, w ramach prowadzonej współpracy naukowej pomiędzy NIGRiR i WAT. Walidację urządzenia do wielomiejscowego pomiaru PWV przeprowadzono na 108 osobach (56 mężczyzn i 52 kobiety) w wieku od 20 do 91 lat, z podziałem na trzy grupy wiekowe. W pomiarach walidacyjnych zastosowano referencyjne urządzenie SphygmoCor XCEL (https://atcormedical.com/,aktualnie https://cardiex.com/). Warto zwrócić uwagę, że urządzenie SphygmoCor XCEL jest uznawane jako złoty standard w nieinwazyjnym pomiarze centralnego PWV. Uzyskane wyniki PWV z urządzenia MPPT porównano do referencyjnej wartości cfPWV. Korelacje Pearsona wynosiły od 0,66 do 0,79, a odchylenie standardowe było zwykle mniejsze niż 1,5 m/s. W artykule 1 pokazano, że wielomiejscowa fotopletyzmografia stanowi alternatywną metodę pomiaru PWV i może być używana do diagnostyki chorób sercowo-naczyniowych. W ocenie pomiaru za pomocą urządzenia MPPT najlepsze rezultaty uzyskano przy pomiarach z czujników umieszczonych na głowie i palcach stóp, jako wspólnego pomiaru centralnej i regionalnej PWV. Wynik ten potwierdza potencjał tej technologii jako bardziej dostępnej i tańszej alternatywy dla konwencjonalnych pomiarów cfPWV i wskazuje na potrzebę dalszych badań nad dostępnymi dla szerokiej populacji urządzeniami do pomiaru sztywności tętnic.

Artykuł 2 pt. „Relationship between the Central and Regional Pulse Wave Velocity in the Assessment of Arterial Stiffness Depending on Gender in the Geriatric Population", opublikowany w czasopiśmie Sensors, dotyczy zależności między centralną a regionalną prędkością fali tętna w ocenie sztywności tętnic w populacji geriatrycznej, ze szczególnym uwzględnieniem różnic ze względu na płeć. Badanie porównuje centralną PWV mierzoną za pomocą urządzenia SphygmoCor XCEL oraz regionalną, wielomiejscową PWV mierzoną za pomocą urządzenia MPPT. W badaniu wzięło udział 118 pacjentów (35 mężczyzn i 83 kobiety) w wieku średnio 77,2 lat. Wyniki pokazują, że mężczyźni mają wyższe wartości cfPWV niż kobiety, co sugeruje większą sztywność tętnic w tej grupie, mimo że inne czynniki ryzyka sercowo-naczyniowego miały podobny rozkład w obu grupach. Natomiast regionalne pomiary PWV nie wykazały istotnych różnic między płciami. Wyniki badania pokazują, że centralna PWV lepiej ocenia sztywność tętnic w starszej populacji niż regionalne pomiary. Pozwala to domniemywać, iż na ocenę sztywności tętnic większy wpływ mają wartości PWV centralnej mierzonej w dużych tętnicach - szczególnie aorcie i jej bezpośrednich rozgałęzieniach, niż składowe z tętnic o mniejszym kalibrze, mających budowę głównie

mięśniową. Badanie podkreśla znaczenie oceny różnic płci w kontekście sztywności tętnic oraz ryzyka sercowo-naczyniowego oraz sugeruje dalsze eksploracje prospektywne w tym kierunku.

Artykuł 3 pt. „The Impact of COVID-19 on Carotid-Femoral Pulse Wave Velocity: A Systematic Review and Meta-Analysis", to systematyczny przegląd i metaanaliza, które badają wpływ zakażenia COVID-19 na sztywność tętnic estymowaną za pomocą cfPWV. Z dziewięciu badań, które włączono do metaanalizy, wynika, że cfPWV u pacjentów z COVID-19 wynosiła 9,5 m/s [± 3,7] w porównaniu do 8,2m/s [± 2,2] w grupach kontrolnych (MD=1,32; 95% CI: 0,38 - 2,26; p=0,006), co wskazuje na wzrost sztywności tętnic u chorych. Wyniki sugerują, że zakażenie COVID-19 przyczynia się do wzrostu ryzyka powikłań sercowo-naczyniowych zarówno w krótkim, jak i długim okresie. Sztywność tętnic jest ważnym wskaźnikiem ryzyka sercowo-naczyniowego, a wyniki sugerują, że COVID-19 może przyspieszać procesy starzenia układu naczyniowego, co podkreśla potrzebę monitorowania pacjentów w dłuższym okresie.

Artykuł 4 pt. „Is the association between pulse wave velocity and bone mineral density the same for men and women? - A systematic review and meta-analysis'' stanowi systematyczny przegląd i metaanalizę badającą związek między prędkością fali tętna w tętnicach ramienno-kostkowych (baPWV) a gęstością mineralną kości (BMD), z uwzględnieniem różnic płciowych. Celem badania było ustalenie czy między tymi wskaźnikami istnieje współzależność oraz czy ten związek jest taki sam u mężczyzn i kobiet. Do metaanalizy wykorzystano sześć artykułów. We wszystkich publikacjach uwzględnionych w metaanalizie łączna liczba badanych osób wyniosła 3800, w tym 2054 kobiety i 1746 mężczyzn. Wyniki wskazują, że baPWV jest negatywnie skorelowana z BMD, co oznacza, że wzrost sztywności tętnic wiąże się ze spadkiem gęstości kości. Zbiorczy współczynnik korelacji wynosił - 0,24 (95% CI: - 0,34; - 0,15) w populacji kobiet i - 0,12 (95% CI: - 0,16; - 0,06) w populacji mężczyzn. Sugeruje to, że płeć odgrywa istotną rolę w relacji między zdrowiem sercowo-naczyniowym a zdrowiem kości, kobiety wykazywały silniejszy związek między sztywnością tętnic a zmniejszeniem gęstości kości niż mężczyźni. Osteoporoza, charakteryzująca się obniżeniem BMD i zwiększonym ryzykiem złamań, często współwystępuje z miażdżycą, co sugeruje, że istnieją wspólne mechanizmy patofizjologiczne dla tych schorzeń. Miażdżyca powoduje wzrost sztywności tętnic, a jednocześnie

może wpływać na obniżenie gęstości kości poprzez mechanizmy takie jak stan zapalny czy stres oksydacyjny.

Podsumowując wyżej przedstawione wnioski, pomiar prędkości fali tętna uznano za przydatny do oceny czynników ryzyka chorób sercowo naczyniowych oraz cywilizacyjnych. Nowe technologie, takie jak czujniki PPG, mogą ułatwić jego pomiar. Kobiety mogą być bardziej narażone na współwystępowanie miażdżycy i osteoporozy, podczas gdy mężczyźni częściej wykazują wyższe wartości cfPWV, co zwiększa ich ryzyko sercowo-naczyniowe. Powyższe wnioski wskazują na konieczność rozwoju medycyny spersonalizowanej z uwzględnieniem płci pacjenta. Wiek, płeć oraz stan zdrowia, w tym przebycie COVID-19, schorzenia współistniejące jak osteoporoza mają znaczący wpływ na PWV, co ma istotne znaczenie dla profilaktyki i leczenia chorób układu krążenia.

3. Streszczenie w języku angielskim

Arterial stiffness is recognized as an important risk marker of cardiovascular diseases (CVD). Pulse wave velocity (PWV) is commonly used for assessing arterial stiffness. Currently, many techniques and devices for PWV measurement are known, but they are usually expensive and require operator experience. The measurement of PWV between the carotid artery and the femoral artery (cfPWV) is considered the gold standard in the assessment of arterial stiffness. Increased arterial stiffness remains the main cause of elevation of pulse pressure with aging. Intensified decrease of arterial compliance due to stiffness affects primarily the aorta and proximal elastic arteries and, to a lesser extent, peripheral muscular arteries. As regional pulse wave velocity examines smaller areas of arteries which may provide additional information concerning vascular health there is a need for broader research on the relationship between central and regional PWV measurements. The impact of such factors as gender and age on this variable should also be analyzed.

An important aspect is the evaluation of the potential relationship between arterial stiffness and bone mineral density (BMD), which are key markers of cardiovascular health and bone strength. These parameters are of major significance in the assessment of risk associated with cardiovascular diseases and osteoporosis. Osteoporosis, a civilization disease, leads to decrease of bone density and often coincides with atherosclerosis which suggests common pathophysiological mechanisms of these diseases. This research was aimed to assess arterial stiffness in different population groups and analyze association between arterial stiffness and BMD as well as to assess the influence of gender and age on these parameters in geriatric population.

The aim of the study was to evaluate the usefulness of measuring pulse wave velocity for assessing risk factors for cardiovascular and civilization diseases.

This doctoral thesis was based on four original articles published in reviewed journals (two research articles and two meta-analyses).

Published papers:

1. Validation of a new device for photoplethysmographic measurement of multi-site arterial pulse wave velocity. Tadeusz Sondej, Iwona Jannasz, Krzysztof Sieczkowski, Andrzej Dobrowolski, Karolina Obiała, Tomasz Targowski, Robert Olszewski. Biocybernetics and Biomedical Engineering. Volume 41, Issue 4,2021, Pages 1664- 1684, ISSN 0208-5216, https://doi.org/10.1016/j.bbe.2021.11.001.

2. Relationship between the Central and Regional Pulse Wave Velocity in the Assessment of Arterial Stiffness Depending on Gender in the Geriatric Population. Jannasz Iwona, Sondej Tadeusz, Targowski Tomasz, Mańczak Małgorzata, Obiała Karolina, Dobrowolski Andrzej Piotr, Olszewski Robert. Sensors (Basel). 2023 Jun 22;23(13):5823. doi: 10.3390/s23135823. PMID: 37447671; PMCID: PMC10347145.

3. The Impact of COVID-19 on Carotid-Femoral Pulse Wave Velocity: A Systematic Review and Meta-Analysis. Jannasz Iwona, Pruc Michał, Rahnama-Hezavah Mansur, Targowski Tomasz, Olszewski Robert, Feduniw Stepan, Petryka Karolina, Szarpak Łukasz. J Clin Med. 2023 Sep 4;12(17):5747. doi: 10.3390/jcm12175747. PMID: 37685813; PMCID: PMC10488425.

4. Is the association between pulse wave velocity and bone mineral density the same for men and women? - A systematic review and meta-analysis. Jannasz Iwona, Brzeziński Jakub, Mańczak Małgorzata, Sondej Tadeusz, Targowski Tomasz, Rysz Jacek, Olszewski Robert.Arch Gerontol Geriatr. 2024 Apr; 119:105309. doi: 10.1016/j.archger.2023.105309. Epub 2023 Dec 11. PMID: 38171030.

The 1st paper, “Validation of a new device for photoplethysmographic measurement of multi-site arterial pulse wave velocity” concerns the validation of a new device designed to measure pulse wave velocity using photoplethysmography (PPG), a convenient, cost- effective method that allows for continuous measurement of PWV. 108 subjects (56 men and 52 women) aged 20-91 years divided into three age groups participated in the study. The pioneering , the custom designed MPTT device, developed by experts from the Faculty of Electronics at the Military University of Technology in Warsaw, measured PWV at multi-site points using PPG. The multi-site measurement collected data from seven sensors placed

on the forehead, earlobes, fingers, and toes. The results were compared to cfPWV values measured with the SphygmoCor XCEL, as reference device. The results demonstrated strong consistency between the methods, especially for the measurements from PPG sensors placed on the forehead and toes. The values of Pearson's correlation coefficient ranged from 0.66 to 0.79 and standard deviation was less than 1.5 m/s. The study shows that multi-site photoplethysmography is an alternative method for measuring PWV and can be used for diagnosis of cardiovascular diseases. Evaluation of the measurements taken with MPTT device showed that the best results were obtained from sensors placed on the forehead and toes, serving as a combined measurement of central and regional PWV. These results confirm the potential of this technology as a more accessible and cost-effective alternative to conventional cfPWV measurements and indicate the need for further research on devices for assessing arterial stiffness that are available to the general public.

The 2nd paper, "Relationship between the Central and Regional Pulse Wave Velocity in the Assessment of Arterial Stiffness Depending on Gender in the Geriatric Population", published in "Sensors", concerns the association between central and regional pulse wave velocity in the evaluation of arterial stiffness in geriatric population with particular emphasis on gender differences. The study compared central PWV measured with SphygmoCor XCEL and regional PWV measured with multi-site approach (MPTT). 118 patients (35 men and 83 women) with a mean age of 77.2 years participated in the study. The results demonstrated that, although other cardiovascular risk factors were similarly distributed between the two groups, men had higher cfPWV values than women which suggests greater arterial stiffness. In contrast, regional PWV measurements did not show statistically significant differences between the sexes. It is therefore suggested that in elderly population central PWV assesses arterial stiffness more accurately than regional measurements. This implies that the value of arterial stiffness is impacted more by the central PWV measured in the bigger arteries – especially the aorta and its direct branches – than measurements from smaller, primarily muscular arteries. The study emphasizes the importance of evaluation of gender differences in the context of arterial stiffness and cardiovascular risk and recommends further prospective studies in this domain.

The 3rd paper, "The Impact of COVID-19 on Carotid-Femoral Pulse Wave Velocity: A Systematic Review and Meta-Analysis" is a systematic review and meta-analysis exploring the impact of COVID-19 on carotid-femoral pulse wave velocity (cfPWV), used for the evaluation of arterial stiffness. The data from the 9 studies included in the meta-analysis

show that cfPWV in patients with COVID-19 was 9.5 m/s [± 3.7] in comparison to 8.2 m/s [± 2.2] in control groups (MD=1.32; 95% CI: 0.38 – 2.26; p=0.006), which indicates increased arterial stiffness in these patients. The results suggest that COVID-19 contributes to both short-term and long-term risk of cardiovascular complications. Arterial stiffness is a key marker of cardiovascular risk. The results suggest that COVID-19 may accelerate aging of the cardiovascular system and thus underscore the need for long-term patient monitoring.

The 4th paper, "Is the association between pulse wave velocity and bone mineral density the same for men and women? - A systematic review and meta-analysis" are a systematic review and meta-analysis examining the association between pulse wave velocity in brachial and tibial arteries (brachial-ankle pulse wave velocity, baPWV) and bone mineral density (BMD) with the consideration of gender differences. The aim of the study was to determine if there is a correlation between these markers and if the correlation is different depending on gender. Six articles were included in the meta-analysis. The total number of patients from all included studies was 3800, consisting of 2054 women and 746 men. The results showed that baPWV is negatively correlated with BMD which means that increased arterial stiffness is correlated with decreased bone density. The pooled correlation coefficient was -0.24 (95% CI: -0.34; -0.15) in the female population and -0.12 (95% CI: -0.16; -0.06) in the male population which suggests that gender plays an important role in the association between cardiovascular and bone health. The correlation between arterial stiffness and decreased bone density was higher in women than in men. Osteoporosis, characterized by decreased BMD and increased risk of bone fractures, often coincides with atherosclerosis which suggests common pathophysiological mechanisms of these diseases. Atherosclerosis causes increased arterial stiffness and can concomitantly contribute to the decrease of bone density via such mechanisms as inflammation and oxidative stress.

To summarize the conclusions presented above, the measurement of pulse wave velocity was recognized as a useful tool for assessing risk factors for cardiovascular and civilization diseases. New technologies, such as PPG sensors, can facilitate the measurement. Women can be more susceptible to the co-occurrence of atherosclerosis and osteoporosis whereas men more often have higher values of cfPWV which increases their cardiovascular risk. The presented results indicate the need for the development of personalized medicine accounting for patient's gender. Age, gender, overall health, including a history of COVID-19 infection, and comorbidities, such as osteoporosis, significantly affect PWV. This fact is crucial for the prevention and treatment of cardiovascular diseases.

4. Wstęp

Pomiar prędkości fali tętna (ang. PWV – Pulse Wave Velocity) jest uznanym wykładnikiem subklinicznego uszkodzenia narządów w nadciśnieniu tętniczym oraz parametrem o istotnym znaczeniu rokowniczym zarówno w populacji ogólnej, jak i wśród chorych o podwyższonym ryzyku sercowo-naczyniowym. Istnieje kilka metod pomiaru PWV, za pomocą których możemy nieinwazyjnie ocenić sztywność tętnic [1]. Badania nad analizą graficzną fali tętna mają swój początek w XIX wieku, kiedy to w 1887 r. Fredrick Akbar Mahomet opisał zmiany kształtu fali tętna zależne od wieku badanych. Przepływ krwi w tętnicach wyzwalany jest wyrzutem krwi z serca powodowanym skurczem mięśnia lewej komory serca. Kluczową rolę pełnią tętnice z funkcją amortyzującą oraz transportującą. Sztywność tętnic zależy od czynników genetycznych, wieku, jak i od czynników środowiskowych (dyslipidemii, hiperglikemii oraz innych klasycznych czynników ryzyka) [2]. Zwiększenie sztywności tętnic jest główną przyczyną wzrostu ciśnienia skurczowego i tętna oraz zmniejszenia ciśnienia rozkurczowego w procesie starzenia się organizmu. Nasilenie zmniejszenia podatności tętnic w przebiegu sztywności dotyczy głównie aorty i proksymalnych, elastycznych tętnic oraz w mniejszym stopniu obwodowych tętnic mięśniowych. Prędkość, z jaką fala tętna przemieszcza się po ścianach tętnic, jest bezpośrednio związana z ich elastycznością [3]. Tętnice zdrowe, o dużej elastyczności, pozwalają fali przemieszczać się wolniej, natomiast w przypadku naczyń sztywniejszych, z powodu takich procesów jak miażdżyca czy starzenie się, prędkość fali tętna wzrasta. W ten sposób PWV staje się czułym wskaźnikiem sztywności tętnic, a co za tym idzie - ryzyka chorób układu sercowo-naczyniowego [4]. W przeszłości, uniwersalnie stosowaną metodą pośredniej oceny sztywności tętnic był tradycyjny pomiar ciśnienia tętniczego z oceną ciśnienia tętna. Ciśnienie tętna, czyli różnica między ciśnieniem skurczowym i rozkurczowym dostarcza jedynie informacji orientacyjnej, gdyż na jej wartość wpływa wiele czynników dodatkowych, takich jak: objętość wyrzutowa, opór obwodowy, obecność niedomykalności aortalnej, przetok tętniczo-żylnych [5]. Metody diagnostyczne służące do precyzyjnej oceny sztywności tętnic, można podzielić na inwazyjne i nieinwazyjne. Złotym standardem pomiaru ciśnienia centralnego jest metoda inwazyjna, w której pomiar dokonywany jest zwykle za pomocą cewnika wprowadzanego do aorty i lewej komory serca z dostępu naczyniowego techniką Seldingera, która wymaga doświadczonego specjalisty oraz wiąże się z możliwymi powikłaniami zdrowotnymi. Metody nieinwazyjne można podzielić na kilka grup: ocenę zależności średnicy i pola przekroju naczynia od ciśnienia tętna; analizę prędkości fali tętna; ocenę morfologiczną

fali tętna; ocenę wskaźnika sztywności tętnic (AASI Ambulatory Arterial Stiffness Index). Rejestracji fali tętna można dokonać za pomocą metody: osłuchowej [6], piezoelektrycznej [7], ultrasonograficznej [8]. Za punkt referencyjny na wykresie fali tętna, gdzie oceniany jest czas propagacji fali, przyjmuje się koniec rozkurczu, tuż przed miejscem początku stromego narastania fali tętna [9,10]. Ocena prędkości fali tętna przy pomocy tonometrii aplanacyjnej pozwala określić ciśnienie wewnątrz badanej tętnicy w sposób nieinwazyjny [11,12,13]. Najczęściej stosowanym wskaźnikiem w klinicznej ocenie sztywności tętnic jest prędkość fali tętna mierzona między tętnicą szyjną a udową (ang. carotid-femoral PWV, cfPWV), która uznawana jest za "złoty standard" w tej dziedzinie [14]. PWV mierzy się zazwyczaj za pomocą nieinwazyjnych urządzeń medycznych, które rejestrują czas przejścia fali tętna między dwiema odległymi od siebie tętnicami. W tradycyjnych metodach pomiaru używa się tonometrów aplanacyjnych oraz urządzeń wykorzystujących technologię Dopplera [15]. W ostatnich latach rozwijają się jednak nowoczesne, mniej skomplikowane metody, takie jak fotopletyzmografia (PPG), która opiera się na analizie zmian w natężeniu światła przechodzącego przez tkanki. Zmiany te spowodowane są przepływem krwi i odzwierciadlają rytm uderzeń serca [16]. Fotopletyzmografia, używając czujników umieszczanych na różnych częściach ciała (np. na palcach czy płatkach uszu), poprzez analizę czasu przejścia fali tętna (czasu propagacji fali tętna), pozwala na szybkie, łatwe i stosunkowo tanie wykonywanie pomiarów PWV. Co więcej, umożliwia ona ciągłe monitorowanie pacjentów, co ma szczególne znaczenie w profilaktyce i monitorowaniu progresji chorób sercowo-naczyniowych [17].

Pomiar PWV ma szczególne znaczenie w kontekście prewencji chorób sercowo-naczyniowych. Wzrost PWV jest jednym z pierwszych objawów patologicznych zmian w naczyniach, nawet u osób, które nie wykazują jeszcze widocznych objawów klinicznych. Dlatego pomiar PWV jest coraz częściej wykorzystywany do wczesnej identyfikacji pacjentów z podwyższonym ryzykiem wystąpienia zawału serca, udaru mózgu, czy innych poważnych komplikacji zdrowotnych. Im wyższa prędkość fali tętna między tymi tętnicami, tym większe jest ryzyko rozwoju chorób układu krążenia, co ma związek z pogorszeniem się elastyczności naczyń [18].

Na przełomie lat dyskusyjne było ustalenie wartości referencyjnych PWV, które determinują zwiększone ryzyko sercowo naczyniowe. Kluczowe okazały się opublikowane w 2010 roku wyniki wieloośrodkowego projektu Reference Values for Arterial Stiffness Collaboration [19], do którego włączono ponad 16 500 badanych z 13 europejskich ośrodków.

Opisano w nich wartości PWV ustalone w oparciu o badanie osób zdrowych, bez zdiagnozowanych chorób sercowo-naczyniowych (nadciśnienia tętniczego, dyslipidemii) oraz cukrzycy. Wyszczególniono podgrupę osób z optymalnym i normalnym ciśnieniem tętniczym, bez dodatkowych czynników ryzyka sercowo-naczyniowego, w której określono wartości fizjologiczne PWV. Wartości referencyjne wyznaczono natomiast w oparciu o badanie pozostałych osób posiadających czynniki ryzyka choroby sercowo-naczyniowej, stanowiących populację najbardziej zbliżoną do ogólnej. Jako technikę referencyjną obliczania czasu propagacji fali (t), ze względu na największą stałość i miarodajność wyników, zastosowano metodę użytą w aparacie SphygmoCor [20]. Wg powyższych danych obliczono, iż w zdrowej populacji wartość PWV wzrasta z wiekiem od średniej wartości 6,2 m/s u osób poniżej 30. roku życia do 10,9 m/s w grupie powyżej 70. roku życia. Uwzględnienie aPWV poprawia dopasowanie modelu i reklasyfikuje ryzyko przyszłych zdarzeń sercowo-naczyniowych w modelach, które uwzględniają standardowe czynniki ryzyka. aPWV może umożliwić lepszą identyfikację populacji wysokiego ryzyka, które mogą odnieść korzyści z bardziej agresywnego zarządzania czynnikami ryzyka chorób sercowo-naczyniowych. Nowe spojrzenie pokazała również metaanaliza obejmująca dane 17 635 osób, która wykazała, że wyższa wartość aPWV jest związana z większym ryzykiem choroby wieńcowej, udaru i ogólnych zdarzeń sercowo-naczyniowych, nawet po uwzględnieniu tradycyjnych czynników ryzyka. Szczególnie u młodszych pacjentów aPWV lepiej prognozuje ryzyko, poprawiając klasyfikację pacjentów do grup ryzyka [21].

Wartość rokownicza pomiaru aortalnej PWV została odnotowana w wytycznych European Society of Cardiology (ESC) i European Society of Hypertension (ESH) już w 2007r.; wówczas uznano wynik PWV powyżej 12 m/s jako wykładnik sztywności tętnic u pacjentów w średnim wieku cierpiących na nadciśnienie tętnicze [22]. W wytycznych ESC/ESH 2013 wartość progową PWV 10m/s (12 m/s dla bezpośredniego pomiaru) dołączono do listy wykładników subklinicznego uszkodzenia narządów [23,24]. W rekomendacjach amerykańskich (American Heart Association z 2015) podkreślono, iż sztywność aorty powinna być określona nieinwazyjnie przez pomiar cf PWV (klasa I, poziom wiarygodności A). PWV mierzone w innych segmentach naczyniowych (np. baPWV) jest użyteczne w prognozach dotyczących incydentów sercowo-naczyniowych w populacjach azjatyckich, ale badania długoterminowe w Stanach Zjednoczonych i Europie za pomocą tych metod były niewystarczające (I, B). Pomiar sztywności tętnic znajduje uzasadnienie w dostarczaniu dodatkowych informacji, poza standardowymi czynnikami ryzyka, w przewidywaniu przyszłych zdarzeń sercowo-

naczyniowych (IIa, A) [25]. W kolejnym dokumencie ESC/ESH z 2018 r. [26] podtrzymano twierdzenia wskazujące zwiększoną sztywność tętnic jako patofizjologiczny wyznacznik izolowanego nadciśnienia skurczowego i zależnego od wieku wzrostu ciśnienia tętna [27]. Ponadto jako złoty standard dla pomiaru sztywności tętnicy podtrzymano pomiar cfPWV [26,28]. Najnowsze wytyczne ESC z 2024r wprowadziły proponowane wartości zwiększonej sztywności tętnic, które sygnalizują zwiększone ryzyko zdarzeń sercowo-naczyniowych: cfPWV powyżej 10 m/s oraz odpowiednio baPWV powyżej 14 m/s [29].

Jednym z głównych niemodyfikowanych czynników ryzyka sercowo - naczyniowego o uznanym wpływie na PWV jest wiek [30]. Tymczasem ocena zależności pomiędzy kolejnym czynnikiem niemodyfikowanym płcią a PWV, jest wciąż dyskutowana w literaturze w kontekście czynników anatomicznych, hormonalnych oraz związanych z procesem starzenia [31]. Istotną rolę w modulacji sztywności naczyń odgrywają hormony płciowe, szczególnie estrogeny, które działają ochronnie na śródbłonek naczyniowy i zmniejszają sztywność tętnic. U kobiet w wieku rozrodczym, wysoki poziom estrogenów wiąże się z niższymi wartościami PWV w porównaniu do mężczyzn w tym samym wieku. Po menopauzie, spadek poziomu estrogenów prowadzi do wzrostu sztywności naczyń, a wartości PWV u kobiet zaczynają zbliżać się do wartości obserwowanych u mężczyzn [32]. Dodatkowo należy zwrócić uwagę na fakt, że sztywność tętnic i związany z nią wzrost PWV wzrasta z wiekiem u obu płci. Niemniej jednak, u kobiet proces ten jest opóźniony w porównaniu do mężczyzn, co wynika z ochronnego wpływu estrogenów przed menopauzą. Po menopauzie jednak różnice te się zacierają. PWV u kobiet rośnie szybciej, co może być powodowane obniżonym poziomem ochronnych hormonów płciowych [33].

Sztywność tętnic poza zwiększeniem ryzyka sercowo-naczyniowego może mieć związek z innymi chorobami cywilizacyjnymi, takimi jak osteoporoza [34]. Osteoporoza to choroba, która prowadzi do obniżenia gęstości mineralnej kości (BMD – Bone Mineral Density), co zwiększa ryzyko złamań [35]. Badania sugerują, że u pacjentów obserwowana jest korelacja między sztywnością tętnic a gęstością mineralną kości, co wskazuje na wspólne mechanizmy patofizjologiczne między tymi dwiema chorobami [36,37].

W ostatnich latach badano także zależność pomiędzy prędkością fali tętna a chorobą koronawirusową 2019 (Coronavirus Disease 2019 COVID-19). Wstępne dowody sugerują, że zakażenie Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), wywołującym COVID-19, może mieć istotny wpływ na układ sercowo-naczyniowy,

w tym na sztywność naczyń, co przekłada się na wzrost wartości PWV [38]. Może to wynikać z tego, że COVID-19 wiąże się z nasilonym stanem zapalnym i burzą cytokinową, które wpływają na funkcję śródbłonka naczyniowego. Procesy zapalne prowadzą do dysfunkcji śródbłonka, co z kolei zwiększa sztywność naczyń [39]. W badaniach klinicznych wykazano, że pacjenci z COVID-19, zwłaszcza w ciężkim przebiegu choroby, mają podwyższone wartości PWV w porównaniu do populacji zdrowej. Dodatkowo zakażenie SARS-CoV-2 może prowadzić do długotrwałych zmian w układzie sercowo-naczyniowym, w tym do przewlekłej dysfunkcji śródbłonka i utrzymywania się podwyższonej sztywności naczyń. U pacjentów, którzy przeszli COVID-19, obserwuje się wzrost PWV nawet wiele tygodni lub miesięcy po zakończeniu ostrej fazy infekcji, co sugeruje, że wirus może mieć długoterminowy wpływ na stan naczyń krwionośnych [40,41,42,43,44]. COVID-19 jest związany z podwyższonym ryzykiem powikłań sercowo-naczyniowych, takich jak zawał mięśnia sercowego, zapalenie mięśnia sercowego oraz zakrzepica. Te schorzenia mogą dodatkowo zwiększać sztywność naczyń i przyczyniać się do wzrostu PWV. Wynika to z uszkodzenia tkanek, zwiększonego stresu oksydacyjnego oraz zmian hemodynamicznych, które wpływają na funkcjonowanie tętnic [45]. Dodatkowym aspektem, poruszanym przez naukowców jest fakt, że u pacjentów z ciężkim przebiegiem COVID-19 często występuje hipoksemia oraz stres oksydacyjny, które mogą przyspieszać proces starzenia się naczyń i prowadzić do zwiększenia ich sztywności [46].

5. Założenia i cel pracy

Zwiększona sztywność tętnic, oceniana za pomocą prędkości fali tętna (Pulse Wave Velocity - PWV), jest istotnym klinicznie problemem ze względu na początkowo subkliniczny przebieg, a następnie możliwe powikłania (rozwój nadciśnienia tętniczego, zaawansowanie procesu miażdżycowego prowadzące do zawału mięśnia sercowego, udaru mózgu), które stanowią pogorszenie stanu zdrowia, w konsekwencji czego mogą prowadzić do śmierci. W ostatnich latach podkreślano wartość prognostycznych markerów uszkodzeń narządowych m.in. w celu oceny ryzyka sercowo-naczyniowego oraz prób zapobiegania szybkiej progresji miażdżycy.

Celem pracy była ocena przydatności pomiaru prędkości fali tętna do oceny czynników ryzyka chorób sercowo naczyniowych oraz cywilizacyjnych.

Badania własne koncentrowały się na ocenie wartości PWV jako wskaźnika diagnostycznego w kontekście przewidywania ryzyka sercowo-naczyniowego. Metaanalizy, które stanowiły integralną część cyklu, miały na celu kompleksową ocenę przydatności PWV w kontekście rozpoznawania i monitorowania przebiegu chorób cywilizacyjnych.

Materiał prac oryginalnych stanowili pacjenci – seniorzy w Klinice i Poliklinice Geriatrii Narodowego Instytutu Geriatrii, Reumatologii i Rehabilitacji (NIGRIR), jak również ochotnicy stanowiący grupę kontrolną. Analizie poddano badania przeprowadzone w latach 2018-2020. Na przeprowadzenie badań uzyskano zgodę Komisji Bioetycznej przy Narodowym Instytucie Geriatrii, Reumatologii i Rehabilitacji (NIGRiR) w Warszawie (nr KBT 4/1/2017 z dnia 27.04.2017 r. oraz KBT 1/9/2019 z dnia 31.01.2019r.).

Cel pracy zrealizowano, analizując wyniki pomiarów prędkości fali tętna, używając dwóch urządzeń – badających centralne jak również regionalne PWV u seniorów oraz zdrowych ochotników. Wyniki przeprowadzonych badań własnych przedstawiono w dwóch następujących artykułach opublikowanych w recenzowanych czasopismach:

1. Validation of a new device for photoplethysmographic measurement of multi-site arterial pulse wave velocity.
   Tadeusz Sondej, Iwona Jannasz, Krzysztof Sieczkowski, Andrzej Dobrowolski, Karolina Obiała, Tomasz Targowski, Robert Olszewski.
   Biocybernetics and Biomedical Engineering. Volume 41, Issue 4,2021, Pages 1664- 1684, ISSN 0208-5216, https://doi.org/10.1016/j.bbe.2021.11.001.

2. Relationship between the Central and Regional Pulse Wave Velocity in the Assessment of Arterial Stiffness Depending on Gender in the Geriatric Population.
   Jannasz Iwona, Sondej Tadeusz, Targowski Tomasz, Mańczak Małgorzata, Obiała Karolina, Dobrowolski Andrzej Piotr, Olszewski Robert.
   Sensors (Basel). 2023 Jun 22;23(13):5823. doi: 10.3390/s23135823. PMID: 37447671; PMCID: PMC10347145.

Ponadto w szerszym odniesieniu do chorób cywilizacyjnych ocenie poddano wpływ pandemicznego zakażenia SARS-CoV 2 na sztywność naczyń, jak również wpływ wartości prędkości fali tętna w odniesieniu do zmniejszonej gęstości kości prowadzącej do osteoporozy w poniższych metaanalizach:

3. The Impact of COVID-19 on Carotid-Femoral Pulse Wave Velocity: A Systematic Review and Meta-Analysis.
   Jannasz Iwona, Pruc Michał, Rahnama-Hezavah Mansur, Targowski Tomasz, Olszewski Robert, Feduniw Stepan, Petryka Karolina, Szarpak Łukasz. J Clin Med. 2023 Sep 4;12(17):5747. doi: 10.3390/jcm12175747. PMID: 37685813; PMCID: PMC10488425.
4. Is the association between pulse wave velocity and bone mineral density the same for men and women? - A systematic review and meta-analysis.
   Jannasz Iwona, Brzeziński Jakub, Mańczak Małgorzata, Sondej Tadeusz, Targowski Tomasz, Rysz Jacek, Olszewski Robert.
   Arch Gerontol Geriatr. 2024 Apr; 119:105309. doi: 10.1016/j.archger.2023.105309. Epub 2023 Dec 11. PMID: 38171030.

6. Materiały i metody

Pierwszy artykuł zatytułowany *"Validation of a New Device for Photoplethysmographic Measurement of Multi-Site Arterial Pulse Wave Velocity"* opisuje badanie mające na celu walidację nowego urządzenia, które za pomocą czujników fotopletyzmograficznych (PPG) mierzy prędkość fali tętna (PWV) w wielu miejscach na ciele człowieka. Badanie przeprowadzono na 108 osobach (56 mężczyznach i 52 kobietach) w wieku od 20 do 91 lat. Użyto czujników PPG, które są powszechnie stosowane w klinicznej pulsoksymetrii. Czujniki umieszczono w różnych punktach ciała: czoło, małżowiny uszne, palce dłoni i palce stóp. Miało to na celu zmierzenie PWV w wielu miejscach. Każdy pomiar trwał 15 minut i był wykonywany w pozycji leżącej po 15 minutach odpoczynku. Czas przejścia fali tętna (PTT – ang. Pulse Transit Time) mierzono poprzez obliczenie różnicy czasowej między sygnałami uzyskanymi z czujników PPG zlokalizowanych w powyższych miejscach ciała. Następnie PWV obliczano, dzieląc odległość między czujnikami przez zmierzony czas przejścia fali tętna. Wyniki uzyskane z nowego urządzenia porównano z wynikami pochodzącymi z urządzenia SphygmoCor XCEL, które jest uznawane za złoty standard w pomiarze PWV, opierającego się na tonometrii aplanacyjnej.

Drugi artykuł zatytułowany „*Relationship between the Central and Regional Pulse Wave Velocity in the Assessment of Arterial Stiffness Depending on Gender in the Geriatric Population*" szczegółowo bada temat sztywności tętnic w populacji geriatrycznej. Badanie miało na celu ocenę wpływu płci na sztywność tętnic mierzonych zarówno centralnie, jak i regionalnie u osób starszych. W badaniu wykorzystano dwa rodzaje pomiarów PWV: cfPWV oraz regionalną PWV (mierzoną za pomocą urządzenia MPPT). Pomiary przeprowadzano po okresie odpoczynku, w kontrolowanych warunkach środowiskowych, aby zapewnić spójność wyników. Z badania zostały wykluczone osoby z aktywną chorobą nowotworową, brakiem kończyn oraz zaawansowaną demencją, która uniemożliwiłaby oświadczenie świadomej zgody oraz współpracę podczas badań. Pomiar cfPWV polegał na jednoczesnym rejestrowaniu pulsu w tętnicy szyjnej (przy użyciu tonometru) oraz w tętnicy udowej (poprzez mankiet umieszczony na górnej części uda – tj. automatyczny pomiar zmian ciśnienia w mankiecie wywołany przepływem krwi w tętnicy udowej). Na tej podstawie wyznaczano czas przejścia fali tętna pomiędzy tętnicą szyjną a udową. Obliczenia były wykonywane na podstawie zmierzonej odległości między miejscem pomiaru a wyznaczonymi punktami anatomicznymi (np. wcięciem mostkowym) oraz czasu przejścia fali tętna.

Wszystkie pomiary wykonywano z dokładnością do 0,5 cm. Do mierzenia regionalnej prędkości fali tętna wykorzystano specjalnie zaprojektowany system pomiarowy MPPT, który mierzy prędkość fali tętna w różnych częściach ciała, korzystając z czujników fotopletyzmograficznych (PPG). Czujniki PPG były umieszczane na czole, uszach, palcach dłoni i palcach stóp, co umożliwiało ocenę regionalnej PWV. Dla pomiaru sygnału PPG wykorzystywano światło podczerwone (IR – ang. infrared, długość fali 905 nm). Obliczenia PWV wykonywano offline, za pomocą dedykowanego oprogramowania MATLAB.

Procedura pomiaru rozpoczynała się odpoczynkiem badanego przed pomiarami przez 15 minut. Następnie osoby badane były zapoznawane z celem i procedurą badania oraz uzyskiwana była pisemna zgoda na udział w badaniu. Dalej mierzono ciśnienie krwi na tętnicy ramiennej – skurczowe ciśnienie krwi (bSBP - brachial Systolic Blood Pressure) i rozkurczowe ciśnienie krwi (bDBP - brachial Diastolic Blood Pressure) oraz aortalnej – skurczowe (aSBP -aortic Systolic Blood Pressure) i rozkurczowe (aDBP - aortic Diastolic Blood Pressure) – za pomocą SphygmoCor XCEL. Następnie pacjenci leżeli w pozycji horyzontalnej, podczas gdy główne pomiary za pomocą urządzenia MPPT trwały 15 minut. Pomiary cfPWV były wykonywane co 3 minuty, tymczasem gdy regionalne PWV były mierzone w sposób ciągły. Wszystkie pomiary przeprowadzał ten sam operator, w godzinach ok. 10:00–13:00, w oddzielnym pokoju, w temperaturze ok. 22–24°C. Analizę statystyczną przeprowadzono za pomocą oprogramowania MATLAB, R oraz Statistica v.13. Wyniki uważano za istotne statystycznie przy $p < 0,05$. Testy obejmowały: test Shapiro-Wilka (dla normalności rozkładu), test t- Studenta (dla porównania zmiennych ciągłych o normalnym rozkładzie), test U Manna-Whitneya (dla zmiennych o nienormalnym rozkładzie), oraz analizę korelacji liniowej Pearsona. Do analizy badań włączono 118 pacjentów geriatrycznych (83 kobiety i 35 mężczyzn), średnia wieku wynosiła 77,2 [± 8,1] lat. Obie grupy były homogeniczne pod względem występowania chorób współistniejących, takich jak nadciśnienie tętnicze, cukrzyca, zespół metaboliczny, niewydolność serca czy przewlekła obturacyjna choroba płuc.

Kolejny artykuł pt. *Impact of COVID-19 on carotid-femoral pulse wave velocity: a systematic review and meta-analysis* jest systematycznym przeglądem i metaanalizą, której celem było zbadanie wpływu COVID-19 na sztywność tętnic poprzez pomiar prędkości fali tętna między tętnicą szyjną a udową (cfPWV). Badanie przeprowadzono zgodnie z wytycznymi PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), co zapewnia

rygorystyczne standardy dla systematycznych przeglądów i metaanaliz. Protokół badania zarejestrowano w międzynarodowej bazie danych PROSPERO (nr CRD42023434326).

Poszukiwanie literatury obejmowało okres od stycznia 2020r. do czerwca 2023r. w następujących bazach danych: PubMed, Web of Science, Embase i Cochrane Library. Wyszukiwanie obejmowało kombinacje słów kluczowych, takich jak:

- "Pulse wave velocity" OR "PWV" OR "arterial stiffness"
- AND "COVID-19" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus-2".

Autorzy dodatkowo przeglądali cytowania w znalezionych badaniach, aby zidentyfikować dalsze odpowiednie prace. Wszystkie wyniki były gromadzone w oprogramowaniu Endnote (do zarządzania cytowaniami), a zduplikowane wpisy zostały usunięte.

Do analizy włączono badania, które spełniały następujące kryteria:

- Porównywały cfPWV u pacjentów z aktywną lub przebytą infekcją COVID-19 z grupą kontrolną.
- Publikacje musiały być dostępne w języku angielskim. Wykluczono publikacje, które nie zawierały odpowiednich danych, nie miały grupy kontrolnej, były recenzjami, raportami z konferencji, listami do redaktora lub artykułami redakcyjnymi.

Do oceny jakości metodologicznej badań wykorzystano skalę Newcastle-Ottawa (Newcastle-Ottawa Scale - NOS), która przydziela punkty na podstawie kryteriów dotyczących: (A) selekcji (4 punkty); (B) porównywalności (2 punkty); (C) ekspozycji (3 punkty). Badania, które uzyskały wynik ≥7 punktów, uznano za wysokiej jakości. Do analiz statystycznych wykorzystano oprogramowanie Review Manager (wersja 5.4) oraz Stata (wersja 14). Stosowano współczynniki różnicy średnich (MD) dla danych ciągłych i współczynniki szans (OR) dla danych dychotomicznych, z przedziałami ufności na poziomie 95%. Istotność ustalono na poziomie $p < 0,05$. Spośród 837 początkowo zidentyfikowanych artykułów, po wykluczeniu duplikatów oraz prac, które nie spełniały kryteriów włączenia, ostatecznie do metaanalizy wybrano 9 badań. Badania te obejmowały łącznie 536 pacjentów. Średni wiek pacjentów z COVID-19 wynosił 50,8 [± 15,1] lat, a w grupach kontrolnych 51,3 [±15,0] lat.

Badania przeprowadzono w różnych krajach: USA (3 badania); Grecji (2 badania); Brazylii, Austrii, Rumunii oraz Holandii (po jednym badaniu).

Czwarty artykuł wykorzystany do przygotowania niniejszej rozprawy doktorskiej pt. *Is the association between pulse wave velocity and bone mineral density the same for men and women? - A systematic review and meta-analysis* bada, czy związek między prędkością fali tętna ramienno-kostkowego (baPWV) jako wskaźnika sztywności tętnic, a gęstością mineralną kości (BMD) - jako wskaźnika wytrzymałości kości, różni się w zależności od płci. Badanie oparte jest na przeglądzie systematycznym i metaanalizie dostępnych badań, mając na celu zbadanie specyficznych różnic płciowych. Przeprowadzono przegląd badań opublikowanych do 30 kwietnia 2023 r., korzystając z baz danych PubMed, Web of Science, Scopus i Cochrane. Wyszukiwania obejmowały frazy takie jak bone mineral density [Title/Abstract]) AND (arterial stiffness [Title/Abstract]); (bone mineral density [Title/ Abstract]) AND (pulse wave velocity [Title/Abstract]); (bone mineral density [Title/Abstract]) AND (brachial ankle pulse wave velocity [Title/Abstract]). Aby badanie zostało włączone do publikacji, musiało mierzyć współczynnik korelacji między gęstością mineralną kości (BMD) a prędkością fali tętna ramienno-kostkowego (baPWV). W celu ujednolicenia próby, do analizy włączono jedynie badania, które mierzyły BMD w odcinku lędźwiowym kręgosłupa, wykluczając te, które mierzyły BMD w innych miejscach.

Do analizy włączono łącznie sześć badań, które dostarczyły danych dla populacji obejmującej 3800 osób (2054 kobiety i 1746 mężczyzn). Gęstość mineralna kości była mierzona przy użyciu densytometrii rentgenowskiej z podwójną energią (DXA) w odcinku lędźwiowym kręgosłupa. Natomiast prędkość fali tętna (baPWV) mierzono za pomocą nieinwazyjnych metod, polegających na analizie fal tętna w tętnicach ramiennych i kostkowych.

W celu oszacowania współczynników korelacji między baPWV a BMD zastosowano model efektów losowych. Oddzielne analizy przeprowadzono dla mężczyzn i kobiet, a do oceny heterogeniczności badań wykorzystano test Cochran Q oraz indeks niezgodności I^2. Jakość włączonych badań oceniono, jak w artykule trzecim, przy pomocy skali oceny jakości NOS. Większość badań uzyskała wysokie oceny, z wyjątkiem jednego, które wykazało pewne ograniczenia metodologiczne.

7. Wyniki

Wyniki badań płynące z artykułu ***"Validation of a New Device for Photoplethysmographic Measurement of Multi-Site Arterial Pulse Wave Velocity"*** wskazują, że wartości PWV uzyskane z nowego urządzenia wykazały silną korelację z cfPWV mierzonym za pomocą SphygmoCor XCEL. Wartości współczynnika korelacji (r) wahały się od 0,66 do 0,79 w zależności od lokalizacji czujników. Najlepsze wyniki uzyskano, gdy czujnik PPG znajdował się na głowie (czole lub uchu), a drugi czujnik na palcu stopy. Korelacja dla konfiguracji czoło-prawy palec stopy wyniosła r = 0,75, a dla prawe ucho-prawy palec stopy r = 0,79. Średnia różnica między PWV mierzonym przez nowe urządzenie a cfPWV wynosiła od 0,11 do 0,95m/s, co mieści się w granicach akceptowalnego poziomu dokładności zgodnie z wytycznymi Artery Society [93] (md < 1,0 m/s, SD ≤ 1,5 m/s). Standardowe odchylenie (SD) dla większości konfiguracji wynosiło mniej niż 1 m/s, a najniższe wartości uzyskano dla konfiguracji ucho-palec stopy (SD = 0,91 do 0,96 m/s). Najwyższą zgodność z cfPWV uzyskano dla konfiguracji, w której czujnik PPG umieszczony był na prawym uchu i prawym palcu stopy (średnia różnica 0,11 m/s, SD = 0,96). Konfiguracje, w których czujnik znajdował się na palcach dłoni i stóp, miały niższe wartości korelacji i większe odchylenia standardowe, co sugeruje mniejszą dokładność w porównaniu z konfiguracjami głowa-stopa.

W drugim artykule zatytułowanym „***Relationship between the Central and Regional Pulse Wave Velocity in the Assessment of Arterial Stiffness Depending on Gender in the Geriatric Population***" oceniono związek pomiędzy centralną a regionalnymi wartościami PWV u pacjentów geriatrycznych holistycznie, jak również uwzględniając różnicę w podziale na płeć. Wśród badanych pacjentów w podziale uwzględniającym płeć, osoby z obu grup nie różniły się statystycznie pod względem wartości wieku; wyniku badań krwi, takich jak: stężenie LDL (Low-Density Lipoprotein), trójglicerydów, glukozy. W porównaniu z kobietami mężczyźni wykazywali istotnie niższe stężenie HDL (High-Density Lipoprotein) (p < 0,001); wyższe stężenie kwasu moczowego (p < 0,001) i NTproBNP (p = 0,047). Mężczyźni charakteryzowali się statystycznie istotnie wyższymi wartościami cfPWV niż kobiety (mediana cfPWV 10,52 m/s vs. 9,36 m/s, odpowiednio; p = 0,001). Najwyższe korelacje z PWV w całej grupie stwierdzono dla skurczowego ciśnienia tętniczego, zarówno obwodowego mierzonego na tętnicy ramiennej bSBP (r = 0,443), jak i skurczowego ciśnienia centralnego szacowanego pomiaru aorty aSBP (r = 0,411). Ponadto wszystkie parametry ciśnienia (bDBP, bMAP, aDBP, aPP i aMAP) wykazały istotny związek z PWV. Najistotniejszymi parametrami w całej grupie były dwa czynniki modyfikowalne: ciśnienie

skurczowe (β 0,398; p < 0,001) i podwyższone stężenie kwasu moczowego (β 0,172; p = 0,034) oraz dwa niemodyfikowalne: płeć męska (β 0,251; p = 0,003) i wiek (β 0,250; p = 0,003). W analizie regresji wieloczynnikowej w grupie kobiet, oprócz wartości skurczowego ciśnienia tętniczego (β 0,355; p < 0,001), wieku (β 0,276; p = 0,006) i stężenia kwasu moczowego (β 0,240; p = 0,010), wartość NTproBNP (β 0,208; p = 0,034) miała również istotny wpływ na cfPWV. Natomiast w analizie wieloczynnikowej dotyczącej grupy mężczyzn istotna była tylko wartość skurczowego ciśnienia tętniczego (β 0,394; p = 0,010). W pomiarach regionalnych PWV nie stwierdzono istotnych różnic płciowych. Ponadto mężczyźni wykazywali wyższe wartości cfPWV niż regionalnego PWV.

Kolejny artykuł: ***Impact of COVID-19 on carotid-femoral pulse wave velocity: a systematic review and meta-analysis*** przedstawia zwiększenie sztywności tętnic u pacjentów z COVID-19 w porównaniu do grupy kontrolnej. Przeprowadzona analiza wykazała, że średnia wartość cfPWV u pacjentów z COVID-19 wynosiła 9,5 [± 3,7] m/s, natomiast w grupach kontrolnych 8,2 [± 2,2] m/s. Wartość średniej różnicy (MD) wyniosła 1,32 m/s (95% CI: 0,38 - 2,26; p = 0,006), co oznacza istotny statystycznie wzrost sztywności tętnic u pacjentów, którzy przeszli zakażenie COVID-19. Chociaż ogólna analiza wykazała istotny wzrost cfPWV u pacjentów z COVID-19, jedno badanie (Van der Sluijs i in.) nie wykazało takiej zależności, a inne (Skow i in.) odnotowało pozytywną, lecz nieistotną korelację. Pomimo tych wyjątków, pozostałe badania jednoznacznie wskazują na korelację między infekcją COVID-19 a zwiększeniem sztywności tętnic.

Czwarty artykuł wykorzystany do przygotowania pracy pt. ***Is the association between pulse wave velocity and bone mineral density the same for men and women? - A systematic review and meta-analysis*** wskazuje na obecną u kobiet umiarkowaną, statystycznie istotną negatywną korelację między prędkością fali tętna a gęstością mineralną kości, z ogólnym współczynnikiem korelacji wynoszącym -0,24 (przedział ufności 95%: -0,34 do -0,15), co oznacza, że wraz ze wzrostem sztywności tętnic (wyrażonej przez baPWV) dochodzi do obniżenia gęstości mineralnej kości. Natomiast u mężczyzn związek ten był znacznie słabszy. Połączony współczynnik korelacji wynosił -0,12 (przedział ufności 95%: -0,18 do - 0,06), co oznacza bardzo słabą negatywną korelację, która w niektórych przypadkach może być interpretowana jako brak korelacji. Wyniki sugerują, że wpływ sztywności tętnic na gęstość mineralną kości u mężczyzn jest znikomy w porównaniu do kobiet. Współczynnik heterogeniczności w grupie kobiet był umiarkowany ($I^2 = 43\%$), co wskazuje na pewne różnice

w wynikach poszczególnych badań, choć nie na tyle znaczące, aby podważały ogólny wynik. W przypadku mężczyzn heterogeniczność była niska ($I^2 = 0\%$), co sugeruje, że wyniki w tej grupie były bardziej jednorodne.

8. Podsumowanie i wnioski

Przegląd wyników badań dotyczących przydatności pomiaru prędkości fali tętna do oceny czynników ryzyka chorób sercowo naczyniowych oraz cywilizacyjnych wykazał, że:

- W ocenie pomiaru za pomocą urządzenia MPPT najlepsze rezultaty uzyskano przy pomiarach z czujników umieszczonych na głowie i stopach, jako wspólnego pomiaru centralnej i regionalnej PWV. Wynik ten potwierdza potencjał tej technologii jako bardziej dostępnej i tańszej alternatywy dla konwencjonalnych pomiarów cfPWV i wskazuje na potrzebę dalszych badań nad dostępnymi dla szerokiej populacji urządzeniami do pomiaru sztywności tętnic.

- U mężczyzn stwierdzono wyższą cfPWV, co sugeruje zwiększoną sztywność tętnic centralnych, natomiast w mniejszych tętnicach - zbudowanych głownie z tkanki mięśniowej nie zaobserwowano istotnych różnic płciowych. Przyczyna tej zależności jest nadal niejasna oraz wskazuje na potrzebę dalszych badań. Obecnie nie można jej jednoznacznie wyjaśnić rozkładem klasycznych czynników ryzyka sercowo-naczyniowego między płciami. Ponadto, biorąc pod uwagę mniej wyraźnie zróżnicowane regionalne wartości PWV uzyskane przez MPPT, należy założyć, że głównym czynnikiem wpływającym na sztywność tych tętnic są komponenta elastycznych wielkich tętnic centralnych. Istotą zwiększonej sztywności tętnic, a tym samym wszystkich konsekwencji klinicznych związanych ze starzeniem się populacji, jest miażdżyca i zwapnienie, dotyczące głównie aorty, a w znacznie mniejszym stopniu obwodowych tętnic mięśniowych. Wnioski płynące z tego badania mogą również wskazywać na konieczność personalizacji podejmowanych działań prewencyjnych i leczniczych w zależności od płci pacjenta.

- W grupie osób którzy przebyli COVID-19 występuje zwiększona sztywność tętnic. Średnia cfPWV była istotnie wyższa u osób po infekcji w porównaniu do grup kontrolnych, co sugeruje negatywny wpływ COVID-19 na układ naczyniowy. Wobec czego istotna jest szczególnie wnikliwa dalsza ocena stanu zdrowia. w tym czynników ryzyka rozwoju, lub zaawansowania już obecnych, chorób sercowo naczyniowych w tej grupie osób.

- Występuje negatywna korelacja między PWV a BMD u kobiet, co sugeruje związek między sztywnością tętnic a ryzykiem rozwoju osteoporozy. Związek ten był znacznie

słabszy u mężczyzn. Powyższe dane mogą sugerować, aby szczególnie u kobiet z zwiększoną sztywnością tętnic wcześniej rozważyć profesjonalną diagnostykę w kierunku osteoporozy, jak również jej zapobiegania.

Podsumowując **pomiar prędkości fali tętna uznano za przydatny do oceny czynników ryzyka chorób sercowo naczyniowych oraz cywilizacyjnych**.

Nowe technologie, takie jak czujniki PPG, mogą ułatwić jego pomiar. Wiek, płeć oraz stan zdrowia, w tym przebycie COVID-19, mają istotny wpływ na PWV, co ma kluczowe znaczenie dla profilaktyki i leczenia chorób układu krążenia.

9. Przedstawienie opublikowanych prac

Publikacja 1: Validation of a new device for photoplethysmographic measurement of multi-site arterial pulse wave velocity.

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Original Research Article

Validation of a new device for photoplethysmographic measurement of multi-site arterial pulse wave velocity

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ABSTRACT

Pulse wave velocity (PWV) is commonly used for assessing arterial stiffness and it is a useful and accurate cardiovascular mortality predictor. Currently, many techniques and devices for PWV measurement are known, but they are usually expensive and require operator experience. One possible solution for PWV measurement is photoplethysmography (PPG), which is convenient, inexpensive and provides continuous PWV results. The aim of this paper is validation of a new device for PPG sensor-based measurement of multi-site arterial PWV using a SphygmoCor XCEL (as the reference device) according to the recommendations of the Artery Society Guidelines (ASG). In this study, 108 subjects (56 men and 52 women, 20–91 years in 3 required age groups) were enrolled. The multi-site PWV was simultaneous measured by 7 PPG sensors commonly used in pulse oximetry in clinical settings. These sensors were placed on the forehead, and right and left earlobes, fingers and toes. Pulse transit time (PTT) was measured offline as the difference of time delay between two onsets of the pulse wave determined by the intersecting tangent method. The PWV was calculated by dividing the distance between PPG sensors by PTT. During PPG signals measurement, reference carotid to femoral PWV (cfPWV) was performed with a SphygmoCor XCEL system. The Pearson correlation coefficient (r) between the obtained PWV results was calculated. The Bland-Altman method was used to establish the level of agreement between the two devices. Mean difference (md) and standard deviation (SD) were also calculated. The multi-site PWV was highly correlated with accuracy at the ASG-defined level of "Acceptable" (md < 1.0 m/s and SD ≤ 1.5 m/s) with cfPWV: forehead - right toe (r = 0.75, md = 0.20, SD = 0.97), forehead - left toe (r = 0.79, md = 0.18, SD = 0.91), right ear - right toe (r = 0.79, md = 0.11, SD = 0.96), left ear - left toe (r = 0.75, md = 0.43, SD = 0.99), right ear - left toe (r = 0.78, md = 0.40, SD = 0.93), left ear - right toe (r = 0.78, md = 0.11, SD = 0.96), right finger - right toe (r = 0.66, md = 0.95, SD = 1.29), left finger - left

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toe (r = 0.67, md = 0.68, SD = 1.35). This study showed that PWV measured with the multi-site PPG system, in relation to the obtained numerical values, correlated very well with that measured using the commonly known applanation tonometry method. However, it should be noted, that the measured PWV concerns the central and muscular part of the arterial tree while the cfPWV is only for the central one. The best results were obtained when the proximal PPG sensor was placed on the head (ear or forehead) and the distal PPG sensor on the toe. PPG sensors can be placed in many sites at the same time, which provides greater freedom of their configuration. Multi-site photoplethysmography is an alternative method for PWV measurement and creates new possibilities for the diagnostics of cardiovascular diseases.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality globally [1,2]. Classic risk factors for CVD development are divided into non-modifiable ones i.e. age and family history of heart diseases, as well as modifiable risk factors, such as hypertension, hyperlipidemia, smoking, diabetes and obesity [3]. Arterial stiffness [4] has been shown to have an independent predictive value for cardiovascular events in people with hypertension, diabetes [5], and end-stage renal disease [6], in the elderly [7,8], and in the general population. In addition, there are discussions as to whether increased arterial stiffness is the result or perhaps the cause of hypertension. While the "secondary" increase in large artery stiffness is attributable to an increase in mean pressure that occurs in hypertension, evidence now exists that the "primary" increase in large artery stiffness that accompanies aging gives rise to an increase in large vessel stiffness that proceeds an elevation of arterial pressure [8]. Aortic stiffness is an independent predictor of fatal stroke in patients with essential hypertension [9]. A review of PVW as a measure of arterial stiffness in patients with familial hypercholesterolemia was presented in [10].

Pulse wave velocity (PWV) measurement is an established method of assessing arterial stiffness and it is a useful and accurate cardiovascular mortality predictor [11]. The prognostic value of the aortic PWV measurement was also reflected in the guidelines of the European Society of Cardiology and the European Society of Hypertension [12]. PWV measurement may refer to both the aorta and the peripheral segments of the arteries [13]. The carotid to femoral PWV (cfPWV) is indicative of the stiffness in the central-elastic artery, while the carotid to radial PWV (crPWV) can provide information about the peripheral-muscular arteries [14]. In a review [15], authors provide an overview of the numerous methods and underlying technologies within devices that claim to measure arterial stiffness in humans and demonstrate advantages and disadvantages of methods aiming to measure aortic PWV and local arterial stiffness. Despite devices dedicated to PWV measurement (for example, SphygmoCor, Complior, Artegiograph [16,17]), the possibilities of assessing arterial stiffness are analyzed by tools commonly used in radiology - such as magnetic resonance [18], ultrasound [19] or a promising technique used in cardiological ultrasonography - two-dimensional speckle tracing [20]. Assessment of arterial compliance may be done by fusion of oscillometry and PWV information also [21]. Besides to the PWV measurement, attention should be paid to the additional information from Pulse Wave Analysis (PWA), which parameters allow estimation of cardiac output based on continuous analysis of the arterial blood pressure waveform tested according to many algorithms [22].

The study of PWV and factors influencing PWV is still an important and current topic. The impact of heart rate (HR) on cfPWV was investigated in [23] under a simulated case. It has been shown that relatively small HR changes may only slightly affect cfPWV. In turn, it was shown in [24,25] that the brachial to ankle PWV (baPWV) could be a useful screening tool for the early detection of adverse cardiac features among untreated hypertensive patients. In [26] it was shown that both an orthostatic blood pressure drop and rise were associated with elevated PWV. The usefulness of baPWV in the detection of diabetic changes was investigated in [27] and indicated that baPWV may be a convenient, noninvasive, and reproducible method for detecting early diabetic nephropathy. In [28] was shown that baPWV is associated with plasma fibulin-1 level in patients with asymptomatic hyperuricemia. A positive association between baPWV and white blood cells counts in patients with hypertension was revealed in study [29]. In addition to the classic cfPWV measurement and the more peripheral baPWV [24], studies of other indicators of arterial stiffness are being undertaken, such as the measurement of heart-femoral PWV (hfPWV) [30] or completely new assessment methods that correlate with PWV, such as neutrophil-to-lymphocyte ratio (NLR) [31]. Research is growing in the field of PWV's algorithms as well. In [32] various methods of coronary PWV determination in anesthetized pigs were examined. The tangent intersection method applied to the backward waves and template matching method has been shown to be the most appropriate for clinical studies. Machine learning (ML) algorithms used to measure the PTT and PWV by analyzing PPG signal waves acquired by a digital camera recording two regions were presented in [33]. In [34] was presented an approach using ML pipelines to estimate the cfPWV from the peripheral pulse wave measured at a single site (e.g. the radial pressure wave). Once more, a solution where cfPWV is combined with crPWV

and ML for estimating aortic characteristic impedance and arterial compliance is presented in [35]. All these above-mentioned studies indicate the need for further work in the field of PWV.

PWV can be measured by several techniques: invasive methods, applanation tonometry, cuff-based oscillometry, magnetic resonance imaging, photoplethysmography, using piezoelectric mechanotransducers and ultrasound techniques. An overview of the above-mentioned techniques has been described in previous works [36–39]. The invasive technique is the most accurate, is considered as the gold standard but its use is very limited, usually only during an angiography procedure. The most commonly used and developed methods are non-invasive. Several commercial devices using non-invasive techniques are available and largely used worldwide: SphygmoCor CvMS-PWV, SphygmoCor XCEL, PulsePen, Complior, Arteriograph, Vicorder. Also, there are known non-commercial solutions as custom or individual designs. An approach based on two multiplexed fiber-optic Fabry-Perot interferometric sensors was presented in [40], based on a piezoelectric sensor array in [41], magnetic transducers in [42,43], MEMS-based sensors (pressure and accelerometer) in [44–46]. A combined phonocardiographic (PCG), impedance cardiographic (ICG), electrocardiographic (ECG) and PPG approach was presented in [47]. A method based on ECG and two blood pressure measuring cuffs was presented in [48]. An aortic PWV measurement may be also realized by inductive plethsymography [49]. For easy-to-use PWV measurement miniaturized handheld laser Doppler vibrometer arrays in silicon photonics platform was presented in [50].

Photoplethysmography technique is extensively used in pulse oximetry and for determining other cardiovascular parameters [51,52]. A PPG sensors are usually placed in one site or in multi-site simultaneously [53,54]. Photoplethysmography can be used for PWV assessment as a non-invasive, inexpensive and easy-use technique also. For PWV measurement it requires two sensors, placed in different sites and containing a light source (usually a LED diode) and a photodetector (usually a photodiode). Examples of use of PPG sensors for PWV measurement are known in the literature. In [55] was presented a device called pOpmètre containing a PPG sensor positioned on the finger and the toe. PWV was calculated using pulse transit time (PTT) between the toe and the finger. The distance covered by the pulse was estimated using subject height. A similar solution was used in [56] but the distance was the difference between the distance measured from the sternal notch to the toe and from the sternal notch to the finger. In [57] a custom probe was presented containing two PPG sensors placed at constant distance of 23 mm. The probe was tested on the carotid artery. For PWV assessment a local PTT was used (i.e. between two PPG sensors on the probe). A low cost measurement system for local PWV assessment was presented in [58]. It consist two PPG sensors placed at radial artery (at wrist). In [59] was presented an approach using two synchronized, wireless reflectance PPG sensors placed on the wrist and finger of the same hand at a constant distance of 224 mm. A local PWV can be also assessed with the multi-photodiode array technique [60]. There are also examples of calculating the PWV based on the time delay between the peak of the ECG R wave and the foot of the PPG pulse wave [61–63]. In [64] was presented a concept of a new method to approximate central PWV based on pulse arrival time (PAT) segmentation into cardiac isovolumic contraction and vascular PTT. PAT refers to the interval between the ECG R-peak and the systolic foot identified in a peripheral pressure waveform, typically acquired by a PPG sensor. The paper [33] describes the development and evaluation of a new contactless cardiovascular monitor, which can measure PTT and PWV by analyzing the PPG signal obtained by an RGB camera's green channel.

In this article we present a measure method and obtained results of simultaneous and continuous PWV measurement using seven PPG sensors placed on many sites of the body. According to the authors' knowledge, this is the first paper presenting the validation of a synchronous and multi-site PWV measurement using PPG signals. This article is continuation of our preliminary work presented in [65].

2. Materials and methods

2.1. Multi-site measurement system

For multi-site arterial pulse wave velocity measurements, we used a custom made system called MPPT. The MPPT is a precise, multi-site system for the simultaneous, real-time, synchronous measurement of photoplethysmographic and electrocardiographic signals as well as simultaneous NiBP (non-invasive blood pressure) pressure assessment. This system was described in detail in [66]. It was validated with the Fluke ProSim 8 patient simulator. For multi-site PWV measurement, we used 7 PPG sensors as shown in the MPPT configuration diagram (Fig. 1). Also localization of the SphygmoCor XCEL sensors (tonometer and cuff on right body site) is shown in Fig. 1.

A significant problem in simultaneous measurement of many signals is data synchronization. As described in detail in [66], all PPG channels use the same AFE (analog-front-end) i.e. AFE4490 by Texas Instruments. The clock input of all these AFEs was connected to the common central clock of the microprocessor system. Therefore, the PPG data synchronization error is less than one sampling period. The circuits of the AFE applied include a LED driver, a transimpedance amplifier for a photodiode and a high-resolution 22-bit analog-digital converter. No filters (analog or digital) in the MPPT device were used.

The PPG sensors, manufactured by Unimed, were used i.e. transmission clamps on fingers, toes (type U410-01) and earlobes (type U910-01) and a reflectance sensor on the forehead (type U803-01V). Each of these sensors has one RED diode (wavelength 660 nm) and one IR diode (wavelength 905 nm). According the recommendations for validation of new devices, presented in [67], the MPPT sampling frequency has been increased to 1 kHz. The MPPT device was connected to a computer via a galvanic separation USB interface. Dedicated computer software was responsible for control, online data transfer and visualization of raw (unprocessed) signals as well as data archiving. Signal processing and calculation of PWV was performed after completed measurements (offline mode).

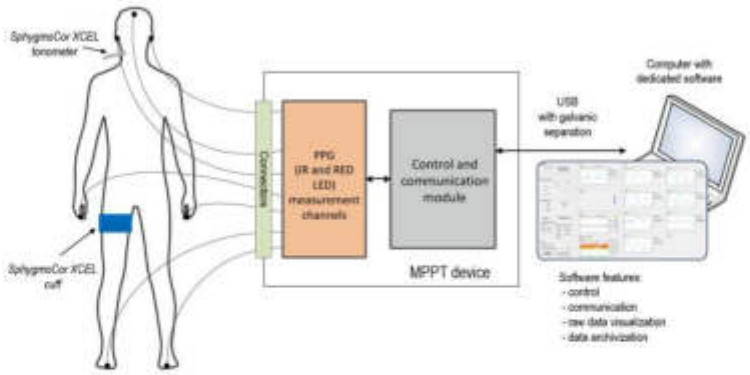

Fig. 1 – Block diagram of MPPT system configured for multi-site PWV measurement (with SphygmoCor XCEL sensors).

2.2. *Reference devices*

The reference PWV measurement (marked as cfPWV) was performed with a SphygmoCor (XCEL version) device by ATCOR. The SphygmoCor has been validated as per the ARTERY PWV validation guidelines [67–69] and it is most widely used and considered as the noninvasive gold standard technique. The SphygmoCor XCEL device simultaneously acquires a carotid pulse through applanation tonometry and femoral pulse by volumetric displacement within a cuff around the upper thigh [70]. Then, the device calculates the pulse transit time (cfPTT) between the feet of the carotid and femoral pulse. The path length (distance) to determine cfPWV was obtained with the subtraction method. The single measurement recording time was 10 s. For each subject (person) we performed usually three or more cfPWV measurements with an interval of approximately 3 min. We reported the cfPWV as the median of the measurements.

2.3. *Study population*

The study population meets the required criteria specified in [67]. Characteristics of the study group are shown in Table 1.

2.4. *Path length measurement*

Due to the short pulse transit time in the vessels, the correct determination of the path length is of great importance for the PWV measurement result. The basic rule is to determine the length of the blood flow path between two measurement sites. The direction of the blood flow should also be taken into account. Various methods of determining the path length are known and it is described in detail in the [71,72]. As recommended in [67], in our validation work we used the subtraction method. For path length determination we defined some distances as shown in Fig. 2.

In the reference measurement (cfPWV) with the use of SphygmoCor XCEL, the path length (d_{SC}) was calculated according to operator's manual (Revision 4.0):

$$d_{SC} = d_2 - d_1 - d_3 \quad (1)$$

where:

d_1 – distance from the carotid artery measurement site (on the neck) to the sternal notch,
d_2 – distance from sternal notch to the top edge of the femoral cuff,
d_3 – distance from femoral artery to the top edge of the femoral cuff.

Table 1 – Characteristics of the study group.

Variable	Mean (SD) [Min–Max] or number
Number of subject	108
Sex, male/female	56/52
Age, years old	48 (21) [20–91]
<30 years group	31
30–60 years group	42
>60 years group	35
Height, cm	171 (12) [146–196]
Weight, kg	72.6 (12.0) [46–100]
Body Mass Index - BMI, kg/m^2	24.8 (2.5) [18.4–30.0]

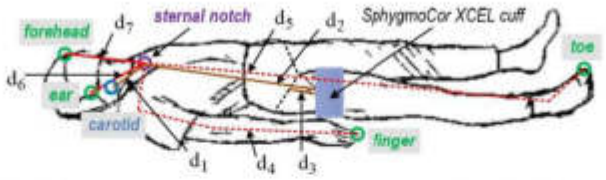

Fig. 2 – The distances used to calculate the PWV in the SphygmoCor XCEL (d_1, d_2, d_3) and the MPPT system (d_4, d_5, d_6, d_7).

All the distances were obtained directly with a tape measure with a reading accuracy of ±0.5 cm.

Multi-site PWV calculation required several other distance measurements. As for the SphygmoCor XCEL device, the starting point was the sternal notch. Moreover, we assumed that the distance between the sternal notch and the left or right measurement point is the same. The distances were measured with a tape, in a straight line (ear – d_6, forehead – d_7) or a broken line (finger – d_4, toe – d_5):

d_4 – distance from the sternal notch to the center of the PPG sensor placed on the right finger, obtained as sum of the three lines (as shown in Fig. 2),
d_5 – distance from the sternal notch to the center of the PPG sensor placed on the right toe, obtained as sum of the two lines (as shown in Fig. 2),
d_6 – straight line distance from the sternal notch to the center of the PPG sensor placed on the right ear,
d_7 – straight line distance from the sternal notch to the center of the PPG sensor placed on the center of the forehead.

The path length for PWV measurements in MPPT were defined as:

d_{htT} - path length for MPPT forehead-toe PWV (htPWV),
d_{ET} - path length for MPPT ear-toe PWV (etPWV),
d_{FT} - path length for MPPT finger-toe PWV (ftPWV),

$$d_{htT} = d_5 - 1.9 \times d_7 \quad (2)$$

$$d_{ET} = d_5 - d_6 \quad (3)$$

$$d_{FT} = d_5 - d_4 \quad (4)$$

The real length of the blood vessels between the sternal notch and the sensor in the forehead is much bigger than the direct d_7 measurement. The d_7 shows the shortest path between the measurement points in a straight line, while the arteries, due to their flexibility and the location between other tissues of the body (muscles, tendons, bones), do not run in straight lines, but have a physiological tortuous location among other structures of the body and are therefore naturally longer. Therefore, for the calculation of d_{htT}, we proposed a length correction to $1.9 \times d_7$. This correction coefficient was selected experimentally on the basis of the obtained results. Path length results for our study group are shown in Table 2.

Table 2 – Characteristics of the path length.

Parameter	Mean (SD) [Min–Max]
d_{SC}, cm	50.1 (3.7) [42.0–62.0]
(d_{SC}/height) × 100, %	29.4 (2.1) [25.3–36.4]
d_{htT}, cm	112.9 (8.9) [93.2–132.3]
(d_{htT}/height) × 100, %	66.1 (2.2) [59.2–71.6]
d_{ET}, cm	137.5 (9.9) [118.0–158.0]
(d_{ET}/height) × 100, %	80.5 (1.7) [76.8–86.8]
d_{FT}, cm	65.6 (5.6) [52.0–81.0]
(d_{FT}/height) × 100, %	38.4 (1.5) [34.4–42.0]

The shortest path lengths are for d_{SC} ([42.0–62.0] cm). It should be noted that the shorter the path, the greater the impact of accuracy of the distance on the PWV result. Therefore, all distance measurements were made with great care.

2.5. *The validation protocol*

108 volunteers were qualified for the validation studies. They had been informed of the purpose and procedure of the study before the measurements. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and has been approved by the Bioethics Committee at the National Institute of Geriatrics, Rheumatology and Rehabilitation in Warsaw (Doc number: KB 4/1/2017 and KB 1/9/2019). Before inclusion in the study, all the participants were made to provide a written informed consent.

The tests were carried out during the day, in a separate and quiet room, at about 22–24 °C. Measurements were made in the supine position after about 15 min of supine rest on a medical settee (height 75 cm). It should be stressed that the reference measurements with the SphygmoCor XCEL (cfPWV) device were performed simultaneously with the measurements with the MPPT device, as shown in Fig. 3.

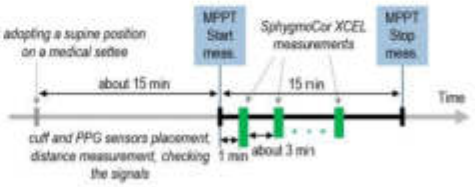

Fig. 3 – Timeline of the measurement protocol.

All measurements were performed by the same operator. The MPPT device measured the signals continuously for 15 min. The recording duration was adopted so that several cfPWV measurements could be performed. The PPG sensors were in the fixed sites. The number of cfPWV reference measurements depended on the quality of the signal obtained from the carotid artery (signal quality was shown by the SphygmoCor XCEL software). In some cases, it was difficult to get the required carotid signal quality. For one person, the cfPWV measurement was not correctly performed. This person was not included in the results of this study.

2.6. Signal processing

Signal processing only concern to the MPPT measurement system. As previously mentioned, signal processing and PWV calculation were performed offline, in MATLAB environment (version R2019a), after all 15-minute recordings had been completed. The primary goal of the signal processing algorithms was to indicate the onset of the pulse wave (Fig. 4), calculate the appropriate PTT times and then calculate the PWV.

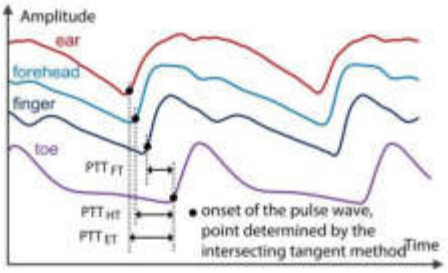

Fig. 4 – Sample of signals from PPG sensors and PTT delays for multi-site PWV calculation.

For PWV calculation we used PPG signals from IR diodes, because they usually have a greater amplitude than the signals from the RED diodes [73]. A Butterworth bandpass ([0.5–15] Hz) filter of order 4 was used to filter the PPG signals. Such a filter is a maximally flat magnitude filter that rolls off slower and without ripples around the cutoff frequency [52,74] which is especially important when determining the onset of the pulse wave. Each PPG signal was filtered with the same method and, in addition, zero-phase digital filtering was used ("filtfilt" function of the MATLAB). As a result, there were no delays between signals due to signal processing. After filtration, for each of the PPG signals (forehead, ears, fingers, toes), the onset of the pulses wave was determined using the intersecting tangent method [39,67,75].

Next, the pulse transit times were calculated between the forehead and toe (PTT_{HT}) for left and right leg, the ear and toe (PTT_{ET}) for left and right site and the finger and toe (PTT_{FT}) for left and right site. Multi-site PWVs were defined as:

$$htPWV = d_{HT}/PTT_{HT} \quad (5)$$

$$etPWV = d_{ET}/PTT_{ET} \quad (6)$$

$$ftPWV = d_{FT}/PTT_{FT} \quad (7)$$

where:

htPWV – pulse wave velocity calculated from the signals of the forehead and toe sensors,
etPWV – pulse wave velocity calculated from the signals of the ear and toe sensors,
ftPWV – pulse wave velocity calculated from the signals of the finger and toe sensors.

The applied signal processing takes approximately 0.4 s (Matlab 2019a, Core i7-3770K @3.5 GHz, 16 GB RAM) to calculate one PWV variant (e.g. forehead-toe) for a 15-minute PPG signal. Signal filtration and determination of onset points of the pulse wave takes the longest time (about 99% of the processing time).

2.7. Data analysis

The calculated multi-site PWV values are momentary values calculated for each heart beat. The final multi-site PWV (htPWV, etPWV, ftPWV) value was calculated for each subject as the mean of the 15-minute recording. Apart from the mean value, standard deviation was determined. Likewise, for each subject the average of the all SphygmoCor XCEL cfPWV readings was calculated and used in the subsequent analysis.

In order to compare the results reference PWV (cfPWV) and multi-site PWV values were determined for each subject. Subjects with the number of multi-site momentary PWV values smaller than 50 (in a 15 min recording) and SD >2 m/s were excluded from the analysis. The analysis of the results was performed using the Bland-Altman methodology and relationship (linear regression) between cfPWV and multi-site PWV for various PPG sensor variants. The linear equation (y) showing the relationship can be written generally as: $y = ax + b$, where a represents the slope and b intercept. For each of the analyzed multi-site variants, the values of a and b were determined. For the relationship, the Pearson correlation coefficient (r) and p-value (p) based on the "corrcoef" function of MATLAB were computed also.

In order to analyze the proportional bias, according to the recommendation [76], a linear regression line was fitted to the Bland–Altman plots.

3. Results

The obtained results are presented in the relationship and Bland-Altman plots with additional analysis of the proportional bias and summary in the table. The analysis of the proportional bias (PB) is marked on the Bland-Altman plots with the red lines (the relationship line is marked in thick, the 95 % prediction interval is marked thin). In the presented below, the symbols mean:

n – number of valid data pairs	SD – standard deviation
r – Pearson correlation	CV – coefficient of
RMSE – root mean squared error	variation (SD of mean
y – relationship linear equation	values in %)
	PB – proportional bias

3.1. Comparison between cfPWV and forehead - right toe htPWV (variant no. 1)

In this variant, signals from PPG sensors placed on the forehead and right toe were processed. htPWV was calculated based on Eq. (5). The results are shown in a relationship plot (Fig. 5a) and a Bland-Altman plot (Fig. 5b).

3.2. Comparison between cfPWV and forehead - left toe htPWV (variant no. 2)

In this variant, signals from PPG sensors placed on the forehead and left toe were processed. htPWV was calculated based on Eq. (5). The results are shown in a relationship plot (Fig. 6a) and a Bland-Altman plot (Fig. 6b).

3.3. Comparison between cfPWV and right ear - right toe etPWV (variant no. 3)

In this variant, signals from PPG sensors placed on the right ear and right toe were processed. etPWV was calculated based on Eq. (6). The results are shown in a relationship plot (Fig. 7a) and a Bland-Altman plot (Fig. 7b).

3.4. Comparison between cfPWV and left ear - left toe etPWV (variant no. 4)

In this variant, signals from PPG sensors placed on the left ear and left toe were processed. etPWV was calculated based on Eq. (6). The results are shown in a relationship plot (Fig. 8a) and a Bland-Altman plot (Fig. 8b).

3.5. Comparison between cfPWV and right ear - left toe etPWV (variant no. 5)

In this variant, signals from PPG sensors placed on the right ear and left toe were processed. etPWV was calculated based on Eq. (6). The results are shown in a relationship plot (Fig. 9a) and a Bland-Altman plot (Fig. 9b).

3.6. Comparison between cfPWV and left ear - right toe etPWV (variant no. 6)

In this variant, signals from PPG sensors placed on the left ear and right toe were processed. etPWV was calculated based on Eq. (6). The results are shown in a relationship plot (Fig. 10a) and a Bland-Altman plot (Fig. 10b).

3.7. Comparison between cfPWV and right finger- right toe ftPWV (variant no. 7)

In this variant, signals from PPG sensors placed on the right finger and right toe were processed. ftPWV was calculated based on Eq. (7). The results are shown in a relationship plot (Fig. 11a) and a Bland-Altman plot (Fig. 11b).

3.8. Comparison between cfPWV and left finger- left toe ftPWV (variant no. 8)

In this variant, signals from PPG sensors placed on the left finger and left toe were processed. ftPWV was calculated based on Eq. (7). The results are shown in a relationship plot (Fig. 12a) and a Bland-Altman plot (Fig. 12b).

Based on the graphs presented above, it can be seen that for each of the variants similar results were obtained. Table 3 summarizes these results. Table 3 also shows the results for variants where the distal PPG sensor was placed on the head (ear or forehead) and the proximal PPG sensor was placed on the finger (variants no. 9–12).

For these variants, the correlation coefficient r has a very small value which may indicate a lack of correlation with the cfPWV. This matter is considered in the Discussion section.

A high value of the Pearson correlation coefficient (r) was obtained (variants no. 1–8). It ranges from 0.66 to 0.79. The RMSE error is ≤0.8 m/s for variants no. 1–6 and the maximum is 1.34 m/s for variant no. 8. For our results, the linear regression parameter a is in the range [0.52–0.85] and the parameter b is in the range [0.45–3.8]. The mean difference between

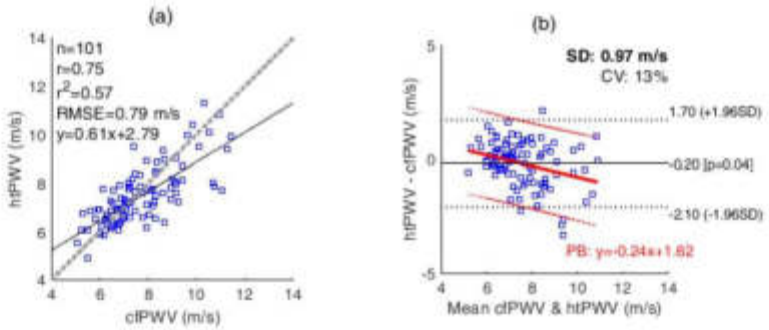

Fig. 5 – Relationship (a) and difference (b) between carotid-femoral PWV (cfPWV) and MPPT device PWV (htPWV). MPPT measurement site: forehead - right toe.

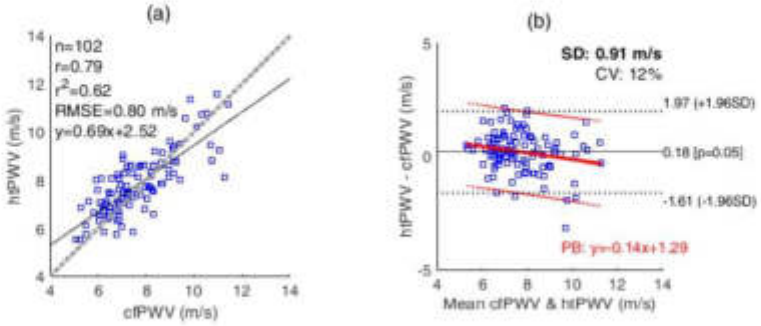

Fig. 6 – Relationship (a) and difference (b) between carotid-femoral PWV (cfPWV) and MPPT device PWV (htPWV). MPPT measurement site: forehead – left toe.

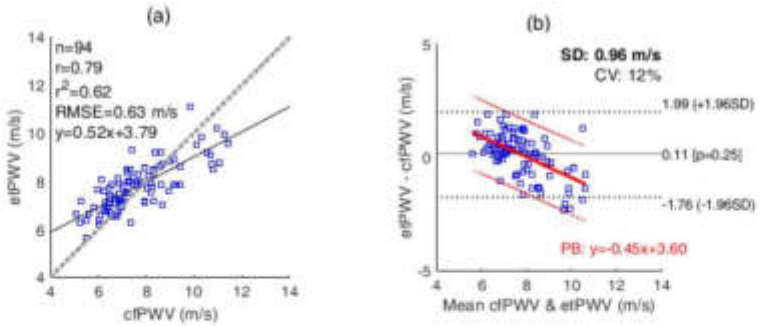

Fig. 7 – Relationship (a) and difference (b) between carotid-femoral PWV (cfPWV) and MPPT device PWV (etPWV). MPPT measurement site: right ear - right toe.

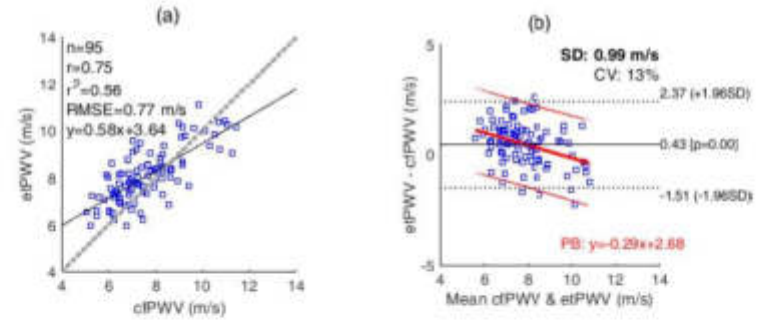

Fig. 8 – Relationship (a) and difference (b) between carotid-femoral PWV (cfPWV) and MPPT device PWV (etPWV). MPPT measurement site: left ear - left toe.

cfPWV and multi-site PWV is within the range [0.11–0.95] and it is the smallest for variants no. 3 and 6 and the highest for variant no. 7. Standard deviation (SD) is <1 m/s for variants no. 1–6 and <1.4 m/s for variants no. 7 and 8. The variability of the obtained results of PWV measurement, represented by the coefficient of variation (CV), is ≤13% for variants no. 1–6 and ≤19% for variants no. 7 and 8.

The most important parameters for validating of the new device are mean difference and SD [67]. The PWV results for our MPPT device obtained, for each of the variants (no. 1–8)

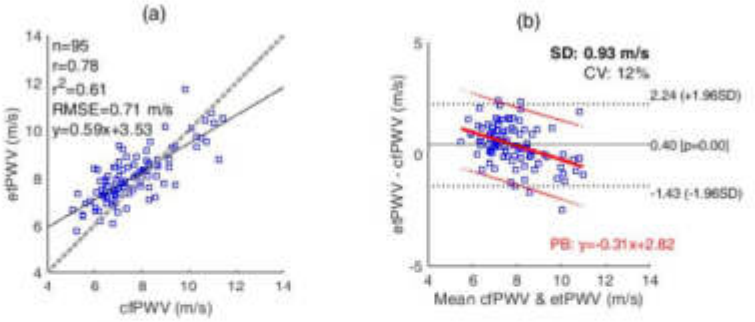

Fig. 9 – Relationship (a) and difference (b) between carotid-femoral PWV (cfPWV) and MPPT device PWV (etPWV). MPPT measurement site: right ear – left toe.

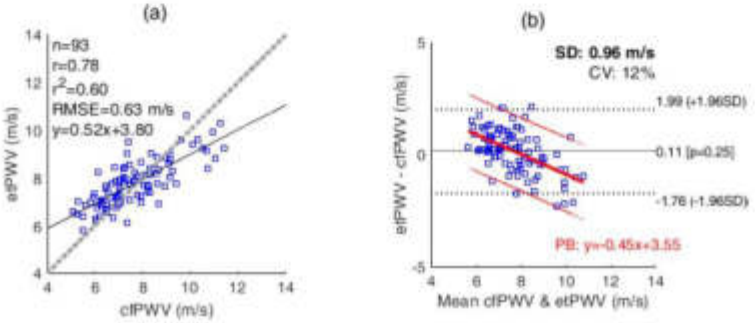

Fig. 10 – Relationship (a) and difference (b) between carotid-femoral PWV (cfPWV) and MPPT device PWV (etPWV). MPPT measurement site: left ear - right toe.

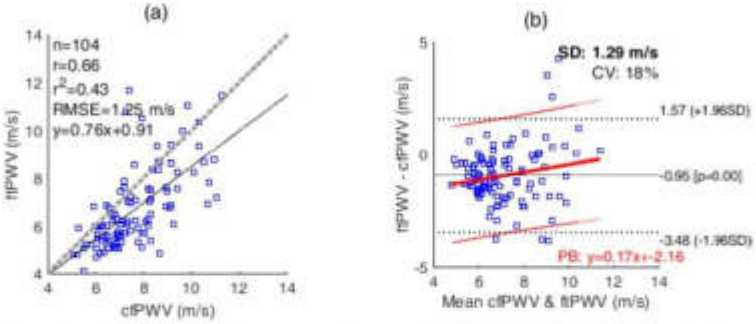

Fig. 11 – Relationship (a) and difference (b) between carotid-femoral PWV (cfPWV) and MPPT device PWV (ftPWV). MPPT measurement site: right finger - right toe.

meet the accuracy criteria at the level of Acceptable (mean difference <1.0 m/s and SD ≤1.5 m/s).

In order to increase the accuracy of the measurement, it is also possible to average the PWV results obtained from selected variants. The mean PWV obtained after averaging the results from variants no. 1–6 are shown in Fig. 13 (a - relationship plot, b - Bland-Altman plot).

After the averaging of the results from variants no. 1–6 (msaPWV), a higher value of the correlation coefficient (r = 0.89), a smaller mean difference (0.12) and a smaller stan-

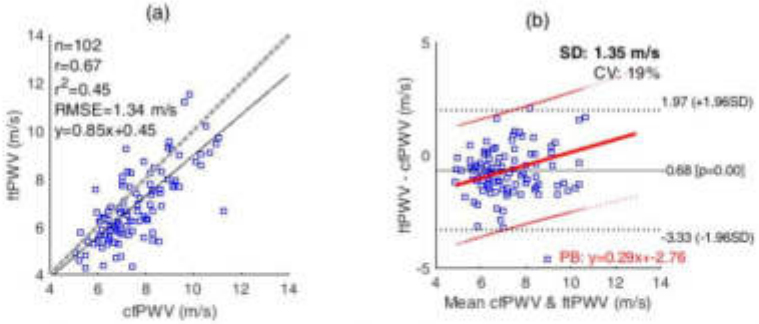

Fig. 12 – Relationship (a) and difference (b) between carotid-femoral PWV (cfPWV) and MPPT device PWV (ftPWV). MPPT measurement site: left finger - left toe.

dard deviation (SD = 0.72) were obtained. This result, in relation to the obtained numerical values, meets the requirements of "excellent" accuracy level with reference cfPWV (according to [67]). However, the measured arterial tree in msaPWV differs from the central cfPWV and these results should require commentary. More about this was considered in the Discussion section.

4. Discussion

4.1. *Reference PWV measurement*

In our study, the SphygmoCor XCEL device was used for the reference PWV measurement, similarly to the other works. To the SphygmoCor as reference the oscillometric technique (the Arteriograph [16], Vicorder [77] and Mobil-O-Graph [78] devices) and piezoelectric mechanotransducer (the Complior [79] and Aortic [80] devices) were validated. Although the SphygmoCor device (the first CvMS-PWV version and newest - XCEL version) is commonly considered as the noninvasive gold standard, its PWV measurement method is different from that of the validated MPPT device. The SphygmoCor XCEL uses a tonometer on the carotid and a cuff on the femoral artery, whereas the MPPT device only uses the photoplethysmographic sensors. As far as the signal recorded by the tonometry technique is similar to that from the PPG technique [52,81,82], the auscultatory signal in the cuff (pressure changes in the cuff caused by the flowing pulse wave) is different from the PPG signal. Other methods of acquiring the signal of the validated reference device may cause slight differences in the obtained results. Moreover, it is obvious that each device has its own measurement error. However, the most important factor influencing the obtained differences in the results is different location of the sensors (measurement site). In the case of SphygmoCor, these sites were the right carotid artery (proximal site) and the right femoral artery (distal site). For the MPPT device, the right ear and forehead were closest to the right carotid artery (distance from over a dozen to tens of cm), while the corresponding sensor for the right femoral artery was only on the right toe (distance of even 1 m). For this reason, the regional reference value (cfPWV) could differ from the regional PWV value measured by the MPPT device.

4.2. *Analysis of own PWV results*

According to the above remark, regarding the reference PWV measurement, it is worth noting that the best agreement with the reference cfPWV was achieved with the variant (no. 3) of the PPG sensor placed on the right ear and right toe ($r = 0.79$ and mean difference = 0.11 m/s). It should be noted, that the greatest dispersion of MPPT PWV measurements was obtained for variants no. 7 and 8, in which the PPG sensor was placed on the fingers and toes. For these variants, the lowest values of the correlation coefficient r and the highest RMSE, mean difference and SD were obtained. Concurrently, for these variants, the highest value of the slope (a) and the smallest value of the intercept (b) describing the relationship linear equation (y) were obtained. These results show that fingers and toes can be good and easy-to-use sites for measurements with PPG sensors (like [55]). Moreover, for fingers and toes we can use widespread transmission pulse oximeters clamps.

As shown in Table 3, for variants no. 9–12, in which the distal PPG sensor was placed on the head and the proximal PPG sensor was placed on the finger, no correlation was obtained between the measured PVW and the reference cfPWV. It should be noted that for these variants the measurement of the arterial path does not include the central arterial path used by the SphygmoCor XCEL. Moreover, the lack of correlation can be explained by the physiology of the arteries because the results from variants no. 9–12 mostly cover the velocity in the peripheral arteries - physiologically built of muscles, not the central arteries which are elastic. As regards the physiological blood flow and vascular structure - cholesterol and calcium deposits are mainly deposited in large, elastic arteries made of fibers, which also explains the greater difference in velocity in these arteries than in less stressed peripheral arteries made up mainly of muscles.

In relation to the physiological context, the measurements consistent with the cfPWV (assessing PWV predominantly in the elastic central artery - the aorta) are measured with the

Table 3 – Summary of comparison between cfPWV and MPPT multi-site PWV measurement.

Variant no.	PPG sensor localization	n	r	RMSE [m/s]	relationship linear equation	Mean difference	p-value	SD [m/s]	CV [%]	Accuracy level [67]
1	forehead - right toe	101	**0.75**	0.79	y = 0.61x + 2.79	**0.20**	0.04	**0.97**	13	Acceptable
2	forehead - left toe	102	**0.79**	0.80	y = 0.69x + 2.52	**0.18**	0.05	**0.91**	12	Acceptable
3	right ear - right toe	94	**0.79**	0.63	y = 0.52x + 3.79	**0.11**	0.25	**0.96**	12	Acceptable
4	left ear - left toe	95	**0.75**	0.77	y = 0.58x + 3.64	**0.43**	0.00	**0.99**	13	Acceptable
5	right ear - left toe	95	**0.78**	0.71	y = 0.59x + 3.53	**0.40**	0.00	**0.93**	12	Acceptable
6	left ear - right toe	93	**0.78**	0.63	y = 0.52x + 3.80	**0.11**	0.25	**0.96**	12	Acceptable
7	right finger- right toe	104	**0.66**	1.25	y = 0.76x + 0.91	**0.95**	0.00	**1.29**	18	Acceptable
8	left finger- left toe	102	**0.67**	1.34	y = 0.85x + 0.45	**0.68**	0.00	**1.35**	19	Acceptable
9	right ear - right finger	92	**0.06**	1.37	y = 0.05x + 9.28	**2.02**	0.00	**1.98**	23	Poor/no correlation
10	left ear - left finger	89	**0.12**	1.37	y = 0.11x + 9.08	**2.21**	0.00	**1.91**	23	Poor/no correlation
11	forehead - right finger	101	**0.01**	1.90	y = 0.01x + 9.48	**1.94**	0.00	**2.39**	28	Poor/no correlation
12	forehead - left finger	94	**0.01**	1.58	y = 0.01x + 9.98	**2.27**	0.00	**2.16**	25	Poor/no correlation

n – number of valid data pairs (sample size); r – Pearson correlation; RMSE – root mean squared error; SD – standard deviation, CV – coefficient of variation (SD of mean values - relative standard deviation - in %).

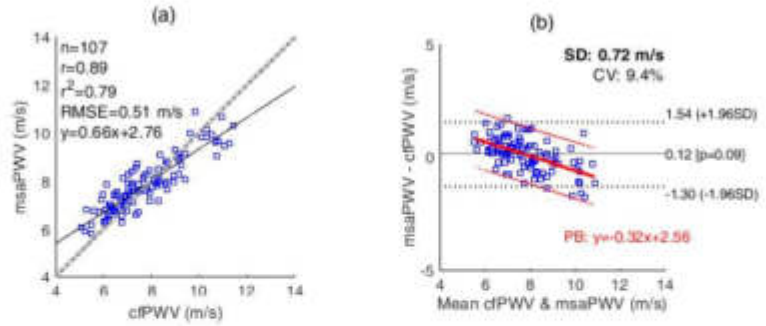

Fig. 13 – Relationship (a) and difference (b) between carotid-femoral PWV (cfPWV) and average MPPT device PWV (msaPWV). msaPWV is the mean of variants no. 1–6.

MPPT device for variants no. 1–6. This is consistent to a lesser extent for variants no. 7–8 because these variants contain a connection of peripheral flow in the entire upper limb (peripheral - mainly muscular arteries, then from the brachial - elastic) as well as the flow in the aorta (elastic). In contrast, variants no. 9–12 measure mainly PWV in peripheral arteries with a naturally different physiological structure. Therefore, the measurement method where PPG sensors are only on the head and finger (variants no. 9–12) should not be used to assess the central PWV.

Another important issue observed in the Bland-Altman plots is the proportional bias, i.e. the difference from the reference value depends on the value of the mean value. This effect shows up for variants no. 1–8 (in the Figs. 5 to 12) and is most evident for variants no. 3,5,6 (in Fig. 7,9 and 10). For variants no. 1–6, the Bland-Altman plots highlighted a negative proportional bias, showing an underestimation of the measured PWV at the highest PWV values. However, for variants 7 and 8, Bland-Altman plots highlighted a positive proportional bias, showing an overestimation of the measured PWV at the highest PWV values. The negative proportional bias occurs in variants where the proximal PPG sensor was placed on the head and the distal PPG sensor on the toe. This is because arterial stiffness arises primarily in the aorta and large arteries, and to a small extent in muscular arteries. For variants no. 1–6 there is a long common arterial path, i.e. the d_2 (see Fig. 2) is within the d_5, so between the cuff on the femoral artery and the toe there are increasingly thinner peripheral arteries and, finally, only muscular arteries. Thus, in these variants there was an underestimation of the measured PWV compared to the cfPWV. For variants no. 7–8 there is also a long common path, (the d_2 is within the d_5), but there is also a long d_4 path with peripheral arteries. In this case, the length of the peripheral arteries path is greater than that of the central ones, so in these variants there was an overestimation of the measured PWV compared to the cfPWV. Small PWV indicates low arterial stiffness, low cardiovascular risk and low risk of atherosclerosis. If there is no atherosclerosis and cholesterol does not accumulate in the central arteries, it will not be deposited in the peripheral arteries that build muscle tissue. Other values, higher for close to central measurements (variants no. 1–6), lower for peripheral (variants no. 9–12) are physiologically explainable by the structure of the arteries - naturally greater stiffness of the arteries with an elastic structure.

Next issue in the multi-site PWV measurement is averaging the results obtained from different sites. The basic criterion for selecting PWV results for averaging were similar sites of the proximal PPG sensors and similar sites of the distal PPG sensors. This is important as the PWV values may vary depending on the measurement site [83,84]. Another criterion was to obtain a similar arterial path as for the reference device. Note that the forehead/ear-to-toe arterial path includes the carotid-to-femoral path used by the SphygmoCor. For the above-mentioned reasons, only the variants where the proximal PPG sensor was placed on the head and the distal PPG sensor on the toe were taken into account (i.e. variants no. 1–6). Although our averaged results, in relation to the obtained numerical values, show an "excellent" accuracy level with the SphygmoCor they should be interpreted with caution. This is because the reference cfPWV is central and MPPT-based is central and muscular arteries PWV. For healthy young people, who usually have low PWV, the difference between central and peripheral PWV is small, whereas for older people (usually with a higher PWV) this difference will be greater. This can be seen in Fig. 15a), where SDavg represents the dispersion between the results. Therefore, the claim of excellence agreement is uncertain and cannot be accepted.

The applied averaging of the results allowed to determine the final proportional bias described by the equation (see Fig. 13b):

$$y = -0.32x + 2.56 \quad (1)$$

The Eq. (1) and Fig. 13 show that for small PWV there is a slight overestimation of the measured PWV with respect to cfPWV, while for large PWV there is an underestimation of the measured PWV with respect to cfPWV. This underestimation is disadvantageous because it occurs with the PWV range which that is more clinically relevant. The obtained Eq. (1) can be treated as a correction equation when calculating the PWV for each of the variants no. 1–6. Then the proportional bias will decrease while good compliance with cfPWV is main-

tained. Moreover, the slope (0.32) of the Eq. (1) can be taken as the quantitative contribution of peripheral stiffness of the legs to central arterial stiffness. However, in order to confirm this conclusion, studies on a larger group are necessary.

It is commonly known that PWV increases with age as a result of increasing vascular stiffness. The relationship between the msaPWV (after averaging variants no. 1–6) and age is shown in Fig. 14. Similar results were obtained also in the studies [62,85].

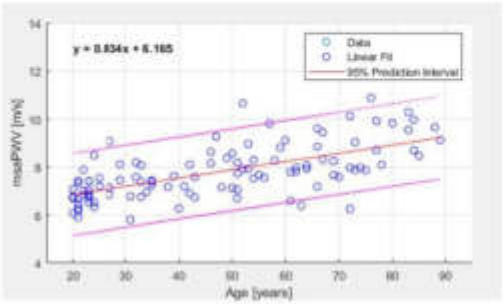

Fig. 14 – Relationship between the msaPWV and subject age.

The stiffness of the vessels may be unequal on the whole arterial tree. This can be manifested by larger differences between PWV measured at different sites. For our multi-site PWV results (variant no. 1–6) we calculated standard deviation (SDavg). The obtained SDavg results, depending on the age and cfPWV, are shown in Fig. 15.

The obtained plots confirm an increase in the spread between site-dependent PWV values with age (similar to the study [85]) or with a greater PWV value.

An important factor affecting the PWV result is also the measurement of the path length [71]. For example, if the pulse transit time is 125 ms, then for the path length measurement error of ±1 cm, the PWV measurement error is approx. ±0.1 m/s. However, for smaller PTT values (caused e.g. a larger PWV or shorter path length), the impact of the accuracy of the path length measurement on the PWV is even greater. For example, for PTT = 50 ms and path length error equal ±2 cm, the PWV measurement error is ±0.4 m/s. Thus, the shorter the path length or the smaller the expected PTT time, the more attention should be paid to the accuracy of the path length measurement. The error in measuring the path length is influenced not only by the accuracy of the reading from the measuring instrument (e.g. a tape measure) but also by the body surface variability, which is particularly important for people with an increased BMI index.

Although 108 subjects participated in the study (see Table 1), the number of valid data pairs (n) is smaller for each of the variants (see Table 3). The main reason for this is that the quality of the PPG signals was not always good enough. This sometimes occurred for ears where the PPG signals obtained were usually of too low amplitude and low perfusion index. However, in each variant, the minimum sample size required by the recommendations [67] was met. In the photoplethysmography method, it should be taken into account that besides the measurement site, the PPG signal is influenced by external factors that may reduce its quality, e.g. ambient light, nail polish, sensor pressure, poor perfusion and motion artifacts [86,87]. Moreover, regardless of the measuring apparatus, PPG signals are characterized by a quasi-periodic course. The repeating "pulses" may naturally differ from one another. Additionally, skin temperature can significantly affect the value of the PPG signal. The above-mentioned factors are a limitation of the PWV measurement using photoplethysmography.

4.3. *Comparison with other related works*

Comparison of the other devices validation results was shown in Table 4. For an appropriate comparison under similar measurement conditions, the studies with SphygmoCor as reference PWV measurement were shown. We used the newest version of SphygmoCor XCEL to validate our MPPT device. It is a version compatible with the previous one using the ECG signal [68,69].

In the presented related works, a different number of subjects were examined, in study [89] and [79] even more than in our case, however only our and for Aortic devices [80] study subjects respected requirements ARTERY recommendation [67]. The best agreement ("excellent" accuracy level according recommendation [65]) was only obtained for the piezoelectric mechanotransducer (for Aortic [78] and Complior [77] devices). It is worth noting, that this sensor is differ then the PPG. Some of the other studies ([46,89,92]) listed in Table 4 showed a high correlation coefficient (similar to MPPT) also, but the level of accuracy according to [65] was lower or not assessable.

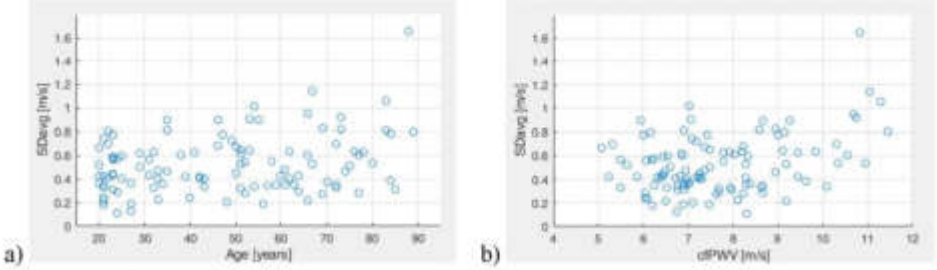

Fig. 15 – The relationship between the SDavg and subject age (a) and cfPWV (b).

Table 4 – Validation results of the other devices with SphygmoCor as reference.

Device	Meas. method used in device	Reference device	No of subjects	Age/Age ranges	Multi-site	Mean PWV difference	r	Accuracy level according [67]	Reference, year
MPPT (our design)	PPG	SphygmoCor (cuff based - XCEL)	108	48 ± 21 [20–91]*	Yes	[0.11–0.95][b] ± [0.91–1.35][b]	[0.66–0.79][b]	acceptable (for all valid variants)	this work
Athos	MEMS force sensors	SphygmoCor (ECG-gated)	10	45 ± 14 [21–63]	No	0.2 ± 0.34	0.93	not assessable	[46], 2021
pOpmètre	PPG	SphygmoCor XCEL	24	5.9 ± 1.4 [4–8]	No	0.36 ± 0.96	NA	not assessable	[88], 2020
Mobil-O-Graph	Cuff-based oscillometry	SphygmoCor (ECG-gated)	234	53 ± 10 [27–78]	No	NA	0.58	not assessable	[89], 2019
			83	50 ± 13 [20–80]	No	0.6 ± 1.3	0.39	acceptable	[78], 2012
pOpmètre	PPG	SphygmoCor (ECG-gated)	101	59 ± 15 NA	No	0.35 ± 0.8	0.76	acceptable	[90], 2017
			86	53 ± 20 NA	No	0.22 ± 2.46	0.43	poor	[55], 2015
Aortic	Piezoelectric mechaniotransducer	SphygmoCor (ECG-gated)	85	46 ± NA [18–80]*	No	0.02 ± 0.84	0.89	excellent	[80], 2015
Complior	Piezoelectric mechanotransducer	SphygmoCor (ECG-gated)	112	47 ± 15 [16–83]	No	0.0 ± 0.7	0.93	excellent	[79], 2014
Arteriograph	Cuff-based oscillometry	SphygmoCor (ECG-gated)	63	48 ± 15 [20–69]	No	1.1 ± 2.05	0.54	not assessable	[16], 2014
			33	54 ± 15 [24–85]	No	1.3 ± 2.75	NA	not assessable	[91], 2011
Vicorder	Cuff-based oscillometry	SphygmoCor (ECG-gated)	30	65 ± 8 NA	No	0.01 ± 0.54	0.67	not assessable	[92], 2013
Mobil-O-Graph	Cuff-based oscillometry	SphygmoCor (ECG-gated)	83	50 ± 13 [20–80]	No	0.6 ± 1.3	0.39	acceptable	[78], 2012

NA – not available.
* – respected requirements for three age groups (<30, 30-60, >60) [67].
b – for detail see Table 3.

Due to the measurement method, which uses PPG signals, the most similar to the MPPT device is the pOpmètre [90]. However, pOpmètre only measures one PWV value based on two PPG sensors (finger and toe). Our MPPT device used seven PPG sensors located in many sites on the body (forehead, ears, fingers, toes). Thanks to this, we can obtain several PWV results simultaneously or we can use sensors only in selected sites, e.g. ear-toe. We can also perform averaging the results. However, it should be noted that there is some limitation on PPG sensor placement. The PPG signals received from the fingers, toes, and forehead are usually of appropriate amplitude and have a high perfusion index, while PPG signals obtained from the earlobes often have low and variable amplitude and low perfusion index. However, to obtain a better PPG signal from the ear, a different sensor design could be used, e.g. similar to the E1® Ear Sensor from Masimo which is placed securely in the cavum conchae (the deep hollow near the ear canal opening). Another limitation is that it is more difficult to put the sensor on the forehead than on the fingers, toes or ears. In addition, a reflectance sensor must be used on the forehead, which sometimes requires little tuning (i.e. repositioning the sensor).

As mentioned in the Introduction, many studies are related to new PWV measurement methods. However, validation of those new solutions did not always done with the SphygmoCor as reference device. In [33] for validation of video-based PPG system a CARDIOS Dyna-MAPA + device was used. However, the results do not include the PWV values, only the Pearson correlation coefficient with the aortic PTT ($r = 0.77$). Also, the study was conducted with 36 subjects. In study [47] the combined ICG and PCG with multichannel reflective PPG device at the sternum was used to detect the PTT and PWV calculation. The study was conducted with 29 subjects and the results were validated with the Complior as reference device. The following results were obtained: $r = 0.88$, md = 1.1 m/s, SD = 2.39 m/s for cfPWV as reference and $r = 0.72$, md = 0.5 m/s, SD = 2.43 m/s for crPWV as reference. In study [48] a custom device with 4 cuffs (2 on the arms and 2 on the legs) was validated with a VaSera VS-1500 device. Authors studied 113 subjects and correlation between the two devices was of 0.93. Validation result of PPG-based multi photodiode array (MPA) with Biopac-system based on a PPG and ECG signals was presented in [60]. The 30 subjects participated in the study and were divided into two groups: young and old. The following results were obtained: $r = 0.94$, md = 2.2 m/s, SD = 1.22 m/s for young and $r = 0.83$, md = 2.6 m/s, SD = 0.46 m/s for old group. Although standard deviation is not very large, the value of mean difference is high. With our MPPT device more successful results were achieved. In study [63] a custom module with PPG finger and ECG sensor was validated with the Mobil-O-Graph for assessment of PWV for 80 subjects. Good results have been achieved ($r = 0.92$, md = 0.3 m/s), which indicate (similar to our MPPT device) that the measurement of PWV obtained from the PPG is a reliable method.

4.4. *Measurement site dependent PWV*

PWV is slightly different in the central - elastic and peripheral - muscular arteries. In addition to the classic cfPWV, the use of other measuring points is also explored. One of the most interesting is baPWV, which measures the longer arterial pathway and is a combination index reflecting the stiffness of the central and peripheral arteries. An Asian meta-analysis found that people with high baPWV had a 2.5-fold higher risk of cardiovascular events, a 2.6-fold higher risk of cardiovascular mortality, and a 1.7-fold higher risk of all-cause mortality than patients with low baPWV [24]. In a study conducted among untreated hypertensive patients, the PWV measurement was related to the parameters of LV remodeling and diastolic function [25]. Interesting conclusions can be drawn from studies conducted among people with diabetes, in which multivariate regression analysis showed that the strongest influence on baPWV was the level of hs-CRP and the duration of diabetes. It should be emphasized that diabetes leads to the destruction of both central (aortic atherosclerosis) and peripheral (nephropathy, retinopathy) vessels, therefore in this group of patients it seems important to examine the condition of the arteries throughout their course [27]. With regard to our MPPT device, the measurement of variants no. 7 and 8 can be considered a measurement similar to the baPWV, with the emphasis that these include even a longer component of peripheral vessels than the classic baPWV. Interesting recent reports on the prognostic effect of baPWV - according to Japanese guidelines, recognized as a study for the detection of vascular damage [93], suggest that clinical assessment of the prognostic value will be crucial in various PWV measurements made with our MPPT in different patient groups.

Several new PWV measurement sites are being tested in the MPPT. It should be emphasized that, in contrast to the classic cfPWV and the baPWV with a more peripheral component, the more central hfPWV seems to be an interesting indicator. The current findings indicate that acute changes in cfPWV are strongly associated with hfPWV [30]. The hfPWV may be a simple alternative to cfPWV in the indication of cardiovascular risk in clinical and epidemiological settings. The hfPWV is estimated from the Cardio-Ankle Vascular Index device (VaSera-1500) by combining phonocardiogram with pulse signals detected by thigh cuffs and is noninvasive measurement. The hfPWV can be automatically measured in an operator-independent manner with cuff-based systems.

In understanding and researching the influence of the measurement site on the PWV result, very useful can be the [94] study. The researchers created a database of pulse waves (PW) simulated by a computer to span a range of CV conditions, representative of a sample of healthy adults. Much attention was also paid to the analysis of PW in the entire arterial tree, i.e. also for the central and muscular arteries. The simulating photoplethysmogram PWs was also performed and issues related to the value of PWV were also discussed. A non-linear relationship between aortic PWV and the arterial stiffness index was also shown. This is especially noticeable for higher aortic PWV values. With regard to our results, this confirms that cfPWV may differ from PWV measured in other sites and other arterial path.

4.5. *Importance of PWV measurement*

Studies on the assessment of arterial stiffness appear to be an important value in predicting cardiovascular risk. The

attempt to compare the estimated cardiovascular risk assessed by PWV with other risk scales, e.g. the recognized SCORE scale, is noteworthy. For example, in the Polish population the calculated cfPWV cut-off point of 11.7 m/s allowed us to classify participants of the study as a high CVD risk group with optimal sensitivity and specificity [95]. When analyzing the parameters of arterial stiffness, one should critically look at the repeatability and reproducibility of the results and the dependence of their possible changes on the measured blood pressure [96]. Despite the studies discussed in the course showing an association of increased PWV with diseases that increase cardiovascular risk, single indicators should be critically assessed and their optimization should be sought - often by creating complex models. An example of the above is in the meta-analysis among patients with familiar hypercholesterolemia (FH) who do not show a significantly altered PWV compared to the control group. Meanwhile, a sub-analysis of studies in which there was intima-media thickness (IMT) is increased in FH patients when compared with controls [10]. The correlations between the increased PWV value and the severity of atherosclerosis assessed using the IMT value were also examined [97]. As well, arterial stiffness was compared parameters in the stratification of patients with peripheral arterial disease, where decreased ankle-brachial index is associated with an increase in cfPWV i decreased subendocardial viability ratio, indicating an important connection between the peripheral arteries and the coronary circulation. Pulse wave propagation is different with clogging peripheral vessels causing the pulse to return earlier wave towards the heart and affect its workload and perfusion [98]. Ambilateral peripheral PWA and PWV measurements are potential new clinical applications, beside duplex sonography, also to assess and monitor functions in non-physiologically altered vessels such as RCF radiocephalic fistula (RCF) [99].

In addition to PWV measurements performed with the use of dedicated devices, attempts are also made to measure it using magnetic resonance [18,100,101], Doppler echocardiography [30,85], or speckle tracking [20]. PWV measurements carried out with classical radiological techniques are already assessed in specific groups of patients. Reference values of carotid PWV for ultrafast ultrasound imaging stratified by sex and age were determined for the first time. Age, blood pressure (BP), and BMI were the dominant determinants of carotid PWV on ultrafast, ultrasound imaging, which should be considered in clinical practice [19]. Measuring carotid PWV using a single slice oblique-sagittal phase contrast MRI is a potential utility in assessment of carotid stiffness and evaluation of cerebroarterial aging and age-related neurovascular disorders [18].

Besides assessment of arterial stiffness PWV can also be used for BP estimation. In [102], an evaluation of the analytical model showing the relationship between BP and PWV was presented. The utility of the PWV measurement for continuous, cuffless, and noninvasive BP monitoring has been demonstrated. In [57] was shown that carotid local PWV and brachial BP were kind correlated ($r = 0.82$ for diastolic BP, $r = 0.69$ for systolic BP, $r = 0.83$ for mean arterial pressure). In the clinical application review [36] the authors indicate, that in recent years there have been tremendous technological advances in regional PWV-based approaches for cuffless evaluation of arterial BP parameters. In turn, interesting results are shown in study [103], where the PAT (determined from the PPG and ECG sensor) time was used for the BP estimation. The proposed model, based on deep learning approach, provided a highly accurate prediction of the systolic (mean difference 2.398 ± 5.623 mmHg) and diastolic BP (mean difference -2.497 ± 3.785 mmHg) compared to arterial line measurements. Note that, the PAT time is also related to the PTT used to calculate the PWV, therefore the PWV as measured by PPG technique can also be useful for continuous cuffless BP imputation.

In the future, apart from classic PWV measurements, other indicators are also sought that can predict an increase in vessel stiffness - such as molecular or genetic tests. Currently there are new studies of markers such as NLR with positive correlation with PWV and increased arterial stiffness [31]. The NLR is used as a marker of subclinical inflammation. It is calculated by dividing the number of neutrophils by number of lymphocytes, usually from peripheral blood sample, but sometimes also from cells that infiltrate tissue, such as tumor. Genome-wide association analysis of PWV traits provide new insights into the causal relationship between arterial stiffness and blood pressure [104]. In performed research it was possible to identify a new locus for arterial stiffness and successfully replicate an earlier proposed locus. PWV shares common genetic architecture with BP and coronary artery disease. BP causally affects PWV. Larger studies are required to further unravel the genetics determinants and effects of PWV [104].

The presented research shows that it is important to create new devices that measure the pulse wave velocity in a multifactorial and multifaceted way.

5. Conclusions

A novel photoplethysmographic device (named MPPT) providing measurement of multi-site pulse wave velocity has been presented. This device has been validated with carotid-femoral PWV using the SphygmoCor XCEL System. The reference cfPWV measurements were performed simultaneously with the MPPT device, which resulted in greater reliability of the validation study. In our study, each variant of multi-site PWV, in relation to the obtained numerical values, strongly correlates with cfPWV („acceptable" accuracy level according to the guide in [67]). However, it should be noted that, the measured MPPT-based PWV concerns the central and muscular part of the arterial tree while the cfPWV is only for the central one. For this reason, the obtained validation results should be interpreted with caution. Our analysis of the results showed that the impact of the contribution of the muscular arteries to the measured PWV can be approximately 30%. However, in order to confirm this finding, further studies are necessary.

The best results were obtained when the proximal PPG sensor was placed on the head (ear or forehead) and the distal PPG sensor on the toe. Placing the PPG sensors on the finger and toe is easier than on the ear or forehead, and usually provides more stable signals, but at the same time, lower correlation with reference cfPWV.

The use of a tonometer to PWV assessment requires a lot of operator experience. This is especially important for the new version of the SphygmoCor (XCEL version) where the correct signal from the carotid artery must be maintained during the inflation of the femoral cuff and next during the final measurement stage. The entire measuring process takes several dozen seconds. At this time, in some cases, there occurred carotid "hiding" and the signal was too small to complete the measurement. PWV measuring by photoplethysmographic method is easier, rapid and convenient for the patient. Moreover, PPG sensors can be placed in many sites at the same time, which provides greater freedom of their configuration and increases diagnostic possibilities. However, not all of these sensors need to be used at the same time. There must be at least two, but a greater number of sensors enables the simultaneous measurement of many PWV channels and averages the results, but it is not obligatory. Simultaneous measurement in the multi-site mode allows for the most reliable comparison of results obtained from different sites.

Photoplethysmography is a cheap, easy to use, and alternative method of pulse wave velocity measurement. Multi-site PWV measurements create new possibilities for the diagnostics of cardiovascular diseases.

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CRediT authorship contribution statement

Tadeusz Sondej: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Project administration, Funding acquisition. **Iwona Jannasz**: Validation, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing. **Krzysztof Sieczkowski**: Conceptualization, Software, Investigation, Resources, Data curation. **Andrzej Dobrowolski**: Conceptualization, Supervision, Project administration, Funding acquisition. **Karolina Obiała**: Data curation. **Tomasz Targowski**: Resources, Supervision. **Robert Olszewski**: Conceptualization, Investigation, Resources, Supervision.

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Publikacja 2: Relationship between the Central and Regional Pulse Wave Velocity in the Assessment of Arterial Stiffness Depending on Gender in the Geriatric Population.

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Relationship between the Central and Regional Pulse Wave Velocity in the Assessment of Arterial Stiffness Depending on Gender in the Geriatric Population

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Abstract: Artery stiffness is a risk factor for cardiovascular disease (CVD). The measurement of pulse wave velocity (PWV) between the carotid artery and the femoral artery (cfPWV) is considered the gold standard in the assessment of arterial stiffness. A relationship between cfPWV and regional PWV has not been established. The aim of this study was to evaluate the influence of gender on arterial stiffness measured centrally and regionally in the geriatric population. The central PWV was assessed by a SphygmoCor XCEL, and the regional PWV was assessed by a new device through the photoplethysmographic measurement of multi-site arterial pulse wave velocity (MPPT). The study group included 118 patients (35 males and 83 females; mean age 77.2 ± 8.1 years). Men were characterized by statistically significantly higher values of cfPWV than women (cfPWV 10.52 m/s vs. 9.36 m/s; $p = 0.001$). In the measurement of regional PWV values using MPPT, no such relationship was found. Gender groups did not statistically differ in the distribution of atherosclerosis risk factors. cfPWV appears to be more accurate than regional PWV in assessing arterial stiffness in the geriatric population.

Keywords: pulse wave velocity; arterial stiffness; cardiovascular risk; geriatrics; gender differences; photoplethysmography; multi-site PWV

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1. Introduction

In recent decades, we have seen an increase in life expectancy, but cardiovascular diseases (CVD) are still the leading cause of morbidity and mortality [1,2]. Cardiovascular risk (CVR) is a result of many interacting risk factors. Commonly recognized classical risk factors for CVD include age, previous family history of heart disease, and modifiable risk factors, such as hypertension, hyperlipidemia, smoking, diabetes, and obesity [3]. In most cases, these factors lead to the formation of atherosclerosis—the main cause of CVD. Atherosclerosis is a progressive process characterized by the collection of lipids, inflammatory cells, and fibrous elements in the walls of arteries, resulting in progressive narrowing and stiffening of the arteries [4]. Artery stiffness increases with age, which is why vascular aging is a risk factor for CVD [5]. An increase in arterial stiffness is a major cause of an increase in systolic blood pressure (SBP) and pulse, as well as a decrease in diastolic blood pressure (DBP) during the aging process [6].

1.1. Pulse Wave Velocity

The measurement of the pulse wave velocity (PWV) between the carotid artery and the femoral artery, which is defined as the carotid–femoral pulse wave velocity (cfPWV), is considered the gold standard for arterial stiffness assessment [7,8]. Over the years, cfPWV measurement has been used for the assessment of the risk of cardiovascular events in the population of healthy people. Patients with a specific disease entity were also assessed, and PWV was compared with other recognized CVR factors [9]. cfPWV has a predictive value for CVD that goes beyond traditional CV risk factors in the general population among patients with various diseases. It may also be useful to stratify the risk of atherosclerosis. Various studies have reported that PWV is a powerful predictor of CV events as well as all-cause mortality that may occur in the future [10].

In addition to the gold standard, which is cfPWV, other parameters resulting from pulse wave analysis (PWA) are often the augmentation index (Aix) or augmentation pressure (AG). AG, defined by the height of the late systolic peak (P1) above the inflection (P2), is the contribution that wave reflection makes to systolic arterial pressure. Aix is calculated as AG divided by pulse pressure (PP) $\times 100$ [7].

1.2. Regional Pulse Wave Velocity

As the function and diameter of arterial vessels decreases, the composition of the arterial wall changes from the central aorta towards the periphery; centrally, the center of a large elastic artery has an ultrastructure of concentric elastic lamellae, intersected by layers of connective tissue, which contain smooth muscle cells. This microstructure gradually disappears, and the increased content of smooth muscle cells in medium-sized and especially smaller vessels takes over [11]. Therefore, apart from the central pulse wave velocity, the importance of the newly examined element increases in the places of regional measurement, including, apart from the elastic aorta, also the greater part of the muscular arteries [12].

1.3. Cardiovascular Risk Factors

Epidemiological studies show that the average life expectancy of men is lower than that of women [13]. In aging adults, gender is considered a significant risk factor for occurrence and curing of CVD [14]. A study on Europeans aged 50 years and over emphasized that the main mortality risk factors were: older age, poor self-rated health, activities of daily living (ADL) deficits, male gender, lower cognition, comorbidity, and presence of depressive symptoms [15]. However, it has not been proven what exactly affects the frequency and the presence of classic risk factors for CVD, which is associated with increased mortality in older men. There is little research explaining why gender, regardless of other classic cardiovascular risk factors, can be a determining factor in life expectancy [16].

2. Materials and Methods

2.1. Design and Participants

The data were collected during the Geriatric Arterial Stiffness Measurement Evaluation study (GAME). This prospective cohort part of the study aims to investigate the influence of gender differences on markers of arterial stiffness. The criterion for inclusion of patients was age over 60 years. The study group included 118 consecutives patients (mean age 77.2 $\pm$ 8.1 years) hospitalized in the Department of Geriatrics of the National Institute of Geriatrics, Rheumatology, and Rehabilitation from December 2018 to July 2019.

The study was designed to be observational and not interventional; we decided the PWV result could not influence a change of therapy. The majority of patients in the study were elderly patients with multiple diseases who received standard, continuous pharmacotherapy in accordance with the latest guidelines and the best medical knowledge, also regarding hypertension or atherosclerosis, if necessary. Given that the patients were in a stable condition (diagnostic hospitalizations), their treatment was established, and

blood pressure values were adjusted before hospitalization—which also implies before PWV measurements.

2.2. Exclusion Criteria

Exclusion criteria were active cancer, lack of limbs, and advanced dementia process preventing collaboration with the investigator's recommendations.

2.3. Consent of the Bioethics Committee

This study's protocol complies with the ethical guidelines of the 1975 Declaration of Helsinki and has been approved by the Bioethics Committee at the National Institute of Geriatrics, Rheumatology, and Rehabilitation in Warsaw. Before inclusion in the study, all participants were made to provide written informed consent.

2.4. Measurement of cfPWV

The cfPWV value was assessed by a SphygmoCor XCEL from ATCOR [17]. The SphygmoCor XCEL device has been validated as per the ARTERY PWV validation guidelines [18]. Although other devices are known, the SphygmoCor is the most widely used and considered the gold standard technique [19]. The principle of cfPWV measurement with the SphygmoCor XCEL device is shown in Figure 1.

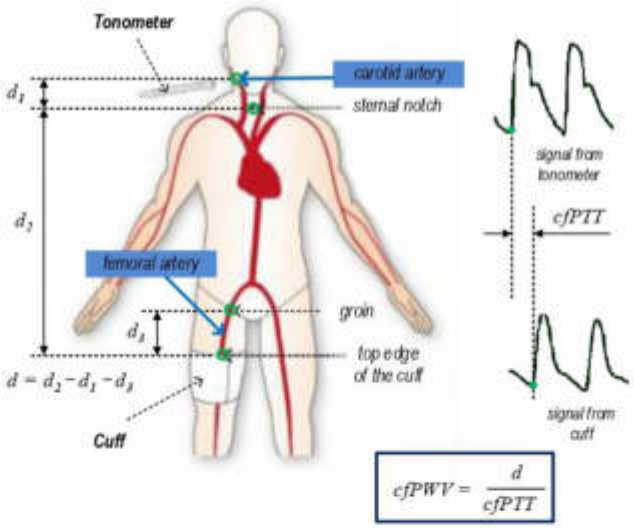

Figure 1. Principle of cfPWV measurement with the SphygmoCor XCEL device.

Measuring cfPWV with the SphygmoCor XCEL apparatus simultaneously detects a carotid pulse by applanation tonometry and a femoral pulse by volumetric displacement with a cuff around the upper thigh [20]. Then, the device measures the pulse transit time (cfPTT) between the diastolic feet of the carotid and femoral pulse. The path length (distance—d) was calculated by subtracting the distance between the carotid artery measurement site and sternal notch (carotid–notch) from the distance between the femoral artery site and the sternal notch (femoral–notch), all measured directly with a tape measure with a reading accuracy of ±0.5 cm. cfPWV was calculated as follows: cfPWV (m/s) = distance/cfPTT. An example screenshot of cfPWV measurement with the SphygmoCor XCEL and additional explanations is shown in Figure 2.

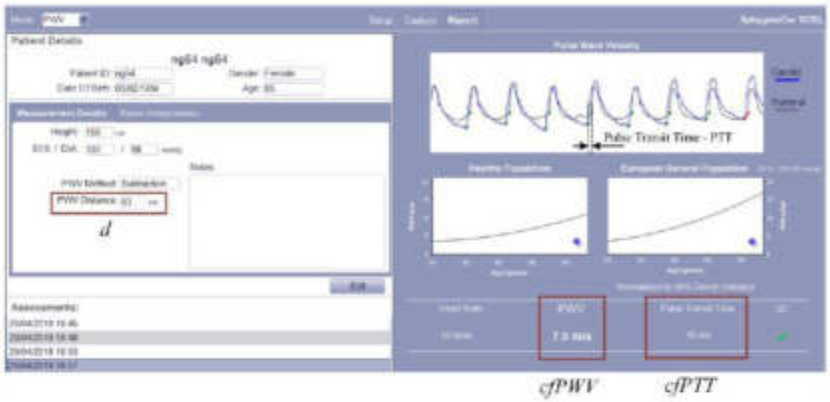

Figure 2. An example screenshot of cfPWV measurement with the SphygmoCor XCEL.

After entering the data about the participant (patient), taking the distance measurements (according to Figure 1), and taking the measurement, the registered signal waveforms from the carotid and femoral arteries, the resulting cfPTT and cfPWV values are displayed on the right side of the window. In addition, the measurement quality index (QC), the heart rate, and the obtained PWV result against the background of the healthy and European general population are displayed.

During the measurements, it was very useful to view the signals from the carotid and femoral arteries. Thanks to this, it was possible to reject noisy or poor-quality measurements.

It is worth noting that the measured signals are usually different for each participant. Representative signals (carotid and femoral pulse waveform) for 4 participants are shown in Figure 3.

Signal graphs come from reports generated by the SphygmoCor XCEL software (version 1.3.2.18). The shown examples of pulse waveforms have different amplitudes, shapes, and durations. These parameters are related to the individual characteristics of the participants. However, this does not have a significant impact on the result because the cfPWV is calculated on the basis of the pulse wave propagation time according to the validated algorithms of the SphygmoCor XCEL apparatus.

2.5. Measurement of Multi-Site PWV

For multi-site arterial pulse wave velocity measurements, we used a custom-made system called MPPT. This system measures the regional PWV. To measure PWV, it uses PPG (photoplethysmographic) sensors located at different sites. This system was described in detail in [21]. For multi-site PWV measurement, we used 7 PPG sensors as shown in the MPPT configuration diagram (Figure 4).

In addition, localization of the SphygmoCor XCEL sensors (tonometer and cuff on right body site) is shown in the block diagram. Multi-site regional PWV measurement with the MPPT device was described in detail in our previous work [22]. The MPPT device synchronously measures several PPG signals from different locations (forehead, ears, fingers, and toes) and then calculates the PWV based on the pulse transit time and distance between the sternal notch and PPG sensors. A reflective sensor was used on the forehead and a transmission sensors on other locations. For PWV calculations we used signals from an IR diode (wavelength 905 nm). The MPPT device was connected to a computer via a USB interface with galvanic separation. Dedicated computer software was responsible for control, online data transfer, and visualization of signals as well as data archiving. Signal processing and calculation of PWV were performed offline in the

MATLAB environment (version R2019a). All distances for regional PWV assessment were obtained directly with a tape measure with a reading accuracy of ±0.5 cm.

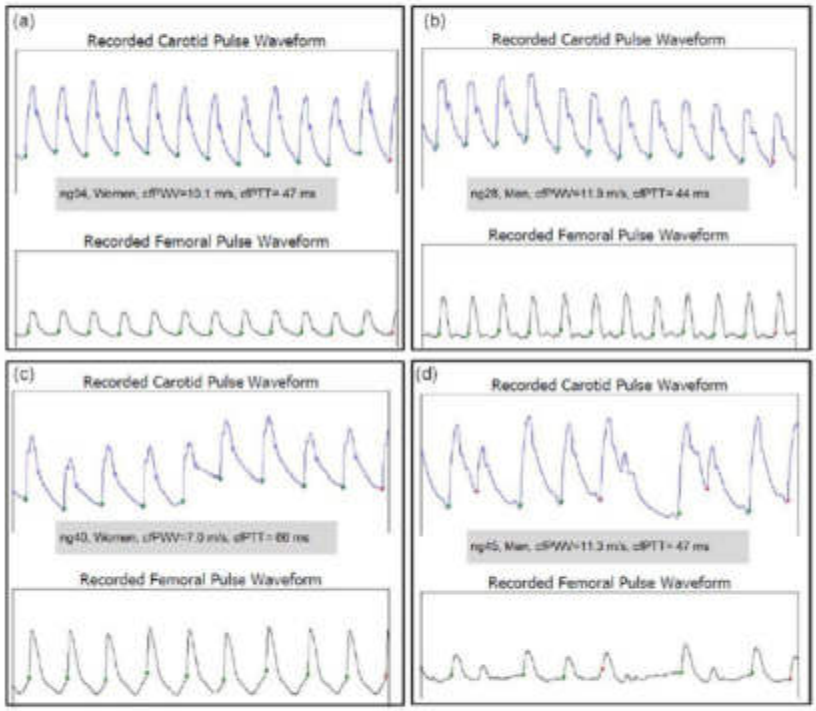

Figure 3. Representative carotid and femoral pulse waveforms for calculating the cfPWV recorded with the SphygmoCor XCEL (for 4 participants with ID = (**a**) ng04, (**b**) ng28, (**c**) ng40 and (**d**) ng45).

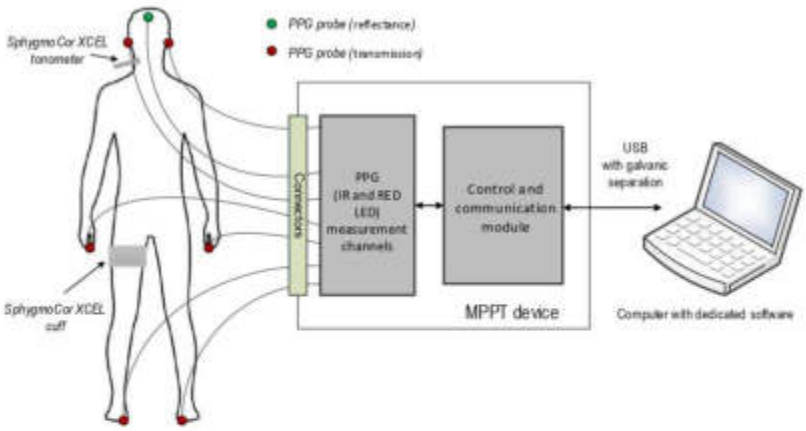

Figure 4. Block diagram of the MPPT system and location of PPG sensors for regional PWV measurement.

The MPPT system calculated the regional PWV from the PPG signals measured at a sampling frequency of 1 kHz. The beginning of the pulse wave for each of the pulses was determined by the intersecting tangent method, according to [22].

Representative PPG signals (synchronously acquired from the right finger, toe, ear, and forehead) measured by MPPT devices for 4 participants are shown in Figure 5.

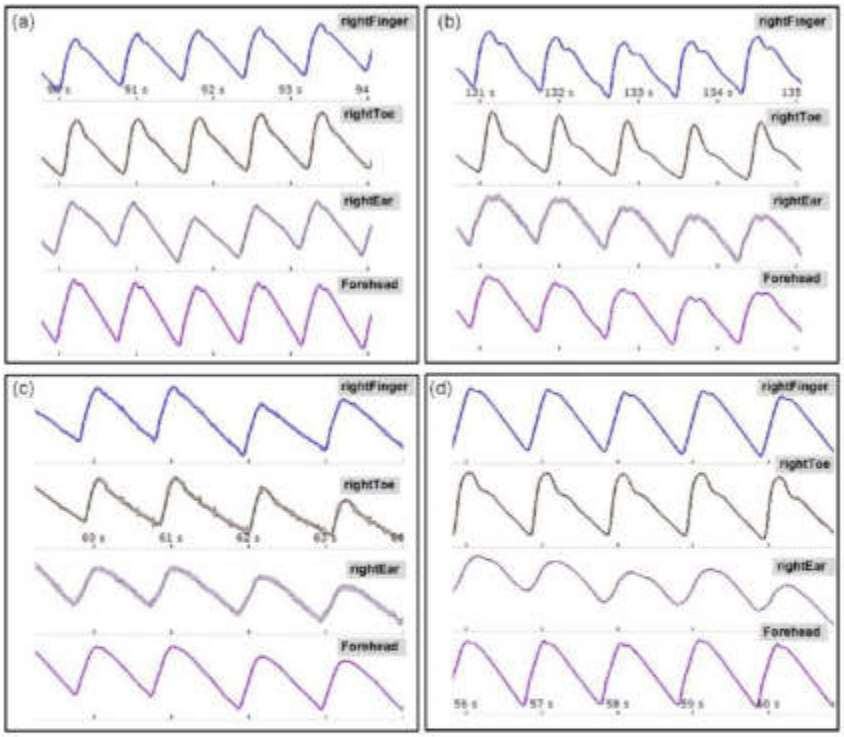

Figure 5. Representative signal plots for calculating the regional PWV recorded with the MPPT apparatus (for 4 participants with ID: (**a**) ng04, (**b**) ng28, (**c**) ng40 and (**d**) ng45).

The presented examples of PPG pulse waveforms differ from each other, especially in shape, depending on the site of measurement and the individual characteristics of the participant. However, this does not have a significant impact on the result because, as for the SphygmoCor XCEL, the regional PWV is calculated on the basis of the pulse wave propagation time according to the validated algorithms of the MPPT apparatus.

2.6. Measurement Protocol

For more accurate results, in our study, we took the measurements according to the same procedure for each participant. After a minimum 15 min rest and after informing the participant about the purpose of the study and obtaining their signed consent, the blood pressure in the left brachial was measured using the SphygmoCor XCEL in pulse wave analysis (PWA) mode. This measurement was performed in the standard sitting position, and its purpose was to determine the brachial (bSBP, bDBP) and the aortic (aSBP, aDBP) blood pressure. Next, the participant assumed a supine position on a medical settee and rested for about 15 min. During this time, the SphygmoCor XCEL and MPPT apparatus sensors were connected, distances were measured, and signals were checked. Subsequently, the main measurement was performed, lasting exactly 15 min. It should be stressed that the

measurements with the SphygmoCor XCEL were performed simultaneously with the measurements with the MPPT apparatus. The MPPT measured the PPG signals continuously for 15 min. At the same time, a minimum of three cfPWV measurements were made at an interval of approximately 3 min. All measurements were performed by the same operator, during working days, from Monday to Friday, from about 10 a.m. to 1 p.m., in a separate and quiet room, with an ambient temperature of about 22–24 °C.

The final regional PWV was calculated offline for each participant as the mean of the 15 min recording. Likewise, for each participant the average of the all cfPWV readings was calculated.

2.7. Analysis

Statistical analysis was performed using Matlab, R environment, and Statistica v.13. $p < 0.05$ was considered statistically significant. For continuous variables, the normal distribution was checked using the Shapiro–Wilk test. Student's *t*-test was used to compare normally distributed continuous variables, and data were reported as means with standard deviations. The Mann–Whitney U test was used to compare non-normally distributed variables, and data were reported as medians and interquartile ranges. The Pearson's chi-square test or chi-square test with Yates correction was used to compare discrete variables depending on the expected values. Linear correlation analysis between PWV and continuous variables was performed, and Pearson's r coefficient was determined. Variables with Pearson's correlation coefficients higher than 0.3 ($p < 0.05$) were included in the multivariable regression model. Brachial systolic blood pressure (bSBP) was chosen as a representative of the strongly correlated variables relating to blood pressure.

3. Results

3.1. Characteristics of the Study Group

Table 1 shows the clinical characteristics of the 118 subjects (35 males and 83 females) in the GAME study. Both gender groups were quite homogeneous in terms of the distribution of comorbidities like hypertension, diabetes mellitus, metabolic syndrome, heart failure, and chronic obstructive pulmonary disease.

Patients of both groups did not statistically differ in the values of age; blood tests such as LDL-C, TG, FPG, eGFR, and TSH; blood pressure values (SBP, DBP, MAP—measured on the brachial artery as well as the central one—and aortic pressure); or anthropometric measurements such as upper-arm circumference and lower-leg circumference. BMI and TC were higher in women, reaching a statistically significant *p*-value ($p = 0.05$). In comparison with females, males exhibited a significantly lower HDL-C level ($p < 0.001$), higher uric acid level ($p < 0.001$), and higher NTproBNP concentration ($p = 0.047$). Women had higher inflammation parameters (CRP $p = 0.047$; ESR $p = 0.050$). Men were characterized by statistically significantly higher values of cfPWV than women (cfPWV median 10.52 m/s vs. 9.36 m/s, respectively; $p = 0.001$).

3.2. Gender Differences in the Analysis of the Impact of cfPWV on Selected Atherosclerosis Risk Factors and Comorbidities

Table 2 shows the correlation coefficients between cfPWV and selected parameters.

The highest correlations in the entire group were found for systolic arterial pressure, both peripheral bSBP (r = 0.443) on the brachial artery as well as systolic pressure of the central estimated aortic measurement aSBP (r = 0.411). Moreover, all pressure parameters (bDBP, bMAP, aDBP, aPP, and aMAP) showed a significant relationship with PWV. In the whole group, other significant parameters associated with arterial stiffness were patients' age (r = 0.341; $p < 0.001$), degree of heart failure expressed as elevated concentration of NTproBNP (r = 0.347; $p < 0.001$), and uric acid level (r = 0.339; $p < 0.001$). cfPWV growth was sometimes observed to have a different potency between the groups. Sometimes the differences were discreet, as in aMAP, which increases cfPWV in both women and men; the correlation coefficient is higher in women, but the difference does not reach statistical

significance. Our study also presents an analysis of the relationship with age—which significantly correlates in women (r = 0.429; $p < 0.001$)—and its importance has not been registered in the group of men (r = 0.193; $p = 0.265$).

Table 1. Comparative characteristics of gender groups.

	Women ($n = 83$)	Men ($n = 35$)	p-Value
cfPWV (m/s)	9.36 (8.28–10.63)	10.52 (9.18–11.65)	0.001
Age (years)	77 (72–83)	76 (69–86)	0.810
TC (mg/dL)	199 (165–226)	167 (135–224)	0.051
HDL-C (mg/dL)	63 (54–72)	51 (39–61)	<0.001
LDL-C (mg/dL)	107.8 (84.0–138.2)	98.4 (64.2–145.0)	0.208
TG (mg/dL)	111 (82–150)	107 (87–170)	0.874
FPG (mg/dL)	95 (87–109)	95 (88–107)	0.751
NTproBNP (pg/mL)	225.4 (128.6–410.0)	322.1 (213.0–1183.0)	0.047
eGFR (mL/min)	62.53 (47.53–80.77)	83.04 (47.57–86.14)	0.819
Uric acid (mg/dL)	5.0 (4.4–5.8)	6.0 (5.3–6.7)	<0.001
CRP (mg/L)	6 (5–11)	5 (5–7)	0.047
ESR (mm/h)	17 (11–27)	13 (5–22)	0.050
TSH (mIU/L)	1.50 (0.94–2.35)	1.27 (0.68–1.87)	0.292
BMI (kg/m^2)	29.38 ± 5.13	27.31 ± 4.67	0.053
Ac (cm)	28 (26–31)	27 (26–30)	0.976
LLc (cm)	35 (33–38)	34 (31–37)	0.135
bSBP	136.54 ± 17.97	134.26 ± 19.23	0.538
bDBP	69.12 ± 9.92	70.49 ± 10.47	0.503
bMAP	91.58 ± 10.79	91.8 ± 12.44	0.923
aSBP	124.19 ± 15.99	121.09 ± 16.75	0.346
aDBP	70.22 ± 10.05	71.76 ± 10.25	0.451
aPP	51.6 (43.5–63.8)	48.7 (42.1–55.7)	0.075
aMAP	90.87 ± 10.82	89.55 ± 12.3	0.563
aHR	67.38 ± 9.57	64.61 ± 8.4	0.141
Hypertension	70 (84%)	33 (94%)	0.238
Diabetes mellitus	22 (27%)	13 (37%)	0.248
MS	33 (40%)	15 (43%)	0.754
COPD	8 (10%)	4 (11%)	0.968
HF	58 (77%)	26 (84%)	0.623
VES 13	5.29 ± 2.78	5.169 ± 3.53	0.739
ADL	5.539 ± 0.71	5.429 ± 1.06	0.957
I ADL	21.499 ± 3.56	19.529 ± 5.45	0.100
MMSE	26.619 ± 2.81	25.469 ± 5.19	0.935
CDT	8.669 ± 2.00	8.889 ± 2.29	0.244

Note 1: Continuous variables with normal distribution are presented as mean ± SD; non-normal variables are presented as median (IQR); binary variables are presented as number (percentage). Note 2: cfPWV, carotid–femoral pulse wave velocity; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; FPG, fasting plasma glucose; NTproBNP, N-terminal pro b-type natriuretic peptide; eGFR, estimated glomerular filtration rate; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; TSH, thyroid-stimulating hormone; BMI, body mass index; Ac, arm circumference; Llc, lower-leg circumference; bSBP, brachial systolic blood pressure; bDBP, brachial diastolic blood pressure; bMAP, brachial mean arterial pressure; aSBP, aortic systolic blood pressure; aDBP, aortic diastolic blood pressure; aPP, aortic pulse pressure, bMAP, brachial mean arterial pressure; aHR, aortic heart rate, MS, metabolic syndrome; COPD, chronic obstructive pulmonary disease; HF, heart failure; VES-13, Vulnerable Elders-13 Survey; ADL, Katz Index of Independence in Activities of Daily Living; IADL, Lawton Instrumental Activities of Daily Living Scale; MMSE, Mini-Mental State Examination; CDT, clock-drawing test.

Table 2. Correlation coefficients of selected parameters and cfPWV in the whole group and by gender.

Parameter	Total		Men (n = 35)		Women (n = 85)	
	r	*p*-Value	r	*p*-Value	r	*p*-Value
Age	0.341	<0.001	0.194	0.265	0.430	<0.001
HDL-C	−0.196	0.033	−0.132	0.448	−0.076	0.493
LDL-C	−0.042	0.653	0.012	0.944	−0.008	0.946
TC	−0.090	0.332	0.118	0.500	−0.095	0.393
TG	0.160	0.083	0.466	0.005	0.056	0.618
FPG	0.108	0.247	0.413	0.014	0.080	0.472
NTproBNP	0.347	<0.001	0.296	0.106	0.329	0.004
Uric acid	0.339	<0.001	0.108	0.536	0.335	0.002
CRP	0.147	0.113	0.018	0.919	0.242	0.028
ESR	0.128	0.171	0.262	0.128	0.166	0.135
TSH	0.088	0.344	0.053	0.764	0.150	0.177
eGFR	−0.212	0.021	−0.051	0.771	−0.300	0.006
BMI	0.097	0.309	0.352	0.052	0.113	0.318
Ac	0.035	0.713	0.192	0.301	0.023	0.839
LLc	−0.013	0.890	0.070	0.707	0.032	0.775
bSBP	0.443	<0.001	0.466	0.005	0.500	<0.001
bDBP	0.229	0.013	0.196	0.259	0.232	0.035
bMAP	0.374	<0.001	0.347	0.041	0.413	<0.001
aSBP	0.411	<0.001	0.450	0.007	0.471	<0.001
aDBP	0.255	0.005	0.223	0.197	0.255	0.020
aPP	0.311	<0.001	0.488	0.003	0.357	0.001
aMAP	0.353	<0.001	0.351	0.039	0.409	<0.001
AorticHR	0.009	0.922	−0.044	0.801	0.089	0.425

Table 3 shows the results of multivariable analysis examining the influence of various parameters on cfPWV in the whole group and the gendered subgroups.

Table 3. Multivariable regression analysis coefficients.

TOTAL GROUP Variable	Unstandardized Coefficients		Standardized Coefficients		*p*-Value
	β	SE	β	SE	
Age	0.053	0.017	0.250	0.081	0.003
NTproBNP	0.000	0.000	0.119	0.085	0.165
Uric Acid	0.201	0.093	0.172	0.080	0.034
bSBP	0.037	0.007	0.398	0.077	<0.001
gender (male)	0.464	0.151	0.251	0.081	0.003
WOMEN GROUP variable	Unstandardized coefficients		Standardized coefficients		*p*-value
	β	SE	β	SE	
Age	0.059	0.021	0.276	0.098	0.006
NTproBNP	0.000	0.000	0.208	0.096	0.034
Uric Acid	0.273	0.104	0.240	0.091	0.010
bSBP	0.033	0.009	0.355	0.093	<0.001
MEN GROUP variable	Unstandardized coefficients		Standardized coefficients		*p*-value
	β	SE	β	SE	
TG	0.007	0.004	0.332	0.173	0.064
FPG	0.008	0.010	0.138	0.175	0.435
bSBP	0.031	0.011	0.394	0.143	0.010

The most significant parameters in the whole group were two modifiable factors: systolic blood pressure (β 0.398; $p < 0.001$) and uric acid value (β 0.172; $p = 0.034$), and two non-modifiable ones: male gender (β 0.251; $p = 0.003$) and age (β 0.250; $p = 0.003$). In the multivariable regression analysis in the group of women, apart from the values of systolic blood pressure (β 0.355; $p < 0.001$), age (β 0.276; $p = 0.006$), and uric acid level (β 0.240; $p = 0.010$), the value of NTproBNP (β 0.208; $p = 0.034$) also had a significant impact on cfPWV. Meanwhile, in the multivariable analysis concerning the group of men, only the value of systolic blood pressure (β 0.394; $p = 0.010$) was significant.

3.3. Multivariable Regression—Comorbidities and Gender

The multivariate regression analysis of the influence of comorbidities, mainly cardiovascular, included in Table 4 was supplemented with the male gender, a recognized cardiovascular risk factor which is not correlated with any of the analyzed diseases. In our analysis, male gender significantly (β 0.251; $p = 0.005$) influences the increase in PWV; only diabetes (β 0.279; $p = 0.002$) is a stronger factor and is characterized by a greater influence than the presence of hypertension (β 0.196; $p = 0.029$).

Table 4. Multivariable regression—comorbidities and gender.

Parameters	Unstandardized Coefficients		Standardized Coefficients		*p*-Value
	β	SE	β	SE	
Hypertension	0.542	0.244	0.196	0.089	0.029
Diabetes Mellitus	0.508	0.162	0.279	0.089	0.002
COPD	0.048	0.238	0.017	0.086	0.842
Heart failure	0.288	0.180	0.139	0.087	0.113
Gender	0.465	0.160	0.251	0.086	0.005

3.4. Analysis of Multi-Site Regional PWV by Gender

Table 5 presents the results of measurements of regional PWV taken at the six body sites discussed above, broken down by gender. In contrast to the central cfPWV measurement, no statistically significant differences between the sexes were noted in any of the regional measurements.

Table 5. Analysis of multisite regional PWV by gender.

Measured Site-Dependent PWV (Regional PWV)	Women Mean [Min–Max]	Men Mean [Min–Max]	*p* Value
forehead–right toe, htPWV	9.40 [6.70–14.10]	9.34 [6.10–13.00]	0.660
forehead–left toe, htPWV	9.51 [6.10–14.10]	9.63 [6.80–14.00]	0.858
right ear–right toe, etPWV	9.41 [7.00–13.50]	9.64 [6.70–13.90]	0.951
left ear–left toe, etPWV	9.25 [6.10–13.70]	9.79 [7.00–13.30]	0.180
right finger–right toe, ftPWV	10.01 [6.10–15.30]	9.43 [6.10–14.40]	0.336
left finger–left toe, ftPWV	9.49 [6.20–13.60]	9.20 [6.50–14.40]	0.286

3.5. Comparison of Central and Regional PWV

Table 6 compares the central PWV with the regional PWV. The difference in mean PWV (mean difference) values was determined. In the overall analysis, the differences between cfPWV and regional PWV are noteworthy, with generally higher values for mean central PWV. In the group of men, each of the regional measurements is statistically significantly lower than the cfPWV value.

Table 6. Comparison of central and regional PWV.

TOTAL GROUP Variable	Central PWV (cfPWV) Mean [Min–Max]	Regional PWV Mean [Min–Max]	Mean Difference	*p*-Value
forehead–right toe, htPWV	9.86 [6.32–14.14]	9.38 [6.10–14.10]	0.48	0.028
forehead–left toe, htPWV		9.55 [6.10–14.10]	0.25	0.060
right ear–right toe, etPWV		9.48 [6.70–13.90]	0.44	0.015
left ear–left toe, etPWV		9.41 [6.10–13.70]	0.42	0.021
right finger–right toe, ftPWV		9.85 [6.10–15.30]	0.03	0.409
left finger–left toe, ftPWV		9.40 [6.20–14.40]	0.55	0.038
WOMEN GROUP variable	central PWV (cfPWV)	regional PWV	mean difference	*p*-value
forehead–right toe, htPWV	9.36 [6.32–13.02]	9.40 [6.70–14.10]	0.07	0.046
forehead–left toe, htPWV		9.51 [6.10–14.10]	0.12	0.166
right ear–right toe, etPWV		9.41 [7.00–13.50]	0.17	0.534
left ear–left toe, etPWV		9.25 [6.10–13.70]	0.26	0.345
right finger–right toe, ftPWV		10.01 [6.10–15.30]	0.46	0.181
left finger–left toe, ftPWV		9.49 [6.20–13.60]	0.12	0.185
MEN GROUP variable	central PWV (cfPWV)	regional PWV	mean difference	*p*-value
forehead–right toe, htPWV	10.52 [8.12–14.14]	9.34 [6.10–13.00]	1.37	0.001
forehead–left toe, htPWV		9.63 [6.80–14.00]	1.01	0.012
right ear–right toe, etPWV		9.64 [6.70–13.90]	1.07	0.005
left ear–left toe, etPWV		9.79 [7.00–13.30]	0.81	0.029
right finger–right toe, ftPWV		9.43 [6.10–14.40]	1.33	0.011
left finger–left toe, ftPWV		9.20 [6.50–14.40]	1.49	0.004

4. Discussion

4.1. Results

To the best of our knowledge, this is the first study that demonstrates differences in cf-PWV between genders in nearly all homogeneous patients in terms of classic comorbidities such as hypertension, diabetes mellitus, metabolic syndrome, chronic obstructive pulmonary diseases, and heart failure among Polish geriatric patients and shows differences in the impact of individual risk factors on the cfPWV value in gender groups. There are some studies that have assessed the relationship between arterial stiffness and gender, but most of them have been conducted in the younger population [23–27]. No significant difference was found for PWV, arterial age, and augmentation index in an analysis of gender and arterial stiffness among smokers (mean age 38). In addition, differences between smoking pack-year values (18.5 pack-years in male and 7.5 pack-years in female) between sexes that increase arterial stiffness were emphasized [23]. In participants with prehypertension (mean age 59.76 + 12.37) selected from the BEST study, males had higher PWV than females (10.89 vs. 10.33 m/s, respectively). However, differences in the distribution of other CV risk factors were observed, such as: (1) age, BMI, FPG, UA, and homocysteine being higher in males compared with females, and (2) TC, HDL-C, and LDL-C being higher in females [24]. In a study conducted among the Tallinn population aged 20–65, a higher PWV was observed in hypertensive men aged equal to or above 50 years, as well as in hypertensive women with diabetes and in apparently healthy women with increased apolipoprotein B [25]. Another research work of carotid stiffness measured with ultrasound echo-tracking presented no significant difference in PWV-β between genders in the age group 54.7 ± 10.6 years. Gender might play a modulatory role in the interconnection between arterial stiffness and some risk factors, where there appears to be a stronger relationship between stiffness and heart rate in men and pulse pressure in women [26]. In a study with morbidly obese patients (BMI of $\geq$40 kg/m^2 or a BMI of $\geq$35 kg/m^2 and obesity-related comorbidity), aged 18 to 65 years, the median PWV was significantly higher in men than women (7.3 m/s

(IQR 6.6–8.0) and 6.8 m/s (IQR 5.9–8.0), respectively); the lower PWV in women appears to diminish in morbidly obese women after menopause [27]. The study emphasized the role of different hormonal balances, including the protective effect of estrogens in premenopausal women compared to young men. However, the initially protective role of female sex hormones in combination with the subsequent acceleration of increased cardiovascular risk remains unclear [28,29]. The advantage of our study is the age of the surveyed population, as they were geriatric patients. Worthy of note is that this group is seldom included in other studies. The age of the group in our study reduces the influence of sex hormones because the women we examined were postmenopausal. This allows to objectively compare their cardiovascular risk to men of the same age. There are single reports about the negative influence of male gender on the advancement of the atherosclerotic process. Male gender was an independent predictor of re-peripheral vascular interventions in a study assessing long-term clinical outcomes in patients with chronic total occlusions of infrainguinal lower-limb arteries [30]. As far as we know, only a few studies concentrated on arterial stiffness in the elderly population. A Parisian geriatric study (mean age 87.1 $\pm$ 6.6) indicated that age and loss of autonomy were the best predictors of mortality, and aortic PWV was the major independent risk predictor for cardiovascular mortality, whereas systolic blood pressure or pulse pressure was not. Unfortunately, a gender analysis was not provided by the researchers [31]. One of the few studies among the elderly (over 80 years of age) assessing the subclinical markers of atherosclerosis, such as endothelial dysfunction and carotid thickness, presents the relationships between them and osteoporosis expressed in decreased bone mass. However, this study did not assess the difference between the sexes [32]. The main result of our GAME study is that PWV is higher in men than in women, despite the similar distribution of other classic CV risk factors (age, blood pressure, LDL cholesterol, and kidney function). Our next task is to look for other discrete factors that can affect increases in PWV in men, which can lead to earlier mortality and other complications of high arterial stiffness. We also analyzed the strength of the impact of individual parameters on increases in PWV in the entire patient group. The strongest factor affecting increases in arterial stiffness turned out to be systolic arterial pressure, both the peripheral value measured on the brachial artery and the central pressure values estimated by the SphygmoCor; following that were the average blood pressure values and age, as well as the NTproBNP values. Interestingly, in the whole group, the parameters of the lipid profile seem to be irrelevant for PWV increases, with only a slightly outlined negative correlation for HDL-C values. Meanwhile, analyzing the impact of specific factors in groups of men and women, we also find different relationships. In men, PWV (apart from SBP values that are significant for both sexes) is significantly affected by the values of triglycerides and glucose. In women (except for the discussed SBP), age, NT-proBNP, uric acid, and renal function (eGFR) have the most significant impacts. The above analysis allows us to suppose that groups of women and men should be analyzed separately, and one should look for different risk factors for arterial stiffness except for classical CVR.

The development of new methods of measuring arterial stiffness allows us to better understand the different components of stiffness as well as to estimate their impact on the real condition of arteries (possible to be fully unambiguous only in autopsy post mortem). [33] Research on arterial stiffness is still an ongoing issue. Attempts have been made to study the construct validity of a measure of PWV estimated from age and blood pressure (ePWV) [34].

Recently, the usefulness of photoplethysmography signals in medicine is being investigated [35]. Methods to take measurements continuously and across multiple body sites using photoplethysmography are also being developed, such as the comparison of overall agreement and repeated measures such as heart–finger PWV (hfPWV) and heart–toe PWV (htPWV). In [36], htPWV measurements were compared to oscillometric carotid–wrist PWV (cwPWV) and carotid–ankle PWV (caPWV) referent measurements in a group of 30 young people (24.6 $\pm$ 4.8 years). In a Czech study by L. Soukup [37] of 220 (age 21–71) normal, healthy, normotensive people who had no history of disease that had a major impact on

PWV values and were not taking any related medications, the reliability of whole-body multi-channel bioimpedance to assesses pulse wave velocity and provide a reference value for measuring whole-body PWV was examined. In addition, a significant age-dependent PWV of the aorta was found in these values measured using the left carotid as the proximal artery. PWV values in the upper and lower limbs do not show a significant dependence on age. Disagreement of a single peripheral measurement of heart–finger pulse wave velocity in comparison to brachial–ankle pulse wave velocity were also noted in a Korean study of healthy adults (92 males and 93 females) of ages ranging from 20 to 66 [38]. Referring to the slightly different results in our study, it should be emphasized that we studied elderly people with multimorbidity, which increases the stiffness of the arteries, mainly the aorta. Most studies to date have been based on young or middle-aged healthy individuals. In our geriatric study, central PWV values, especially in men, were higher than regional values in every measurement. More research is needed, optimizing on a larger group of people and assessing long-term effects, to explain this relationship. Based on current knowledge, we can assume that a greater component of arterial stiffness is the aorta rather than other arteries of smaller caliber as well as intramuscular arteries. Regional measurements show that small arteries are likely to age similarly in men and women.

The advantage and novelty of our study is the group of geriatric patients in whom the atherosclerotic process is already developed, which allows for an objective assessment of arterial stiffness measurement methods.

4.2. Strengths and Limitations

However, certain limitations should also be acknowledged. First, most patients are women (83 women vs. 35 men), and therefore we were unable to obtain statistical significance in some relationships. The gender gap is caused by the predominance of women in the older population as well as the predominance of women among those hospitalized.

As we aimed at a population study among hospitalized people, every patient hospitalized in the Department of Geriatrics of the National Institute of Geriatrics, Rheumatology, and Rehabilitation from December 2018 to July 2019 was included in the study. The only exclusion criteria were active cancer, lack of limbs, and advanced dementia process preventing collaboration on the investigator's recommendations.

The life expectancy of women in Poland is 8 years longer than that of men. In the analyzed period in the Department of Geriatrics of the National Institute of Geriatrics, Rheumatology, and Rehabilitation, which is comparable to the data of the Polish National Health Fund, women constitute about 65–70% of patients hospitalized in geriatric wards. We did not decide to study only a proportion of women to match their numbers with the men, as then the criteria for inclusion or non-inclusion of a specific man could be unclear. We hope that further, larger observational studies may be interesting, being typical studies of entire populations, e.g., cities or countries, and not taking into account the criterion of the need to hospitalize the patient.

The second is the lack of a cut-off point for elevated PWV. It is not described in the current literature, and our study group is too small to extrapolate values recognized by other scientific authorities (e.g., the 12 m/s value recognized as a risk factor for people with hypertension by the European Society of Cardiology [9]). We think that an interesting development of the current work will be prospective observations with an analysis of mortality and cardiovascular incidents in our group that we conducted.

Another limitation of this work is the heterogeneity among geriatric patients in this study. During the measurement process, we did not consider the individual differences of the subjects because our goal was to reproduce the PWV assessment among patients hospitalized in the Department of Geriatrics as authentically as possible. For this reason, we did not use inclusions for chronic diseases (such as diabetes, hypertension, or chronic kidney disease) because they constitute the overall clinical picture of the geriatric patient.

5. Conclusions

In conclusion, the result of the current GAME study shows that cfPWV is higher in men than women in the geriatric population. However, the reason for this relationship is still unclear and cannot be explained by the distribution of classical CV risk factors (age, systolic blood pressure, and total cholesterol) between genders. Because of the attempts made to reduce this important CVD risk factor in the elderly patient population, further studies aimed at deciphering the secret of increased arterial stiffness in men could be remarkably interesting. In addition, it is necessary to look at gender differences separately. In men and women, various factors affect increases in arterial stiffness and thus increase cardiovascular risk. Therefore, it is worth conducting gender-shield analyses as an introduction to personalized medicine. In addition, taking into account the less clearly differentiated regional PWV values obtained by MPPT, it should be assumed that the main factor affecting the stiffness of these arteries is the competitor of the elastic great central arteries. The main problem of arterial stiffness, and thus of all clinical consequences with the aging of the population, is atherosclerosis and calcification, mainly affecting the aorta and, to a much lesser extent, peripheral muscular arteries.

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Publikacja 3: Impact of COVID-19 on carotid-femoral pulse wave velocity: a systematic review and meta-analysis.

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Systematic Review

The Impact of COVID-19 on Carotid–Femoral Pulse Wave Velocity: A Systematic Review and Meta-Analysis

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Abstract: COVID-19 is a complex multisystemic disease that can result in long-term complications and, in severe cases, death. This study investigated the effect of COVID-19 on carotid–femoral pulse wave velocity (cfPWV) as a measurement to evaluate its impact on arterial stiffness and might help predict COVID-19-related cardiovascular (CV) complications. PubMed, Web of Science, Embase, and the Cochrane Library were searched for relevant studies, and meta-analysis was performed. The study protocol was registered in PROSPERO (nr. CRD42023434326). The Newcastle–Ottawa Quality Scale was used to evaluate the quality of the included studies. Nine studies reported cfPWV among COVID-19 patients and control groups. The pooled analysis showed that cfPWV in COVID-19 patients was 9.5 ± 3.7, compared to 8.2 ± 2.2 in control groups (MD = 1.32; 95% CI: 0.38–2.26; $p = 0.006$). A strong association between COVID-19 infection and increased cfPWV suggests a potential link between the virus and increased arterial stiffness. A marked increase in arterial stiffness, a known indicator of CV risk, clearly illustrates the cardiovascular implications of COVID-19 infection. However, further research is required to provide a clearer understanding of the connection between COVID-19 infection, arterial compliance, and subsequent CV events.

Keywords: COVID-19; SARS-CoV-2; pulse wave velocity; PWV; cfPWV; arterial stiffness

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1. Introduction

The COVID-19 pandemic has had wide-ranging global effects, affecting a substantial proportion of the population worldwide. By June 2023, there were over 765 million confirmed cases, and almost 7 million people died as a result of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. Initially, there was limited information about COVID-19, and the disease was thought to be simply an acute respiratory condition. Since then, research has shown that COVID-19 is a complicated multisystemic disease that can lead to death or long-term complications after recovery [3,4]. One significant concern is the close link between COVID-19 and cardiovascular (CV) complications. Patients with pre-existing CV conditions are at a higher risk of an unfavorable prognosis for COVID-19 infection. Moreover, COVID-19 itself may directly or indirectly cause significant CV

complications [5], which persist even after recovering from the virus [6,7]. Not only the severity of COVID-19 in the acute phase but also the duration of symptoms might have an effect on vascular function [8]. Long COVID-19 is described as a condition that can arise after recovery from the primary infection or an unresolved COVID-19 infection, which presents with ongoing symptoms that cannot be attributed to any other disease or condition. Using a conservative 10% estimate, at least 76 million people worldwide are affected by long COVID-19. Furthermore, studies suggest that 10–30% of non-hospitalized and 50–70% of hospitalized individuals experience long COVID-19 symptoms [9]. However, the actual numbers might be higher due to the vast number of unreported cases [10].

COVID-19's cardiovascular (CV) manifestations include arrhythmias, asymptomatic myocardial damage, overt congestive heart failure, and thromboembolic events [5,11,12] and result from the virus's direct cytotoxic effect or the subsequent systemic inflammatory cytokine storm. Endothelial dysfunction seems to be a crucial driver and mediator of the COVID-19 pathophysiologic pathways [13]. Vascular endothelial cells have the angiotensin-converting enzyme 2 cellular receptors (ACE2-R) and the transmembrane serine protease 2 (TMPRSS2), synergistically facilitating SARS-CoV-2 entry into host cells. Infected endothelial cells increase the production of cytokines, promoting inflammation and thrombosis [14]. The resulting vasculitis, which may affect different parts of the body, contributes to the multiorgan failure seen in some COVID-19 patients [15]. There is evidence suggesting that COVID-19 accelerates vascular aging on a macrovascular level [16]. Other proposed mechanisms contributing to cellular senescence and vascular stiffness include COVID-19-induced mitochondrial dysfunction, increased local formation of reactive oxygen species (ROS), and resulting oxidative telomere shortening [17]. Both endothelial dysfunction and continuous subintimal inflammation contribute to the rapid fragmentation of elastin fibers in the arterial wall and their substitution with stiff, fibrous tissue. Given that COVID-19-induced pulmonary fibrosis can only be reversed to a certain level, it has been proposed that arterial stiffness might be a long-term CV consequence in most patients, irrespective of the severity of the initial infection [15,18]. Notably, vascular changes, especially endothelial function and arterial stiffness, may last for a long time after the COVID-19 infection [19].

Arterial stiffness may serve as a reliable indicator reflecting the vascular system's age and the comprehensive health of the CV system. It is an integrated biomarker that evaluates the cumulative detrimental effect on the arteries of genetic and environmental exposures, as well as the influence of established CV risk factors [20]. Numerous studies have established the correlations between arterial stiffness, as measured by pulse wave velocity (PWV), and the elevated risk of CV disease [21]. This correlation is independent of other traditional risk variables that are often considered to be risk factors [22,23]. In order to confirm the arterial stiffness in COVID-19 patients, other tests such as the augmentation index (Aix), the cardio-ankle vascular index (CAVI), the arterial stiffness index (ASI), Young's modulus of elasticity, and pulse pressure (PP) were performed [24–27].

PWV is essential in assessing vascular age and may have a stronger correlation with CV disease onset than metrical age [28]. PWV is a technique that is noninvasive and reproducible, and carotid–femoral pulse wave velocity (cfPWV) is now regarded as the gold standard in assessing arterial stiffness. The progressive stiffening of the arteries adversely affects arterial–ventricular interactions, decreasing the vessel's capacity to alter volume in response to changes in blood pressure, which in turn might lead to heart failure. CfPWV has a high prognostic value since it may help identify individuals who are at a higher risk not just for future CV events, but also for all-cause mortality [19,29].

The purpose of this research is to investigate the effect of COVID-19 on carotid–femoral pulse wave velocity (cfPWV) as a measurement of the complications of COVID-19 on arterial stiffness and subsequent CV complications.

2. Materials and Methods

2.1. Study Design

This study is a systematic review and meta-analysis conducted in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards [30] (Table S1). The research protocol was pre-approved by all co-authors registered in the PROSPERO registry (International Prospective Registry of Systematic Reviews) under registration number CRD42023434326.

2.2. Search Strategy

Two independent reviewers (I.J. and M.P.) evaluated potential papers. Discrepancies were resolved via further discussion or arbitration by a third reviewer (L.S.). The literature search covered the period between January 2020 and June 2023, covering the following databases: PubMed, Web of Science, Embase, the Cochrane Library, as well as Google Scholar. The search included the combination of keywords: "pulse wave velocity" OR "PWV" OR "arterial stiffness" AND "COVID-19" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus-2". Citations of listed studies were examined for further relevant literature. Only the most recent and comprehensive articles from identical authors were included to avoid duplicates. Furthermore, reference lists of relevant publications and systematic reviews were reviewed for potential inclusions. All references were consolidated in Endnote (version X9), duplicated entries were removed, and finally, Rayyan, a software screening tool, was used.

2.3. Inclusion and Exclusion Criteria

Studies qualified if they met the following inclusion criteria: research comparing cfPWV in patients with current or previous COVID-19 infection to a control group, as cfPWV is now regarded as the gold standard in assessing arterial stiffness. This method has a high prognostic value since it may help identify individuals who are at a higher risk not just for future outcomes as motioned in the introduction [19,29]. We excluded studies not detailing desired outcomes, other than cfPWV measurement of arterial stiffness, studies with unclear descriptions of COVID-19 infection, and studies that did not include a comparable group, non-English publications, and other types of publications such as the following: editorials, conference papers, reviews, and letters to the editor. In assessed studies, the study group was people who had been diagnosed with COVID-19 and had recovered. The control group was patients who had never had a positive COVID-19 test.

2.4. Data Extraction and Quality Assessment

Using a pre-defined data extraction form that was designed by L.S., the two independent reviewers (I.J. and M.P.) extracted the data from the research, and disagreements were mediated by the third reviewer (L.S.). The following information was extracted from the relevant publications: study characteristics (including first author, publication year, country of origin, study design, and research groups), and patient data (participant count, age, and carotid–femoral pulse wave velocity across groups). The Newcastle–Ottawa Quality Scale (NOS) was used in order to evaluate the level of methodological rigor that was present in each of the studies that were included in the analysis. Based on the selection, comparability, and exposure criteria, NOS allocates a potential four, two, and three stars, respectively. Studies achieving a NOS score ≥ 7 were deemed high quality [31].

2.5. Statistical Analysis

Statistical analyses used Review Manager (version 5.4, Nordic Cochrane Centre, Cochrane Collaboration, Odense, Denmark) and Stata (version 14, StataCorp, College Station, TX, USA) were used. The odds ratios (ORs) with 95% confidence intervals (CIs) were employed for dichotomous data, whereas mean differences (MDs) with 95% CIs were used for continuous data. Every statistical test was conducted using a two-sided approach, with a significance threshold of $p < 0.05$. For continuous outcomes presented as median,

range, and interquartile range, the means and standard deviations were estimated using the methodology delineated by Hozo et al. [32]. The I^2 statistic was used to determine the degree of heterogeneity, with values of 25% indicating low heterogeneity, values of 25–50% indicating moderate heterogeneity, and values more than 50% showing high heterogeneity [33]. If I^2 was greater than 50%, a fixed-effects model was employed; otherwise, a random-effects model was used. Potential publication bias in the included studies was assessed via Egger's test and funnel plots.

3. Results

3.1. Study Selection and Characteristics

The bibliographic search results and selection process are shown in the PRISMA flow diagram (Figure 1). We identified 837 initial records, which were reduced to 612 after the elimination of duplicates. Titles and abstracts were screened, leading to the exclusion of 564 records. After assessing the remaining 48 articles for eligibility, we excluded 39 articles. As a result, nine studies were selected for qualitative synthesis and meta-analysis [34–42].

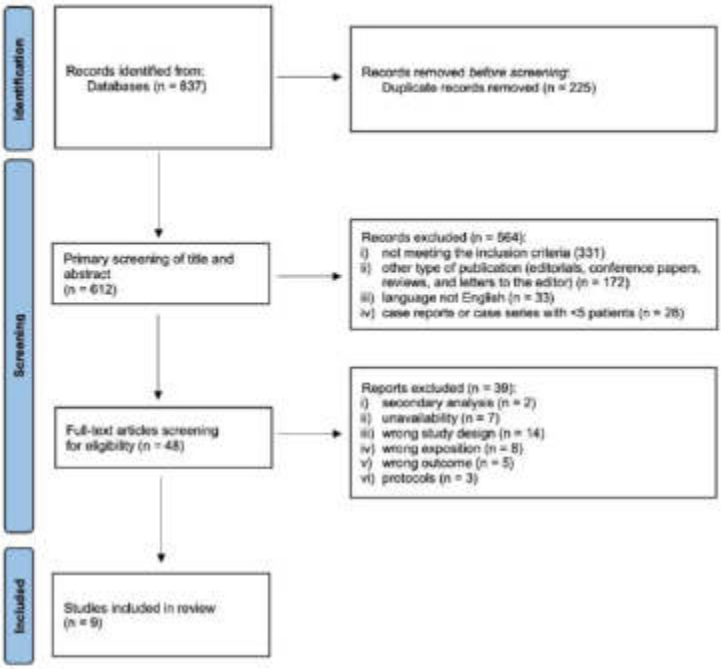

Figure 1. PRISMA systematic review flow diagram.

The essential characteristics of the included studies are outlined in Table 1. A total of nine studies that involved 536 patients were included in this meta-analysis. The mean age of the COVID-19 patient cohort was 50.8 ± 15.1 years, as compared to 51.3 ± 15.0 years in the control groups. Geographically, three studies were conducted in the United States, two in Greece, and the rest in Brazil, Austria, Romania, and the Netherlands. The sample size varied and ranged from 23 to 140 patients. Notably, the NOS scores of all the included studies were ≥7.

Table 1. Characteristics of included studies.

Study	Country	Study Group	No. of Patients	Age	Sex, Male	NOS Scale
Faria et al., 2023 [34]	Brazil	COVID-19	19	47 ± 8	12 (63.2%)	8
		Control	19	43 ± 10	11 (57.9%)	
Tudoran et al., 2023 [35]	Romania	COVID-19	54	47.76 ± 5.43	NS	7
		Control	40	49.47 ± 5.14	NS	
Nandadeva et al., 2023 [36]	United States	COVID-19	12	48 ± 9	NS	7
		Control	11	50 ± 13	NS	
Oikonomou et al., 2023 [37]	Greece	COVID-19	34	57.2 ± 12.9	26 (76.5%)	8
		Control	34	57.4 ± 12.8	23 (67.6%)	
Van der Sluijs et al., 2023 [38]	The Netherlands	COVID-19	31	57.5 ± 3.0	17 (54.8%)	7
		Control	31	56.5 ± 3.0	17 (54.8%)	
Skow et al., 2022 [39]	United States	COVID-19	23	23 ± 3	9 (39.1%)	8
		Control	13	26 ± 4	6 (46.2%)	
Lambadiari et al., 2021 [40]	Greece	COVID-19	70	54.53 ± 9.07	44 (62.85%)	9
		Control	70	54.77 ± 8.95	44 (62.85%)	
		Control	34	57.4 ± 12.8	23 (67.6%)	
Ratchford et al., 2021 [41]	United States	COVID-19	11	20.1 ± 1.1	NS	9
		Control	20	23.0 ± 1.3	NS	
Schnaubelt et al., 2021 [42]	Austria	COVID-19	22	76.0 ± 4.25	11 (50.0%)	8
		Control	22	75.8 ± 4.0	10 (45.5%)	

3.2. Meta-Analysis

All nine studies provided data on cfPWV values among COVID-19 patients and their respective control groups. The pooled analysis showed that cfPWV in COVID-19 patients was 9.5 ± 3.7, compared to 8.2 ± 2.2 in the control groups (MD = 1.32; 95% CI: 0.38 to 2.26; $p = 0.006$; Figure 2). It is important to note that the results from the sensitivity analysis did not alter the direction of the initial findings.

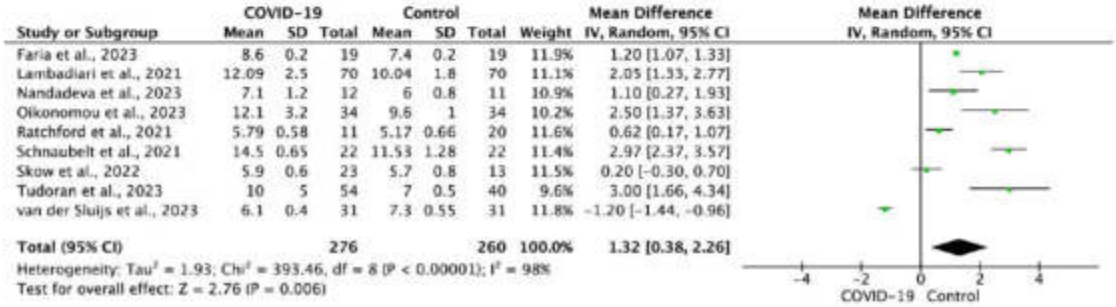

Figure 2. Forest plot of cfPWV in COVID-19 patients vs. non-COVID-19 controls [34–42]. The mean differences for individual studies are represented by the central point of each square, and the associated horizontal line indicates a 95% confidence range. The diamond shapes indicate the consolidated results.

4. Discussion

Our meta-analysis revealed a significant correlation between COVID-19 infection and an increase in cfPWV [34–42]. However, it is worth noting that Van der Sluijs et al. did not observe such a correlation of cfPWV in their research [38], while Skow et al. found a positive, yet insignificant correlation [39]. Nevertheless, the remaining seven analyzed studies demonstrated a clear correlation between cfPWV and COVID-19 infection [34–37,40–42]. These findings suggest that COVID-19 may be responsible for the observed rise in arterial stiffness, which is a well-known marker of cardiovascular (CV) risk [43]. Arterial stiffness reflects changes in blood pressure, flow, as well as vascular diameter, and serves as an

indicator of both the mechanical and functional properties of arterial walls. While the degradation of elastic fibers is the primary factor influencing arterial stiffness, other factors, such as fibrosis on replacement, collagen, elastin cross-linking, and medial calcifications also play important roles.

Studies by Townsend et al. and Lambadiari et al. highlighted that multiple factors contribute to arterial stiffness, including endothelial dysfunction, inflammation, oxidative stress, the turnover of extracellular matrix, and the regulation of smooth muscle tone in muscular arteries [40,44]. SARS-CoV-2 virus targets endothelial cells, entering the cell as soon as it binds to ACE2 receptors, decreasing the number of ACE2 receptors on the cell surface, leading to endothelial cell dysfunction [15,45]. The decreased endothelial function observed in COVID-19 patients results from viral infiltration and increased systemic inflammatory responses [46]. Cytokine storm targets specific receptors located on the surface of endothelial cells, leading to the activation of a number of different mediators, resulting in the activation of platelets and the release of leukocytes into circulation [47]. Uncontrolled systemic inflammation may directly stimulate arterial remodeling or cause adrenoceptor hyporeactivity, impairing vascular responsiveness. Additionally, nitric oxide (NO) deficiency in COVID-19 patients can exacerbate endothelial dysfunction and lead to increased arterial stiffness, impaired smooth muscle relaxation, and increased oxidative stress (further exacerbated by the cytokine storm) [48]. Changes in NO bioavailability, combined with SARS-CoV-2's direct action on endothelial cells after binding to ACE2 receptors, can influence the functions of vascular smooth muscle cells and induce structural alterations in the vascular wall's extracellular matrix, promoting arterial stiffness [49].

This arterial stiffness raises the risk of CV complications, including high blood pressure, heart attacks, and strokes, exerting additional strain on the heart. People with pre-existing CV conditions are particularly susceptible. A study by Faria et al. showed that COVID-19 patients, compared to their healthy counterparts, experienced over-activation of the sympathetic nervous system, vascular dysfunction, decreased physical fitness, and elevated cfPWV values (higher by 1.12 m per second) [34]. This is concerning, considering that previously published studies established PWV as a strong predictor of future CV events and all-cause mortality, and showed that the predictive power of arterial stiffness is higher in subjects with a higher baseline CV risk. This in turn suggests that an increase in arterial stiffness contributes to the elevated CV risk observed in COVID-19 survivors [29]. Elevated risks of stroke are consequences of both COVID-19 and increased arterial stiffness [50]. It is concerning that the effects of COVID-19 seem to last beyond the acute phase of the disease, as the virus may induce post-acute sequelae from COVID-19 (PASC). Nandadev et al. highlighted heightened arterial pressure and cfPWV values in PASC patients, suggesting they could develop CV problems at a faster rate [36]. It is interesting to note that a meta-analysis by Menezes et al. demonstrated that CV disease in COVID-19 patients had both cardioembolic and cryptogenic etiology [51], while factors like atherosclerosis were not directly linked to a COVID-19 positive result. Atrial fibrillation, coronary artery disease, diabetes, and hypertension were shown to be the most prevalent risk factors among COVID-19-positive individuals, increasing the risk of CV disease [51,52].

Ratchford et al. demonstrated a strong association between increased cfPWV and mortality among COVID-19 patients, particularly those with pre-existing chronic conditions, including CV disease [41]. Furthermore, a study by Schnaubelt et al. found that cfPWV among COVID-19 patients who survived the disease was significantly lower than in healthy patients, indicating a potential link with long-term complications [42]. Additionally, Kumar et al. showed increased cfPWV in severe COVID-19 cases as compared to non-severe cases [53]. We can assume that COVID-19 influences arterial stiffness, and this effect correlates with the severity of symptoms.

Research also shows that pre-existing conditions are also major factors that can accelerate arterial aging in the course of COVID-19. Tudoran et al. demonstrated a correlation between aortic and arterial stiffness, as well as diastolic dysfunction, in seemingly healthy individuals with post-acute COVID-19 syndrome patients. Their findings showed that

women with a history of PASC and metabolic syndrome showed elevated cfPWV values and metrics of worsening of their diastolic dysfunction [35]. Throughout a six-month observation period, the values showed improvement; however, they did not revert fully. Oikonomou et al. evaluated cfPWV as well as the impairment of the left ventricle function measured by global longitudinal strain in the 6-month observation. While improvement was noted in both parameters, the values are still worse than in the control group, which may support the hypothesis that after recovering from COVID-19, and there is an increase in both arterial stiffness and the risk of adverse CV events in comparison to the general population [37]. Similarly, a 12-month follow-up study by Iconomidis and their team found COVID-19 survivors to still possess higher cfPWV values compared to controls at the 12-month follow-up evaluation. The authors showed considerable improvements in oxidative stress (levels of MDA), CFR, and myocardial work measures, in addition to a borderline improvement in left ventricular strain, which, nevertheless, continued to be impaired in comparison to the controls [54].

Another crucial area of research pertains to the management of post-COVID complications, including chronic arterial stiffness. While arterial stiffness is not easily reversible with medication or surgical interventions, additional therapies can be explored. One potential approach is the implementation of post-COVID-19 rehabilitation, which could help alleviate symptoms and improve overall outcomes. Comprehensive rehabilitation strategies, including exercise, physiotherapy, lifestyle changes, and cardiovascular rehabilitation, might help combat the long-term implications of arterial stiffness and increase the patient's quality of life post-COVID. Gounaridi et al.'s research showed that a three-month cardiopulmonary post-acute COVID-19 rehabilitation significantly improved PWV, reducing it from 8.2 ± 1.3 m/s to 6.6 ± 1.0 m/s. Thus, rehabilitation could facilitate the recovery of endothelium-dependent vasodilation and arteriosclerosis [55]. Furthermore, exercise training conducted at home lowered cfPWV by a mean of -2.0 ± 0.6 m/s and has the potential to be an invaluable supplement to post-COVID rehabilitation [56].

However, it is essential to consider that the effect of COVID-19 may be dependent on the mutation of the virus. Skow et al. conducted their research on individuals during the Omicron wave of infections and found that arterial stiffness did not differ significantly between groups of individuals who had the Omicron variant of COVID-19 and controls who had never been exposed to COVID-19. According to these findings, the Omicron variant does not pose a threat to the CV health of young, vaccinated individuals who are otherwise healthy [39]. Nevertheless, there are no studies assessing other subtypes and mutations of COVID-19. Therefore, the correlation between the specific COVID-19 types and arterial stiffens remains inconclusive. Future research could provide us with more precise insights.

The measurement of cfPWV has significant clinical implications in terms of risk assessment and timely medical interventions to prevent COVID-19-related mortality and CV complications, particularly in hospitalized patients, patients with a severe disease course, or those who simply struggled with COVID-19. The timely identification of patients with increased arterial stiffness allows for the implementation of appropriate early medical interventions, including aggressive blood pressure management, optimization of medication regimens, and lifestyle changes, such as dietary changes, regular exercise, and smoking cessation. By implementing these interventions early on, healthcare providers can potentially mitigate the adverse CV effects of COVID-19 and improve patient outcomes. Moreover, longitudinal cfPWV monitoring in hospitalized COVID-19 patients can provide valuable information on the progression of arterial stiffness over time, enabling healthcare professionals to implement personalized treatment strategies, make necessary adjustments, and evaluate the effectiveness of interventions. By closely monitoring cfPWV, clinicians can track the response to treatment, identify any worsening of arterial stiffness, and promptly modify the management plan accordingly.

While our study brings valuable insights, it is essential to acknowledge its limitations. To the best of our knowledge, this is the first meta-analysis examining the influence of

COVID-19 disease on arterial stiffness evaluated by cfPWV. The available research on studies investigating the connection between cfPWV and COVID-19 remains limited, both in terms of the number of studies and participant numbers. Furthermore, the observation window is short, covering the period between 2021 and 2023.

5. Conclusions

There is a strong association between COVID-19 infection and an elevated cfPWV, indicating a potential link between the virus and increased arterial stiffness. The substantial rise in arterial stiffness, an established indicator of CV risk, clearly shows the profound impact of COVID-19 on both immediate and long-term health outcomes. By accurately identifying individuals with augmented arterial stiffness, clinicians can tailor interventions and implement strategies that are more targeted toward lowering the CV risks associated with COVID-19. This will also facilitate timely medical and rehabilitation interventions for patients. However, further research is required in order to provide a clearer understanding of the connection between COVID-19 infection, arterial stiffness, and subsequent CV events. Thus, cfPWV measurements will be more useful as a diagnostic and prognostic instrument.

Supplementary Materials: The following supporting information can be downloaded at the following link: https://www.mdpi.com/article/10.3390/jcm12175747/s1. Table S1: PRISMA 2020 Checklist.

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Publikacja 4: Is the association between pulse wave velocity and bone mineral density the same for men and women? - A systematic review and meta-analysis**.**

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Is the association between pulse wave velocity and bone mineral density the same for men and women? - A systematic review and meta-analysis

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HIGHLIGHTS

- baPWV is negatively correlated with BMD.
- Pooled correlation coefficient is statistically significant in women, but not in men.
- Gender differences in baPWV and BMD association exist.

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ABSTRACT

Background: Brachial aortic Pulse Wave Velocity (baPWV) and bone mineral density (BMD) are important indicators of cardiovascular health and bone strength, respectively. However, the gender-specific association between baPWV and BMD remains unclear. The aim of our study is to evaluate the relationship between baPWV and BMD in men and women populations

Methods: A comprehensive search was conducted in electronic databases for relevant studies published between the 1th and 30rd of April 2023. Studies reporting the correlation between baPWV and BMD in both males and females were considered. A random-effects model was used to calculate pooled correlation coefficients (r).

Results: Relevant data for both genders were found in six articles. In all publications included in the meta-analysis, the total number of studied individuals was 3800, with 2054 women and 1746 men. Pooled correlation coefficient was −0,24 (95 % CI: −0.34; −0.15) in women population, and −0.12 (95 %CI: −0.16, −0.06) in men.

Conclusion: Based on the published data, we found that baPWV is negatively correlated with bone density in women. However, in men we do not find such a relationship. These findings suggest the importance of considering gender-specific factors when assessing the cardiovascular and bone health relationship.

1. Introduction

Osteoporosis is a skeletal disorder characterized by reduced bone density mass due to the deterioration of the microarchitecture of the bone, ultimately making the bone brittle and prone to fractures (Curtis et al., 2017; Osterhoff et al., 2016). The gold standard in the diagnosis of osteoporosis is the measurement of bone mineral density (BMD), which is assessed using a radiological (X-ray) measuring method called densitometry (Morgan & Prater, 2017). Decreased bone density, depending on the value, indicates osteoporosis or conditions predisposing to osteoporosis – osteopenia (National Clinical Guideline Centre (UK) 2012). Osteoporotic fracture risk is higher in older women than in older men, and all postmenopausal women should be evaluated for signs of osteoporosis during routine physical examinations (Lane, 2006). For this reason, much attention is paid to updating the guidelines of the management of osteoporosis in postmenopausal women (Management

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of Osteoporosis in Postmenopausal Women, 2021). Arterial stiffness, which is an indicator of the severity of atherosclerosis, is a phenomenon of increased vascular stiffness, loss of elasticity, calcification of the vessel walls and restriction of blood flow that affects endothelium of large and medium-sized arteries (Laurent et al., 2006).The brachial ankle Pulse Wave Velocity (baPWV) is a measure of systemic arterial stiffness measured by brachial and tibial arterial wave analysis. BaPWV measurement is a non-invasive, effortless, repeatable and well standardized (Munakata, 2014; Tomiyama et al., 2016). Early assessment of arterial stiffness is essential because its alteration can precede clinical manifestation of cardiovascular disease (Castelli et al., 2023). Arterial stiffness as well as osteoporosis share common risk factors and clinical manifestations (Avramovski et al., 2016; Crepaldi & Maggi, 2009; McFarlane et al., 2004; Sage et al., 2010; Tankó et al., 2006). Arterial stiffness as well as bone mineral density progressively increases with aging and are independent predictors of cardiovascular disease (CVD) risk (DuPont et al., 2019). In the aging process of the body, inflammatory processes play a significant role, which are an essential factor in the development of atherosclerosis (Melu et al., 2022). This makes them more susceptible to fractures, even from minor injuries or falls. Inflammatory processes, on the other hand, are the body's natural defense mechanisms against injuries or infections. When tissues are damaged, the body triggers an inflammatory response to repair the damage and protect against further harm. There is a connection between osteoporosis and the inflammatory process. The inflammatory process is the body's response to tissue damage and can occur in various parts of the body.

The connection between osteoporosis and inflammation lies in the fact that chronic inflammation, which persists over an extended period, can have a negative impact on bone health (Ginaldi et al., 2005). Inflammatory molecules and cells can interfere with the normal process of bone remodeling, which involves the continuous breakdown and rebuilding of bone tissue. When this balance is disrupted by ongoing inflammation, it can lead to increased bone resorption (breakdown) and decreased bone formation (Terkawi et al., 2022). Over time, this imbalance can contribute to the development and progression of osteoporosis. Therefore, it's important to manage chronic inflammation effectively, not only for overall health but also to reduce the risk of osteoporosis. Moreover, research suggests that chronic inflammation may play a role in the development of osteoporosis. Inflammatory processes can lead to increased bone resorption (the breakdown of bone tissue) and reduced synthesis of new bone tissue. Inflammatory reactions can influence the balance between bone formation and bone breakdown (Epsley et al., 2021).

Chronic inflammation, characterized by persistent and prolonged inflammation in the body, can have detrimental effects on various tissues and organs, including bones. When the body is in a state of chronic inflammation, it releases inflammatory molecules and immune cells that can affect bone health. One of the key mechanisms through which chronic inflammation contributes to osteoporosis is by promoting increased bone resorption. Inflammatory cytokines, which are signaling molecules involved in the immune response, can activate osteoclasts, specialized cells responsible for breaking down bone (Xu et al., 2023). This leads to a higher rate of bone resorption, where bone tissue is broken down more rapidly than it is rebuilt. At the same time, chronic inflammation can interfere with the process of bone formation. It can suppress the activity of osteoblasts, the cells responsible for building new bone tissue. This dual effect—increased bone resorption and reduced bone formation—creates an imbalance in bone remodeling, ultimately resulting in the loss of bone density and increased fragility seen in osteoporosis. Therefore, it is crucial to manage chronic inflammation effectively, not only to prevent osteoporosis but also for overall health. Lifestyle modifications, such as adopting an anti-inflammatory diet, engaging in regular physical activity, and avoiding smoking, can help reduce inflammation. In some cases, healthcare providers may recommend medications to control chronic inflammation and protect bone health, especially for individuals at risk of osteoporosis due to inflammatory conditions or other factors (Ginaldi et al., 2005; Loi et al., 2016).

In the context of conditions like rheumatoid arthritis, where chronic inflammation is a hallmark feature, the persistent presence of these proinflammatory cytokines can disrupt the delicate balance between bone resorption and bone formation (Auréal et al., 2020). This imbalance ultimately leads to bone loss and the increased risk of osteoporosis (Sözen et al., 2017). Therefore, individuals with chronic inflammatory conditions are at greater risk of developing osteoporosis, and it underscores the importance of managing both the underlying inflammation and bone health in these patients. Healthcare providers often work to control inflammation using medications and other strategies, and they may also consider interventions to prevent or treat osteoporosis in individuals with chronic inflammatory diseases (Amaranekara et al., 2015; Kitaura et al., 2020).

The research on the association between Pulse Wave Velocity (baPWV) and Bone Mineral Density (BMD), as outlined in the systematic review and meta-analysis, holds significant implications for the field of gerontology and our understanding of the aging process (Tang et al., 2021).

As individuals age, they often face increased risks of cardiovascular issues and bone health deterioration, both of which can significantly impact their overall well-being and quality of life (Guo et al., 2022). Evidence supports that there are sex differences in the time course of aging-related arterial stiffness and the associated CVD risk, which increases disproportionately in postmenopausal women (DuPont et al., 2019). Since there are many common risk factors for bone loss and the advancement of atherosclerosis, it may be assumed that increased arterial stiffness may be a diagnostic marker for the development of osteoporosis. In the context of aging, preventive measures become increasingly important to maintain the health and well-being of older individuals. One crucial aspect of preventive care is assessing bone mineral density (BMD) in individuals, especially those who may have atherosclerosis. Atherosclerosis is a condition characterized by the buildup of plaque in the arteries, and it is associated with an increased risk of cardiovascular events such as heart attacks and strokes.

Given these connections, assessing BMD in individuals with atherosclerosis may be relevant in certain cases. It can help identify those at increased risk of osteoporosis and its complications, such as fractures resulting from falls (Veronese et al., 2017). If low bone density is detected, appropriate interventions can be implemented, including lifestyle modifications, dietary changes, and potentially medication to strengthen bones. Ultimately, this holistic approach to healthcare, considering the interconnectedness of various health conditions, is in line with the principles of gerontology, which aims to improve the overall well-being and quality of life of older individuals (Mazza et al., 2021). That is why we are looking for a non-invasive diagnostic marker that will help us identify groups of patients at high risk of osteoporosis - requiring in-depth diagnostics and implementation of targeted treatment. The aim of our study is to evaluate the relationship between baPWV and BMD in male and female populations.

2. Materials and methods

Between the 1st and 30th of April 2023, we searched the PubMed, Web of Science, Scopus and Cochrane with the following terms: (bone mineral density [Title/Abstract]) AND (arterial stiffness [Title/Abstract]); (bone mineral density [Title/ Abstract]) AND (pulse wave velocity [Title/Abstract]); (bone mineral density [Title/Abstract]) AND (brachial ankle pulse wave velocity[Title/Abstract]). We additionally searched the reference lists of the retrieved manuscripts and checked the manuscripts citing the retrieved papers. We especially searched through the reference lists of previous narrative reviews of the topic. Fig. 1 presents the flow of the inclusion of studies in the present review.

The review was performed according to the systematic reviews and

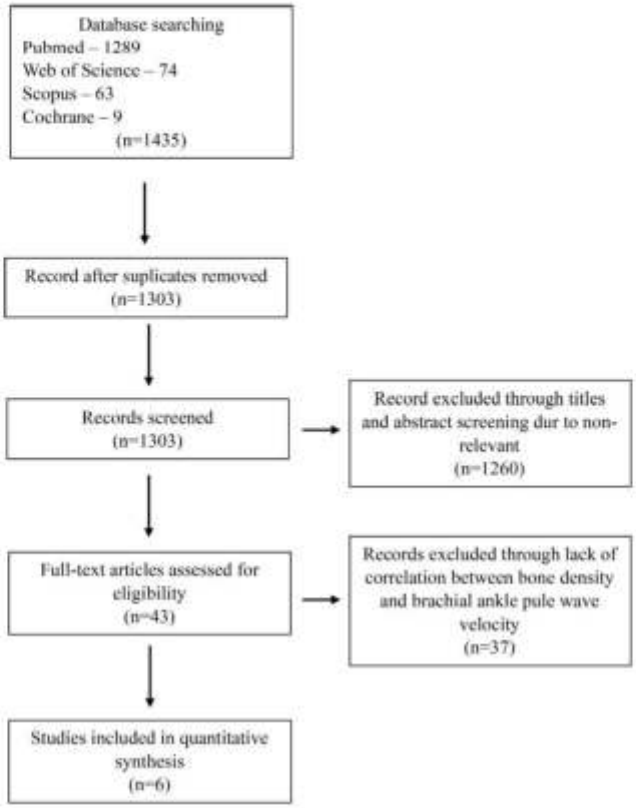

Fig. 1. The PRISM diagram for the review and the meta-analysis).

meta-analysis (PRISMA) guidelines (Moher et al., 2009; Shamseer et al., 2015). The literature search and manuscript selection were performed by two independent researchers (IJ, JB). The data extraction was performed by IJ and RO with the help of MM and JB. The quality of the included studies was rated using Newcastle - Ottawa Quality Assessment Scale (Stang, 2010). The values on this scale pertain to data selection and study groups (A-D). The comparability of primary and secondary factors among groups is also assessed (E). The methods used to collect information from patients are examined as well (F–H). We limited our search to the English language reports of human studies.

2.1. Inclusion and exclusion criteria

Studies were included if they measured correlation coefficient between BMD and baPWV. To increase the homogeneity of the included studies, we decided to include articles that measure BMD at the lumbar spine and exclude articles that measure BMD at other locations. For data from one research study that was published in several articles, the article with the most comprehensive data was included. The following information from the articles was extracted: journal name, first author name, publication year, research type, research population, age, sample size, research area, Pearson correlation coefficients between BMD measurement in lumbar spine and baPWV. The second aspect pertains to the exceptional quality of the publications as measured by the Newcastle–Ottawa Quality Assessment Scale, which scores between 7 and 8 points. Only one article achieved a score below 7 on the aforementioned scale. Moreover, it should be noted that four out of the six studies included were prospective studies. The last advantage is that the studies involved quite large groups of patients. Only one study included in the meta-analysis had fewer than 100 participants.

2.2. Heterogeneity and sensitivity

The heterogeneity of the articles was assessed using the Cochran Q test and I^2 inconsistency index (0–100 %). The higher the I^2, the greater the heterogeneity. The values of 25 %, 50 %, and 75 % indicate low, moderate, and high heterogeneity, respectively. The sensitivity testing was conducted by removing individual studies from the overall result.

3. Results

3.1. The characteristics of the included studies

A total 6 full-text studies were included in the quantitative analysis. Relevant data for both genders were found in six articles, data for women only were in three articles. In all publications included in the meta-analysis, the total number of studied individuals was 3800, with 2054 women and 1746 men. The mean age of patients was less than 60 years in the most included articles. BMD at the lumbar spine (LS) was measured by dual-energy X-ray absorptiometry at all included studies. PWV was assessed using the brachial-ankle cuff, where the waveforms from the arm and calf are obtained with plethysmographic method.

Details are presented in Table 1.

3.2. BMD and baPWV relationship

We decided to provide meta-analysis calculations separately for both genders.

Pooled correlation coefficient was −0,24 (95 % CI: −0.34; −0.15) in women population (Fig. 2).

There was moderate heterogeneity among the included studies: $Q = 8,2$; $p = 0.117$ and inconsistency index $I^2 = 43$ % (95 % CI; 0–77 %).

Sensitivity analysis showed that exclusion of individual studies did not significantly change the results. Correlation coefficient values ranged from −0.22 (95 % CI, −0.32 to −0.13) to −0.28 (95 % CI, −0.36 to −0.20).

Pooled correlation coefficient for men population was −0,12 (95 % CI: −0.18; −0.06). Forest plot is presented in Fig. 3.

Studies analyzing men population demonstrated low heterogeneity: $Q = 0,7$; $p = 0.682$ and inconsistency index $I^2 = 0$ % (95 % CI; 0–91 %).

Sensitivity analysis showed a small impact of individual studies on the overall result. Correlation coefficient values ranged from −0.10 (95 % CI, −0.22–0.02) to −0.13 (95 % CI, −0.20 to −0.06) (Tables 2 and 3).

3.3. Quality assessment

Using the Newcastle–Ottawa Quality Assessment Scale, it appears that the publications included in the meta-analysis show high quality, with the exception of the study by Kim NL, et al. Their study exhibited several methodological flaws and limitations. The retrospective nature of the study restricted the analysis to medical documentation from the participants. Furthermore, this paper does not distinguish between a study and a control group. Therefore, using the Newcastle-Ottawa Quality Assessment Scale, the publication by Kim NL, et al. collected the fewest points. (Table 4).

Table 1
Study characteristics.

Author, publication year, country	Population	Study design	Measured BMD with	Measured PWV with
Kim et al., 2014, Korea	Men – 111 Women - 128	Retrospective study, MC	DXA (Lunar Prodigy Advance, GE Lunar, Madison, WI, USA)	Automatic waveform analyzer (VP-1000; Nippon Colin Ltd., Komaki, Japan
Liang et al., 2014, China	Men – 168 Women - 222	Cross-sectional study, SC	DXA (Osteocore 2; Medilink Inc).	Automatic waveform analyzer (form PWV/ABI; Colin Co
Wang et al., 2015, China	Men – 1467 Women - 1020	Prospective study, MC	DXA (Discovery A, Hologic, USA)	Automatic waveform analyser (Colin Co., Komaki, Japan)
Mikami et al., 2009, Japan	Women - 143	Prospective study, SC	DXA (QDR4500, Hologic Inc., USA	Automated device (form PWV/ABI; Colin Co. Ltd., Komaki, Japan)
Jaalkhoni et al., 2019, Japan	Women - 446	Prospective study, MC	DXA (QDR4500 A, Hologic, Bedford, MA, US)	Volume plethysmographic apparatus (Form PWV/ABI; Fukuda Colin Co., Ltd. Tokyo, Japan)
Sumioka et al., 2006, Japan	Women - 95	Prospective study, SC	DXA (QDR-1000 W, Hologic, Waltham, MA, USA)	Automatic waveform analyser (Colin Co., Komaki, Japan)

4. Discussion

Based on the published data, it has been determined that the presence of bone density in women is negatively correlated with baPWV. The pooled correlation coefficient is −0,24 (95 % confidence interval: −0.34; −0.15). The correlation coefficient in the men population is −0.12 (95 % CI: −0.18; −0.06). We can interpret both of these values as a weak negative correlation. Especially the correlation coefficient in men is very weak. Some rules of interpretation would consider it as a lack of correlation, as a negligible correlation (Mukaka, 2012). To the best of our knowledge, this is the first meta-analysis to demonstrate differences in correlation between PWV and BMD between genders.

Osteoporosis and atherosclerosis share common pathophysiological mechanisms. In osteoporosis, there is a decrease in the amount of calcium present in the bones, which, upon entering the bloodstream, is deposited in the arteries, resulting in an increase in arterial stiffness. Both diseases get worse with age (Fujihara et al., 2017). Furthermore, the inflammatory basis of both osteoporosis and atherosclerosis is taken into account. Osteoporosis is more prevalent in women, whereas atherosclerosis is statistically more advanced in men, which can be attributed to a higher frequency of smoking and more advanced dyslipidemia (Baldwin et al., 2017). In our analysis, it is important to clarify the observed gender-based differences in the impact of the correlation between elevated arterial stiffness (a predictor of atherosclerosis) and decreased bone density (a predictor of osteoporosis). It appears that this partial difference could be explained by the characteristics of the group of people included in the research. Women are more likely to suffer from osteoporosis, even though its severity increases after menopause. In the interim, the presented meta-analysis revealed that the average age in both gender groups fluctuated around 50, indicating a relatively youthful age for men and not indicating menopause in women. It is noteworthy that we did not conduct a correlation analysis between osteoporosis and atherosclerosis, but rather examined the correlations among the factors that predispose to these diseases, specifically lower bone mineral density and elevated peripheral vascular resistance.

Findings from our meta-analysis may impact the decision to diagnose women earlier and with greater attention for both atherosclerosis and osteoporosis. This in mind, we should take the time to actively look for the signs of osteoporosis in people with a history of cardiovascular disease, as well as assessing the cardiovascular risk more thoroughly in women with the condition.

In two articles included in the meta-analysis, BMD was a dependent variable and baPWV was an independent variable, and in four of them it was the opposite: baPWV was a dependent variable and BMD was an independent variable. However, we included in our meta-analysis the values of Pearson's correlation coefficients between BMD and baPWV, which were a preliminary part of the analyzes conducted in these articles. We can therefore treat both variables as independent variables, without indicating which variable is the dependent and which is the independent variable.

In total, 54.1 % of participants in these studies were female. In study Wang et al. (2015) population consisted of 2487 subjects (1467 men, 1020 women) and were selected to be free of major diseases which might affect atherosclerosis and bone metabolism. The average age of men was 45.72 years, and the average age of women was 44.71 years. The baPWV was significantly associated with BMD in both male and female after adjusting for age only. The other variables of subclinical atherosclerosis (ABI, CIMT, eGFR or microalbuminuria) failed to a reach statistical significance with the BMD. They detected that baPWV was an independent factor significantly correlated with BMD. Pearson's correlation was used to identify the BMD associated with the change in baPWV. baPWV was statistically significantly correlated with BMD in both genders. The correlation was stronger in females than in males; in females, the correlation was stronger in post-menopause than pre-menopause. In healthy Han Chinese population (Liang et al., 2014) consequently, 222 women and 163 men, aged 37–87 years, with normal

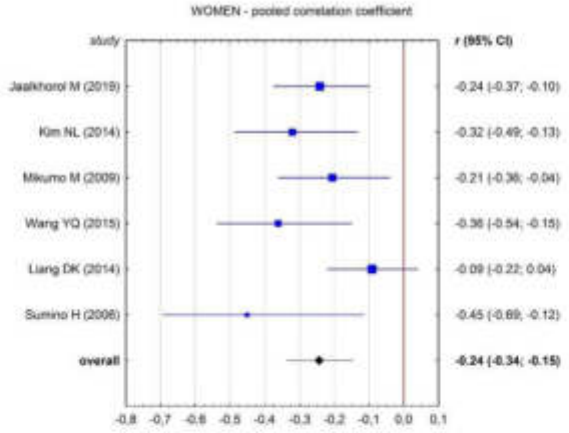

Fig. 2. Forest plot, women.

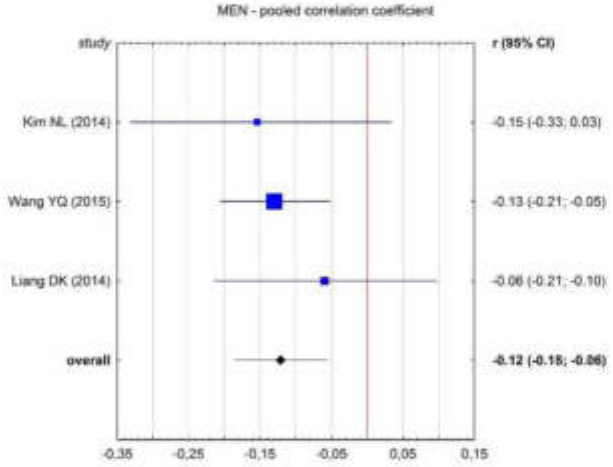

Fig. 3. Forest plot, men.

Table 2
Sensitivity analysis, women.

Excluded study	r	95 % CI	p value	Weight [%]
Jaalkhorol et al. (2019)	−0.25	−0.37; −0.13	<0.001	78 %
Kim et al. (2014)	−0.23	−0.34; −0.12	<0.001	84 %
Mikumo et al. (2009)	−0.26	−0.37; −0.14	<0.001	81 %
Wang et al. (2015)	−0.22	−0.32; −0.12	<0.001	87 %
Liang et al. (2014)	−0.28	−0.36; −0.20	<0.001	76 %
Sumino et al. (2008)	−0.23	−0.32; −0.13	<0.001	94 %
All studies included	*−0.24*	*−0.34; −0.15*	*<0.001*	*100 %*

Table 3
Sensitivity analysis, men.

Excluded study	r	95 % CI	p value	Weight [%]
Kim et al. (2014)	−0.12	−0.18; −0.05	0.001	88 %
Wang et al. (2015)	−0.10	−0.22; 0.02	0.108	29 %
Liang et al. (2014)	−0.13	−0.20; −0.06	<0.001	76 %
All studies included	*−0.12*	*−0.18; −0.06*	*<0.001*	*100 %*

BMD, osteopenia, and osteoporosis were included in the analysis. In both genders, the differences of ABI, PWV, and CIMT among the three groups (BMD-dependent) were not found after adjustment for age. The study by Kim et al. (2014) participated 239 healthy people (women: 128, men: 111), mean age was 53 years old. History of hypertension, diabetes, dyslipidemia, thyroid disease, parathyroid disease, rheumatoid arthritis, history of taking steroids, diagnosed with cancer within the past 5 years, gonad dysfunction, patient taking hormonal agents – were excluded from the study. The other studies in our meta-analysis looked only at women. Mikumo et al. (2009) an investigation carried out on the association between arterial stiffness, lumbar BMD and bone metabolic markers in Japanese 143 postmenopausal women (mean age 57.9 ± 8.3), where there was a significant negative correlation between baPWV and BMD ($r = -0.21$; $P = 0.0135$). An additional analysis included the remaining 75 subjects, but excluded subjects with hypertension and obesity. Here, a more negative correlation between baPWV

Table 4
The Newcastle-Ottawa Quality Assessment Scale.

Author, Year	Selections				Comparability	Outcome			Score
	A	B	C	D	E	F	G	H	
Kim et al. (2014)	1	1	1	1	1				5
Liang et al. (2014)	1	1	1	1	1	1	1		7
Wang et al. (2015)	1	1	1	1	1	1	1		7
Jaalkhorol et al. (2019)	1	1	1	1	2	1	1		8
Mikuno et al. (2009)	1	1	1	1	1	1	1		7
Sumino et al. (2006)	1	1	1	1	1	1	1		7

and BMD ($r = -0.315$; $P = 0.006$), and a positive correlation between baPWV and BAP ($r = 0.248$; $P = 0.032$) were also significant. In earlier Japanese study (Sumino et al., 2006) of 95 Japanese postmenopausal women (mean age: 55.4 ± 6.3 years) exclusion of a person with diabetes, hypertension, severe dyslipidemia, cardiovascular disease, or liver disorder, a history of osteoporotic fracture. Individuals were assigned to one of three groups according to their BMD in the lumbar spine: normal BMD (38 women), osteopenia (a BMD value 1–2.5 S.D. below the mean value for young adults, 32 women), and osteoporosis (a BMD value more than 2.5 S.D). After adjusting for age and years since menopause, women with osteoporosis had a significantly higher baPWV than those with normal BMD (1500 ± 220 cm/s versus 1340 ± 215 cm/s; $P < 0.05$), but no significant differences in baPWV were seen between the osteoporotic and osteopenic groups or between the osteopenic and normal BMD groups. In Jaalkhorol et al. (2019) study they analyzed data from the 446 women with baPWV lower than 1800 cm/s, mean age 62.6 ± 7.9. In this study, there were also people with current and past history of diseases including hypertension (36,6 %), dyslipidemia (23,5 %), and diabetes mellitus (3,5 %).Age and BMDs were significantly correlated with baPWV at follow-up. A strong positive correlation was found between baPWV at baseline and at follow-up.

The negative correlation between baPWV and BMD observed in women suggests that as women age, their cardiovascular health may be intricately linked to their bone strength. This finding underscores the importance of comprehensive healthcare strategies tailored to the unique needs of aging individuals, particularly women, to mitigate the risks associated with cardiovascular diseases and osteoporosis. Moreover, higher absolute value of the correlation coefficient between baPWV and BMD in the group of women than in the group of men implies that gender-specific factors play a pivotal role in how cardiovascular health and bone density interact in aging populations. This underscores the importance of considering gender-specific variables in gerontological research and healthcare practices. In summary, this research bridges the gap between cardiovascular health and bone strength, providing crucial insights into how these factors are interconnected in the context of aging. Such knowledge is essential for gerontologists and healthcare providers alike, as it informs more effective strategies for promoting healthy aging and addressing age-related health challenges in a gender-specific manner.

In a study by Avramovski P et al. 2018, it came out that the significance of age as a factor influencing PWV is evident. By integrating carotid-femoral Doppler PWV measurement into the standard diagnostic toolkit for assessing arterial stiffness, we can identify individuals at risk not only among the elderly population but also among younger patients with heightened cardiovascular risk. This enables earlier identification and prompts recommendations for preventive measures such as managing arterial stiffness, addressing hypertension, or initiating diabetes treatment when necessary (Avramovski et al., 2018).

In a study conducted by Zhang M et al. 2019, involving a cohort of 580 patients with an average age of 64.82 ± 11.4 years, the researchers reported a noteworthy finding. Specifically, they observed a statistically significant correlation between bone mineral density (BMD) in the thoracic spine (referred to as TH BMD) and Cardio-Ankle Vascular Index (CAVI) values among middle-aged and elderly Chinese inpatients. This finding suggests a potential link between the health of the thoracic spine and cardiovascular health, highlighting the importance of further investigation into the relationship between these two variables, especially in aging populations (Zhang et al., 2019).

4.1. Lowering BMD as a prelude to osteoporosis especially in women

With the ageing population osteoporosis is continually increasing, and it has become an important health problem globally. A study involving US adults aged 50 years reported that the prevalence of osteoporosis was 11 %, whereas the prevalence of low bone mass ranged from 28 % to 45 % in 2013 (Looker et al., 2017). Gender differences in the prevalence of the disease are also significant. A meta-analysis of 33 articles revealed that the prevalence of osteoporosis in Chinese people aged >60 years was 36 %; comprising 23 % men and 49 % women (He et al., 2016). Therefore, special studies on the diagnosis and management of osteoporosis in women have been developed (Yong & Logan, 2021). The studies included in our meta-analysis show the correlations of increased arterial stiffness with bone density - at every stage - from normal BMD to osteopenia to osteoporosis.

4.2. Pulse wave velocity as still an important indicator of multimorbidity and mortality

In a meta-analysis by Tomiyama, Matsumoto, Shiina, and Yamashina (2016) and Munakata (2014) demonstrated that the brachial-ankle PWV is an independent predictor of future cardiovascular events. Furthermore, the treatment of cardiovascular risk factors and lifestyle modifications have been shown to improve the brachial-ankle PWV (Tomiyama & Shiina, 2020). Pulse Wave Velocity is also considered marker that may predict cardiovascular and all-cause mortality of hemodialysis patients (Ng et al., 2023); and together with Blood Pressure Variability they constitute prognostic indicators in elderly patients (de la Sierra et al., 2023). In the Sun study (Sun et al., 2021), increased baPWV was shown to be more strongly associated with sarcopenia and arteriosclerosis, which are known to be associated with osteoporosis and cause high mortality among patients.

4.3. Gender differences in arterial stiffness

In the literature, during the analysis of age groups, differences associated with gender in the mean values of the structural and functional parameters of the artery were absent in the age group 4–8 years, but at ~15 years, they began to appear (Lloyd-Jones et al., 2021). Interestingly, for the different age groups, no gender-related difference was observed for arterial stiffness in the upper extremity, whereas, in males, cfPWV was found to be higher (Jang et al., 2014). These results show that starting at ~15 years, for elastic arteries such as the aorta, gender-related differences can be found (Curcio et al., 2016). The research emphasized the role of different hormonal balance, including the protective effect of estrogens in premenopausal women compared to young men. However, the initially protective role of female sex hormones in combination with the subsequent acceleration of increased cardiovascular risk remains unclear (Hayward et al., 2000; Lebrun et al., 2002; Moreau, 2019; Priest et al., 2016; Rodgers et al., 2019; Zaydun et al., 2006).

4.4. Concatenation arterial stiffness and osteoporosis

A very interesting explanation of the pathophysiological mechanisms of the combination of atherosclerosis and bone loss leading to osteoporosis was described by Szekanecz et al. (2019). The "Bermuda triangle" of atherosclerosis, osteoporosis, and inflammation. Under non-inflammatory states, common conventional risk factors and "low–grade" inflammation may link atherogenesis with bone loss. Cardiovascular disease and osteoporosis are crucial health problems (Yang & Huang, 2023). They may occur simultaneously in the general population (den Uyl et al., 2011). Furthermore, both have also been associated with inflammatory rheumatic musculoskeletal diseases, such as rheumatoid arthritis and ankylosing spondylitis (Cabling et al., 2023). Paper Pusztai et al. (2021) describes common pathogenic pathways in inflammatory atherosclerosis and bone loss. In the Zhang et al. (2022) study, it was shown that increased arterial stiffness, as measured by baPWV, was associated with the risk of functional disability, which can cause falls in people with osteoporosis.

4.5. The impact of methodology of PWV assessment and bone mineral density on the meta-analysis results

We should also mention the literature on the subject, which, for reasons not meeting the criteria adopted by us, we did not include in the calculations. In the study Jiang et al. (2018), divided patients into groups depending on baPWV - categorized into a normal (baPWV $<$ 1400 cm/s) or high (baPWV $\geq$ 1400 cm/s) - without giving an average overall correlation. After full adjustment for the relevant covariates, a boundary significant association was found between low BMD in the femoral neck and baPWV in postmenopausal women (odds ratio = 1.77, $p = 0.049$). After full adjustment, neither BMD nor low BMD were significantly associated with subclinical atherosclerosis in men or postmenopausal women. There are isolated reports of gender differences in this topic. In study Ranatunga et al. (2023) demonstrated that markers of arterial stiffness (as aortic means cfPWV, carotid intima media thickness -CIMT) are associated with poorer bone health (whole body BMD) in Indian women, but not in men. In some studies, instead of measuring BMD using densitometry, appropriate questionnaires that could predict osteoporosis were used (Blake & Fogelman, 2007). In the study by Huan Y et al. the authors investigated the correlation between arterial stiffness (baPWV), including a cutoff value, and the risk of osteoporosis as assessed by the Osteoporosis Self-Assessment Tool for Asia (OSTA). They showed a significant correlation between the OSTA index and baPWV, suggesting a potential predictive value of baPWV in elderly patients at high risk of osteoporosis (Xuan et al., 2019).

4.6. Limitations

Our meta-analysis has limitations. First, we chose articles with only baPWV and only lumbar BMD. Articles with cfPWV and other BMD measurement sites were not included in the analyses. We wanted the articles to be more homogeneous to limit heterogeneity. Secondly, all articles in the meta-analysis came from one continent (Asia), so the conclusion as it does not apply into the population applies to the entire population. The meta-analysis contained a few articles. The aim was to reduce heterogeneity by aiming for homogeneity of articles. Moreover, there were significantly fewer publications that contained data pertaining to men in comparison to those pertaining to women. Our meta-analysis also possesses strengths. The first strength is the high degree of homogeneity observed in the included studies during the analysis. Our meta-analysis also possesses strengths. The first strength is the high degree of homogeneity observed in the included studies during the analysis. The last advantage is that the studies involved quite large groups of patients. Only one study included in the meta-analysis had fewer than 100 participants.

5. Conclusion

In conclusion, this systematic review and meta-analysis provide evidence of a moderate negative correlation between baPWV and BMD in the female population, while the correlation in the male appears to be weaker. This study, by investigating the gender-specific relationship between baPWV and BMD, provides valuable insights into the factors that contribute to the age-related health concerns. The findings suggest that gender differences exist in the association between cardiovascular health (baPWV) and bone strength (BMD). These results underscore the importance of considering gender-specific factors when evaluating the connection between cardiovascular and bone health. However, further research is needed to explore the underlying mechanisms driving these gender differences and to elucidate their clinical implications:

1. Age as a Key Factor: Age is a critical factor in both atherosclerosis and osteoporosis, as both conditions tend to worsen with advancing age. It would be beneficial to discuss how age might interact with the observed correlations between baPWV and BMD in men and women. For instance, do these correlations change with age, and if so, in what way?
2. Age-Stratified Analysis: Consider conducting an age-stratified analysis to assess whether the strength of the correlation between baPWV and BMD varies across different age groups within the study population. This can help identify potential age-specific trends.
3. Menopause and Its Influence: Since menopause is a significant event in a woman's life associated with hormonal changes and increased risk of osteoporosis, explore whether the strength of the correlation differs between pre-menopausal and post-menopausal women. Are there age-related trends in post-menopausal women that could explain the observed differences?
4. Gender-Specific Trends: Discuss any gender-specific trends that emerged from the analysis. For instance, if women in the study tended to be younger on average than men, consider whether this age difference may have contributed to the stronger correlation observed in women.
5. Potential Mechanisms: Explore potential mechanisms underlying the observed age and gender differences. Are there biological or physiological explanations for why baPWV and BMD might correlate differently in men and women of different ages?
6. Clinical Implications: Consider the clinical implications of age-specific variations in the correlation between baPWV and BMD. How might these findings impact the diagnosis and management of atherosclerosis and osteoporosis in different age and gender groups?

Future Research Directions: Suggest areas for future research, such as conducting longitudinal studies to track changes in baPWV and BMD over time in individuals of different ages and genders. This could help elucidate the dynamic nature of these relationships

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CRediT authorship contribution statement

Iwona Jannasz: Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jakub Brzeziński:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Conceptualization. **Małgorzata Mańczak:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Tadeusz Sondej:** Validation, Methodology, Investigation, Conceptualization. **Tomasz Targowski:**

Visualization, Data curation, Conceptualization. **Jacek Rysz:** Validation, Methodology, Data curation. **Robert Olszewski:** Writing – original draft, Supervision, Software, Methodology, Conceptualization.

Declaration of Competing Interest

The authors declare no conflict of interest.

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10. Spis rycin i tabel

Publikacja 1.: Validation of a new device for photoplethysmographic measurement of multi-site arterial pulse wave velocity.

(a) i różnica (b) między PWV tętnicy szyjno-udowej (cfPWV) a PWV mierzoną za pomocą urządzenia MPPT (etPWV). Miejsce pomiaru MPPT: lewe ucho – prawy palec u nogi.)

Fig. 11 – Relationship (a) and difference (b) between carotid-femoral PWV (cfPWV) and MPPT device PWV (ftPWV). MPPT measurement site: right finger - right toe. (**Rys. 11** – Zależność (a) i różnica (b) między PWV tętnicy szyjno-udowej (cfPWV) a PWV mierzoną za pomocą urządzenia MPPT (ftPWV). Miejsce pomiaru MPPT: prawy palec dłoni – prawy palec u nogi).

Fig. 12 – Relationship (a) and difference (b) between carotid-femoral PWV (cfPWV) and MPPT device PWV (ftPWV). MPPT measurement site: left finger - left toe. (**Rys. 12** – Zależność (a) i różnica (b) między PWV tętnicy szyjno-udowej (cfPWV) a PWV mierzoną za pomocą urządzenia MPPT (ftPWV). Miejsce pomiaru MPPT: lewy palec dłoni – lewy palec u nogi.)

Table 3 – Summary of comparison between cfPWV and MPPT multi-site PWV measurement. (Tabela 3 – Podsumowanie porównania między cfPWV a wielomiejscowym pomiarem PWV za pomocą urządzenia MPPT.)

Fig. 13 – Relationship (a) and difference (b) between carotid-femoral PWV (cfPWV) and average MPPT device PWV (msaPWV). msaPWV is the meaning of variants no. 1–6. (Rys. 13 – Zależność (a) i różnica (b) między PWV tętnicy szyjno-udowej (cfPWV) a średnią PWV mierzoną za pomocą urządzenia MPPT (msaPWV). msaPWV to średnia z wariantów nr 1–6.)

Fig. 14 – Relationship between the msaPWV and subject age. (**Rys. 14** – Zależność między msaPWV a wiekiem badanych.)

Fig. 15 – The relationship between the SDavg and subject age (a) and cfPWV (b). (Rys. 15 **–** Zależność między SDavg a wiekiem badanych (a) oraz cfPWV (b).)

Table 4 – Validation results of the other devices with SphygmoCor as reference. (Tabela 4 – Wyniki walidacji innych urządzeń w porównaniu z SphygmoCor jako odniesieniem.)

Publikacja 2: Relationship between the Central and Regional Pulse Wave Velocity in the Assessment of Arterial Stiffness Depending on Gender in the Geriatric Population.

Figure 1. Principle of cfPWV measurement with the SphygmoCor XCEL device. (Rys. 1 – Zasada pomiaru cfPWV za pomocą urządzenia SphygmoCor XCEL.)

Figure 2. An example screenshot of cfPWV measurement with the SphygmoCor XCEL. (Rys. 2 – Przykładowy zrzut ekranu pomiaru cfPWV za pomocą urządzenia SphygmoCor XCEL.)

Figure 3. Representative carotid and femoral pulse waveforms for calculating the cfPWV recorded with the SphygmoCor XCEL (for 4 participants with ID = (a) ng04, (b) ng28, (c) ng40 and (d) ng45). (Rys. 3 – Reprezentatywne fale tętna tętnicy szyjnej i udowej do obliczania cfPWV zarejestrowane za pomocą urządzenia SphygmoCor XCEL (dla 4 uczestników z identyfikatorami: (a) ng04, (b) ng28, (c) ng40 i (d) ng45).)

Figure 4. Block diagram of the MPPT system and location of PPG sensors for regional PWV measurement. (Rys. 4 – Schemat blokowy systemu MPPT oraz lokalizacja czujników PPG do pomiaru regionalnego PWV.)

Figure 5. Representative signal plots for calculating the regional PWV recorded with the MPPT apparatus (for 4 participants with ID: (a) ng04, (b) ng28, (c) ng40 and (d) ng45). (Rys. 5 – Reprezentatywne wykresy sygnałów do obliczania regionalnego PWV zarejestrowane za pomocą aparatu MPPT (dla 4 uczestników z identyfikatorami: (a) ng04, (b) ng28, (c) ng40 i (d) ng45).

Table 1. Comparative characteristics of gender groups. (Tabela 1 – Charakterystyki porównawcze grup według płci.)

Table 2. Correlation coefficients of selected parameters and cfPWV in the whole group and by gender. (Tabela 2 – Współczynniki korelacji wybranych parametrów i cfPWV w całej grupie oraz według płci.)

Table 3. Multivariable regression analysis coefficients. (Tabela 3 – Współczynniki analizy regresji wielowymiarowej.)

Table 4. Multivariable regression—comorbidities and gender. (Tabela 4 – Regresja wielowymiarowa — współistniejące schorzenia i płeć.)

Table 5. Analysis of multisite regional PWV by gender. (Tabela 5 – Analiza wielomiejscowego regionalnego PWV według płci.)

Table 6. Comparison of central and regional PWV. (Tabela 6 – Porównanie PWV centralnego i regionalnego.)

Publikacja 3: Impact of COVID-19 on carotid-femoral pulse wave velocity: a systematic review and meta-analysis.

Figure 1. PRISMA systematic review flow diagram. (**Rys. 1** – Diagram przepływu przeglądu systematycznego PRISMA.)

Table 1. Characteristics of included studies. (Tabela 1 – Charakterystyka włączonych badań.)

Figure 2. Forest plot of cfPWV in COVID-19 patients vs. non-COVID-19 controls. The mean differences for individual studies are represented by the central point of each square, and the associated horizontal line indicates a 95% confidence range. The diamond shapes indicate the consolidated results. (Rys. 2 – Wykres leśny cfPWV u pacjentów z COVID-19 w porównaniu z grupą kontrolną bez COVID-19. Średnie różnice dla poszczególnych badań są reprezentowane przez centralny punkt każdej kwadratu, a odpowiadająca pozioma linia wskazuje na 95% przedział ufności. Kształty diamentów wskazują na skonsolidowane wyniki.)

Publikacja 4: Is the association between pulse wave velocity and bone mineral density. the same for men and women? - A systematic review and meta-analysis.

Fig. 1. The PRISM diagram for the review and the meta-analysis). (Rys. 1 – Diagram PRISMA dla przeglądu i metaanalizy.)

Table 1. Study characteristics. (Tabela 1 – Charakterystyka badań.)

Fig. 2. Forest plot, women. (Rys. 2 – Wykres leśny, kobiety.)

Fig. 3. Forest plot, men. (Rys. 3 – Wykres leśny, mężczyźni.)

Table 2. Sensitivity analysis, women. (Tabela 2 – Analiza wrażliwości, kobiety.)

Table 3. Sensitivity analysis, men. (Tabela 3 – Analiza wrażliwości, mężczyźni.)

Table 4. The Newcastle–Ottawa Quality Assessment Scale. (Tabela 4 – Skala oceny jakości Newcastle-Ottawa.)

11. Opinia Komisji Bioetycznej

NARODOWY INSTYTUT
GERIATRII, REUMATOLOGII
I REHABILITACJI
IM. PROF. DR HAB. MED. ELEONORY REICHER

Warszawa, 27.04.2017 r.

Decyzja Komisji Bioetycznej
przy Narodowym Instytucie Geriatrii, Reumatologii i Rehabilitacji w Warszawie
nr KBT-4/1/2017

Komisja Bioetyczna przy Narodowym Instytucie Geriatrii, Reumatologii i Rehabilitacji w Warszawie, ul. Spartańska 1, działająca zgodnie z zasadami GCP, zapoznała się w dniu 27.04.2017 r. z następującymi dokumentami dotyczącymi projektu badawczego pt. **„Ocena przydatności wielopunktowego pomiaru czasu propagacji fali tętna do ciągłego, nieinwazyjnego pomiaru ciśnienia tętniczego i do diagnostyki chorób serca"**:

1. **Podanie kierownika naukowego do Komisji Bioetycznej ze zgodą Kierownika Kliniki i Polikliniki Geriatrii NIGRiR na przeprowadzenie badania;**
2. **Wniosek do Komisji Bioetycznej zawierający:**

- **Skład zespołu badawczego;**
- **Opis programu badania;**
- **Formularz świadomej zgody na udział w badaniu;**
- **Informację dla pacjenta.**

Badania naukowe będą prowadzone z udziałem pacjentów Kliniki i Polikliniki Geriatrii NIGRiR oraz Oddziału Kardiologii i Poradni Kardiologicznej Wojewódzkiego Szpitala Specjalistycznego w Białej Podlaskiej. Projekt będzie realizowany we współpracy z Wydziałem Elektroniki Wojskowej Akademii Technicznej w Warszawie. Kierownikiem naukowym projektu jest prof. wiz. dr hab. n. med. Robert Olszewski.

Komisja Bioetyczna przy Narodowym Instytucie Geriatrii, Reumatologii i Rehabilitacji w głosowaniu tajnym nad akceptacją zgłoszonego projektu wyraziła zgodę na rozpoczęcie badań zgodnie z przedstawionym protokołem.

PRZEWODNICZĄCY
KOMISJI BIOETYCZNEJ
przy Narodowym Instytucie Geriatrii,
Reumatologii i Rehabilitacji w Warszawie
prof. dr hab. n. med. Piotr Głuszko

Komisja Bioetyczna
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KOMISJA BIOETYCZNA
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02-637 Warszawa, ul. Spartańska 1
tel. 22 844-43-41 wew. 428
NIP: 525-001-18-42, REGON: 000288567

Warszawa, 27.04.2017 r.

Lista obecności członków Komisji Bioetycznej przy Narodowym Instytucie Geriatrii, Reumatologii i Rehabilitacji

Prof. dr hab. med. Piotr Głuszko – lekarz
NIGRiR .....

Prof. dr hab. med. Anna Filipowicz-Sosnowska – lekarz
NIGRiR .....

Dr n. hum. Ewa Kujawa – etyk
Centrum Medyczne Kształcenia Podyplomowego .....

P. Barbara Kurek – pielęgniarka
Instytut Kardiologii .....

Prof. nadzw. dr hab. med. Robert Gasik – lekarz
NIGRiR .....

Prof. nadzw. dr hab. med. Brygida Kwiatkowska – lekarz
NIGRiR .....

Ks. dr Włodzimierz Nast – ksiądz
Chrześcijańska Akademia Teologiczna .....

Mec. Maria Grzeszczyk – prawnik
Państwowy Zakład Wydawnictw Lekarskich .....

Prof. nadzw. dr hab. med. Marzena Olesińska – lekarz
NIGRiR .....

Prof. nadzw. dr hab. med. Lidia Rutkowska-Sak – lekarz
NIGRiR .....

Prof. dr hab. med. Tadeusz Styczyński – lekarz
NIGRiR .....

Dr hab. n. farm. Tomasz Pawiński – farmaceuta
Warszawski Uniwersytet Medyczny .....

Dr n. med. Aleksandra Słabik-Ledóchowska – lekarz
Okręgowa Izba Lekarska w Warszawie .....

NARODOWY INSTYTUT
GERIATRII, REUMATOLOGII
I REHABILITACJI
IM. PROF. DR HAB. MED. ELEONORY REICHER

Warszawa, 31.01.2019 r.

Decyzja Komisji Bioetycznej
przy Narodowym Instytucie Geriatrii, Reumatologii i Rehabilitacji w Warszawie
nr KBT-1/9/2019

Komisja Bioetyczna przy Narodowym Instytucie Geriatrii, Reumatologii i Rehabilitacji w Warszawie, ul. Spartańska 1, działająca zgodnie z zasadami GCP, zapoznała się w dniu 31.01.2019 r. z następującymi dokumentami dotyczącymi projektu badawczego pt. **„Ocena przydatności wielopunktowego pomiaru czasu propagacji fali tętna do ciągłego, nieinwazyjnego pomiaru ciśnienia tętniczego i do diagnostyki chorób serca"**:

- **Wniosek kierownika naukowego projektu, nowego współbadacza oraz Kierownika Kliniki i Poliklinik Geriatrii NIGRiR do Komisji Bioetycznej z prośbą o zaopiniowanie planu rozszerzenia projektu.**

Projekt badawczy prowadzony w Klinice i Poliklinice Geriatrii NIGRiR został pozytywnie zaopiniowany przez Komisję Bioetyczną przy Instytucie w 2017 r. (decyzja nr KBT-4/1/2017). Kierownikiem naukowym projektu jest dr hab. n. med. Robert Olszewski, prof. NIGRiR. Obecnie wnioskodawcy wnoszą o rozszerzenie projektu o kolejną grupę badaną oraz włączenie do zespołu badawczego nowej osoby – lek. Iwony Jannasz – pracownika Kliniki i Poliklinik Geriatrii. Wyniki badań naukowych zostaną wykorzystane w pracy doktorskiej dr Iwony Jannasz. Tytuł rozprawy doktorskiej jest tożsamy z tytułem projektu badawczego.

Komisja Bioetyczna przy NIGRiR w głosowaniu tajnym nad akceptacją zgłoszonej aktualizacji wyraziła zgodę na kontynuację badań zgodnie z przedstawionymi zmianami.

PRZEWODNICZĄCY
KOMISJI BIOETYCZNEJ
przy Narodowym Instytucie Geriatrii,
Reumatologii i Rehabilitacji w Warszawie
prof. dr hab. n. med. Piotr Głuszko

KOMISJA BIOETYCZNA
przy Narodowym Instytucie Geriatrii,
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02-637 Warszawa, ul. Sowińskiego 1
tel. 22 844-42-41 www. 428
NIP: 525-001-10-42, REGON: 000288997

Warszawa, 31.01.2019 r.

Lista obecności członków Komisji Bioetycznej przy Narodowym Instytucie Geriatrii, Reumatologii i Rehabilitacji

Prof. dr hab. med. Piotr Głuszko – lekarz
NIGRiR ……

Prof. dr hab. med. Anna Filipowicz-Sosnowska – lekarz
NIGRiR ……

Dr n. hum. Ewa Kujawa – etyk ……

P. Barbara Kurek – pielęgniarka ……

Prof. nadzw. dr hab. med. Robert Gasik – lekarz
NIGRiR ……

Prof. nadzw. dr hab. med. Brygida Kwiatkowska – lekarz
NIGRiR ……

Ks. dr Włodzimierz Nast – ksiądz
Chrześcijańska Akademia Teologiczna ……

Mec. Maria Grzeszczyk – prawnik
Państwowy Zakład Wydawnictw Lekarskich ……

Prof. nadzw. dr hab. med. Marzena Olesińska – lekarz
NIGRiR ……

Prof. dr hab. med. Lidia Rutkowska-Sak – lekarz
NIGRiR ……

Prof. dr hab. med. Tadeusz Styczyński – lekarz ……

Dr hab. n. farm. Tomasz Pawiński – farmaceuta
Warszawski Uniwersytet Medyczny ……

Dr n. med. Aleksandra Słabik-Ledóchowska – lekarz
Okręgowa Izba Lekarska w Warszawie ……

12. Oświadczenia współautorów

Publikacja 1: **Validation of a new device for photoplethysmographic measurement of multi-site arterial pulse wave velocity.** Tadeusz Sondej, Iwona Jannasz, Krzysztof Sieczkowski, Andrzej Dobrowolski, Karolina Obiała, Tomasz Targowski, Robert Olszewski. Biocybernetics and Biomedical Engineering. Volume 41, Issue 4,2021, Pages 1664-1684, ISSN 0208-5216, https://doi.org/10.1016/j.bbe.2021.11.001.

Warszawa, 07.10.2024 r.

dr hab. inż. Tadeusz Sondej, prof. WAT
Prodziekan ds. naukowych
Wydział Elektroniki WAT
Wojskowa Akademia Techniczna im. Jarosława Dąbrowskiego
ul. gen. Sylwestra Kaliskiego 2, 00-908 Warszawa

Oświadczenie

Oświadczam, że w pracy pod tytułem: **Validation of a new device for photoplethysmographic measurement of multi-site arterial pulse wave velocity.** opublikowanej w czasopiśmie: Biocybernetics and Biomedical Engineering. 2021, Vol 41, Issue 4, pp. 1664-1684, doi.org/10.1016/j.bbe.2021.11.001; autorstwa: Tadeusz Sondej, Iwona Jannasz, Krzysztof Sieczkowski, Andrzej Dobrowolski,Karolina Obiała, Tomasz Targowski, Robert Olszewski, mój wkład merytoryczny w przygotowanie publikacji polegał na:

1. koncepcji pracy, postawieniu hipotez
2. zaplanowaniu badań, wybór metodyki badań
3. prowadzeniu badań
4. zbieraniu danych
5. analizie statystycznej
6. interpretacji wyników
7. pisaniu pracy
8. graficznym przedstawieniu wyników
9. zbieraniu piśmiennictwa
10. konsultacji i opieka
11. korekcie pracy przed złożeniem do druku
12. zdobywaniu środków finansowych

Oceniam swój wkład procentowy w publikację na poziomie 65%. Wyrażam zgodę na przedłożenie powyższej publikacji przez lek Iwonę Jannasz jako część rozprawy doktorskiej w formie spójnego cyklu artykułów naukowych opublikowanych w recenzowanych czasopismach naukowych. Jednocześnie oświadczam, iż samodzielna i możliwa do wyodrębnienia część powyższej publikacji wykazuje indywidualny wkład lek. Iwony Jannasz przy tworzeniu koncepcji pracy, postawieniu hipotez, zaplanowaniu badań, wyborze metodyki badań, prowadzeniu badań, zbieraniu danych, pisaniu pracy, zbieraniu piśmiennictwa, korekcie pracy przed złożeniem do druku oraz interpretacji wyników i wniosków tej pracy.

Z poważaniem,

.....
(podpis oświadczającego)

Warszawa, 07.10.2024 r.

dr inż. Krzysztof Sieczkowski
Wydział Elektroniki
Wojskowa Akademia Techniczna im. Jarosława Dąbrowskiego
ul. gen. Sylwestra Kaliskiego 2, 00-908 Warszawa

Oświadczenie

Oświadczam, że w pracy pod tytułem: **Validation of a new device for photoplethysmographic measurement of multi-site arterial pulse wave velocity.** opublikowanej w czasopiśmie: Biocybernetics and Biomedical Engineering. 2021, Vol 41, Issue 4, pp. 1664-1684, doi.org/10.1016/j.bbe.2021.11.001; autorstwa : Tadeusz Sondej, Iwona Jannasz, Krzysztof Sieczkowski, Andrzej Dobrowolski, Karolina Obiała, Tomasz Targowski, Robert Olszewski, mój wkład merytoryczny w przygotowanie publikacji polegał na:

1. koncepcji pracy, postawieniu hipotez
2. zaplanowaniu badań, wyborze metodyki badań
3. prowadzeniu badań
4. zbieraniu danych

Oceniam swój wkład procentowy w publikację na poziomie 4%. Wyrażam zgodę na przedłożenie powyższej publikacji przez lek. Iwonę Jannasz jako część rozprawy doktorskiej w formie spójnego cyklu artykułów naukowych opublikowanych w recenzowanych czasopismach naukowych. Jednocześnie oświadczam, iż samodzielna i możliwa do wyodrębnienia część powyższej publikacji wykazuje indywidualny wkład lek. Iwony Jannasz przy tworzeniu koncepcji pracy, postawieniu hipotez, zaplanowaniu badań, wyborze metodyki badań, prowadzeniu badań, zbieraniu danych, pisaniu pracy, zbieraniu piśmiennictwa, korekcie pracy przed złożeniem do druku oraz interpretacji wyników i wniosków tej pracy.

Z poważaniem,

Krzysztof Sieczkowski
(podpis oświadczającego)

Warszawa, 07.10.2024 r.

prof. dr hab. inż. Andrzej Dobrowolski
Wydział Elektroniki
Wojskowa Akademia Techniczna im. Jarosława Dąbrowskiego
ul. gen. Sylwestra Kaliskiego 2, 00-908 Warszawa

Oświadczenie

Oświadczam, że w pracy pod tytułem: **Validation of a new device for photoplethysmographic measurement of multi-site arterial pulse wave velocity.** opublikowanej w czasopiśmie: Biocybernetics and Biomedical Engineering. 2021, Vol 41, Issue 4, pp. 1664-1684, doi.org/10.1016/j.bbe.2021.11.001; autorstwa: Tadeusz Sondej, Iwona Jannasz, Krzysztof Sieczkowski, Andrzej Dobrowolski, Karolina Obiała, Tomasz Targowski, Robert Olszewski, mój wkład merytoryczny w przygotowanie publikacji polegał na:

1. koncepcji pracy, postawieniu hipotez
2. konsultacji i opiece merytorycznej
3. zdobywaniu środków finansowych

Oceniam swój wkład procentowy w publikację na poziomie 4%. Wyrażam zgodę na przedłożenie powyższej publikacji przez lek. Iwonę Jannasz jako część rozprawy doktorskiej w formie spójnego cyklu artykułów naukowych opublikowanych w recenzowanych czasopismach naukowych. Jednocześnie oświadczam, iż samodzielna i możliwa do wyodrębnienia część powyższej publikacji wykazuje indywidualny wkład lek. Iwony Jannasz przy tworzeniu koncepcji pracy, postawieniu hipotez, zaplanowaniu badań, wyborze metodyki badań, prowadzeniu badań, zbieraniu danych, pisaniu pracy, zbieraniu piśmiennictwa, korekcie pracy przed złożeniem do druku oraz interpretacji wyników i wniosków tej pracy.

Z poważaniem,

(podpis oświadczającego)

Warszawa, 07.10.2024r.

Karolina Obiała

Oświadczenie

Oświadczam, że w pracy pod tytułem: **Validation of a new device for photoplethysmographic measurement of multi-site arterial pulse wave velocity.** opublikowanej w czasopiśmie: Biocybernetics and Biomedical Engineering. 2021, Vol 41, Issue 4, pp. 1664-1684, doi.org/10.1016/j.bbe.2021.11.001; autorstwa : Tadeusz Sondej, Iwona Jannasz, Krzysztof Sieczkowski, Andrzej Dobrowolski,Karolina Obiała, Tomasz Targowski, Robert Olszewski, mój wkład merytoryczny w przygotowanie publikacji polegał na:

1. zbieraniu danych

Oceniam swój wkład procentowy w publikację na poziomie 1 %. Wyrażam zgodę na przedłożenie powyższej publikacji przez lek Iwonę Jannasz jako część rozprawy doktorskiej w formie spójnego cyklu artykułów naukowych opublikowanych w recenzowanych czasopismach naukowych. Jednocześnie oświadczam, iż samodzielna i możliwa do wyodrębnienia część powyższej publikacji wykazuje indywidualny wkład lek. Iwony Jannasz przy tworzeniu koncepcji pracy, postawieniu hipotez, zaplanowaniu badań, wyborze metodyki badań, prowadzeniu badań, zbieraniu danych, pisaniu pracy, zbieraniu piśmiennictwa, korekcie pracy przed złożeniem do druku oraz interpretacji wyników i wniosków tej pracy.

Z poważaniem,

Karolina Obiała
(podpis oświadczającego)

Warszawa, 07.10.2024r.

Prof. dr hab.n. med. Tomasz Targowski
Kierownik Kliniki i Polikliniki Geriatrii
Narodowy Instytut Geriatrii, Reumatologii i Rehabilitacji
Krajowy konsultant w dziedzinie geriatrii
ul. Spartańska 1, 02-637 Warszawa

Oświadczenie

Oświadczam, że w pracy pod tytułem: **Validation of a new device for photoplethysmographic measurement of multi-site arterial pulse wave velocity.** opublikowanej w czasopiśmie: Biocybernetics and Biomedical Engineering. 2021, Vol 41, Issue 4, pp. 1664-1684, doi.org/10.1016/j.bbe.2021.11.001; autorstwa : Tadeusz Sondej, Iwona Jannasz, Krzysztof Sieczkowski, Andrzej Dobrowolski,Karolina Obiała, Tomasz Targowski, Robert Olszewski, mój wkład merytoryczny w przygotowanie publikacji polegał na:

1. zaplanowaniu badań, wyborze metodyki badań
2. prowadzeniu badań
3. konsultacji i opiece merytorycznej

Oceniam swój wkład procentowy w publikację na poziomie 4 %. Wyrażam zgodę na przedłożenie powyższej publikacji przez lek Iwonę Jannasz jako część rozprawy doktorskiej w formie spójnego cyklu artykułów naukowych opublikowanych w recenzowanych czasopismach naukowych. Jednocześnie oświadczam, iż samodzielna i możliwa do wyodrębnienia część powyższej publikacji wykazuje indywidualny wkład lek. Iwony Jannasz przy tworzeniu koncepcji pracy, postawieniu hipotez, zaplanowaniu badań, wyborze metodyki badań, prowadzeniu badań, zbieraniu danych, pisaniu pracy, zbieraniu piśmiennictwa, korekcie pracy przed złożeniem do druku oraz interpretacji wyników i wniosków tej pracy.

Z poważaniem,

KIEROWNIK KLINIKI I POLIKLINIKI GERIATRII Narodowy Instytut Geriatrii, Reumatologii i Rehabilitacji w Warszawie ul. Spartańska 1 prof. dr hab. n. med. Tomasz Targowski

.....
(podpis oświadczającego)

Warszawa, 07.10.2024r.

Dr hab. n. med. Robert Olszewski, Profesor NIGRiR,
Kierownik Zakładu
Gerontologii, Zdrowia Publicznego i Dydaktyki
Narodowy Instytut Geriatrii Reumatologii i Rehabilitacji.
Spartańska 1, 02-637 Warszawa

Instytut Podstawowych Problemów Techniki
Zakład Ultradźwięków
Polska Akademia Nauk
Pawińskiego 5B, 02-106 Warszawa

Oświadczenie

Oświadczam, że w pracy pod tytułem: **Validation of a new device for photoplethysmographic measurement of multi-site arterial pulse wave velocity.** opublikowanej w czasopiśmie: Biocybernetics and Biomedical Engineering. 2021, Vol 41, Issue 4, pp. 1664-1684, doi.org/10.1016/j.bbe.2021.11.001; autorstwa : Tadeusz Sondej, Iwona Jannasz, Krzysztof Sieczkowski, Andrzej Dobrowolski,Karolina Obiała, Tomasz Targowski, Robert Olszewski, mój wkład merytoryczny w przygotowanie publikacji polegał na:

1. koncepcji pracy, postawieniu hipotez
2. zaplanowaniu badań, wyborze metodyki badań
3. zbieraniu piśmiennictwa

Oceniam swój wkład procentowy w publikację na poziomie 4 %. Wyrażam zgodę na przedłożenie powyższej publikacji przez lek Iwonę Jannasz jako część rozprawy doktorskiej w formie spójnego cyklu artykułów naukowych opublikowanych w recenzowanych czasopismach naukowych. Jednocześnie oświadczam, iż samodzielna i możliwa do wyodrębnienia część powyższej publikacji wykazuje indywidualny wkład lek. Iwony Jannasz przy tworzeniu koncepcji pracy, postawieniu hipotez, zaplanowaniu badań, wyborze metodyki badań, prowadzeniu badań, zbieraniu danych, pisaniu pracy, zbieraniu piśmiennictwa, korekcie pracy przed złożeniem do druku oraz interpretacji wyników i wniosków tej pracy.

Z poważaniem,

(podpis oświadczającego)

Publikacja 2**: Relationship between the Central and Regional Pulse Wave Velocity in the Assessment of Arterial Stiffness Depending on Gender in the Geriatric** Population. Jannasz Iwona, Sondej Tadeusz, Targowski Tomasz, Mańczak Małgorzata, Obiała Karolina, Dobrowolski Andrzej Piotr, Olszewski Robert. Sensors (Basel). 2023 Jun 22;23(13):5823. doi: 10.3390/s23135823. PMID: 37447671; PMCID: PMC10347145.

Warszawa, 07.10.2024 r.

dr hab. inż. Tadeusz Sondej, prof. WAT
Prodziekan ds. naukowych
Wydział Elektroniki WAT
Wojskowa Akademia Techniczna im. Jarosława Dąbrowskiego
ul. gen. Sylwestra Kaliskiego 2, 00-908 Warszawa

Oświadczenie

Oświadczam, że w pracy pod tytułem: **Relationship between the Central and Regional Pulse Wave Velocity in the Assessment of Arterial Stiffness Depending on Gender in the Geriatric Population.** opublikowanej w Sensors. 2023; 23(13):5823. doi.org/10.3390/s23135823; autorstwa : Iwona Jannasz, Tadeusz Sondej, Tomasz Targowski, Małgorzata Mańczak, Karolina Obiała, Andrzej Piotr Dobrowolski, Robert Olszewski; mój wkład merytoryczny w przygotowanie publikacji polegał na:

1 koncepcji pracy, postawieniu hipotez
2 zaplanowaniu badań, wybór metodyki badań
3 prowadzeniu badań
4 zbieraniu danych
5 analizie statystycznej
6 interpretacji wyników
7 pisaniu pracy
8 graficznym przedstawieniu wyników
9 zbieraniu piśmiennictwa
10 konsultacji i opiece merytorycznej
11 korekcie pracy przed złożeniem do druku
12 zdobywaniu środków finansowych

Oceniam swój wkład procentowy w publikację na poziomie 30%. Wyrażam zgodę na przedłożenie powyższej publikacji przez lek. Iwonę Jannasz jako część rozprawy doktorskiej w formie spójnego cyklu artykułów naukowych opublikowanych w recenzowanych czasopismach naukowych. Jednocześnie oświadczam, iż samodzielna i możliwa do wyodrębnienia część powyższej publikacji wykazuje indywidualny wkład lek. Iwony Jannasz przy tworzeniu koncepcji pracy, postawieniu hipotez, zaplanowaniu badań, wyborze metodyki, prowadzeniu badań, zbieraniu danych, analizie statystycznej, pisaniu pracy, graficznym przedstawieniu wyników, zbieraniu piśmiennictwa, korekcie pracy przed złożeniem do druku oraz interpretacji wyników i wniosków tej pracy.

Z poważaniem,

(podpis oświadczającego)

Warszawa, 07.10.2024r.

Prof. dr hab. n. med. Tomasz Targowski
Kierownik Kliniki i Polikliniki Geriatrii
Narodowy Instytut Geriatrii, Reumatologii i Rehabilitacji
Krajowy konsultant w dziedzinie geriatrii
ul. Spartańska 1, 02-637 Warszawa

Oświadczenie

Oświadczam, że w pracy pod tytułem: **Relationship between the Central and Regional Pulse Wave Velocity in the Assessment of Arterial Stiffness Depending on Gender in the Geriatric Population.** opublikowanej w Sensors. 2023; 23(13):5823. doi.org/10.3390/s23135823; autorstwa :
Iwona Jannasz, Tadeusz Sondej, Tomasz Targowski, Małgorzata Mańczak, Karolina Obiała, Andrzej Piotr Dobrowolski, Robert Olszewski; mój wkład merytoryczny w przygotowanie publikacji polegał na:

1. koncepcji pracy, postawieniu hipotez
2. zaplanowaniu badań, wybór metodyki badań
3. prowadzeniu badań

Oceniam swój wkład procentowy w publikację na poziomie 4 %. Wyrażam zgodę na przedłożenie powyższej publikacji przez lek Iwonę Jannasz jako część rozprawy doktorskiej w formie spójnego cyklu artykułów naukowych opublikowanych w recenzowanych czasopismach naukowych. Jednocześnie oświadczam, iż samodzielna i możliwa do wyodrębnienia część powyższej publikacji wykazuje indywidualny wkład lek. Iwony Jannasz przy tworzeniu koncepcji pracy, postawieniu hipotez, zaplanowaniu badań, wyborze metodyki, prowadzeniu badań, zbieraniu danych, analizie statystycznej, pisaniu pracy, graficznym przedstawieniu wyników, zbieraniu piśmiennictwa, korekcie pracy przed złożeniem do druku oraz interpretacji wyników i wniosków tej pracy.

Z poważaniem,

(podpis oświadczającego)

Warszawa, 07.10.2024r.

Dr n. med. Małgorzata Mańczak
Zakład Gerontologii, Zdrowia Publicznego i Dydaktyki
Narodowy Instytut Geriatrii Reumatologii i Rehabilitacji.
Spartańska 1, 02-637 Warszawa

Oświadczenie

Oświadczam, że w pracy pod tytułem: **Relationship between the Central and Regional Pulse Wave Velocity in the Assessment of Arterial Stiffness Depending on Gender in the Geriatric Population.** publikowanej w Sensors. 2023; 23(13):5823. doi.org/10.3390/s23135823; autorstwa : Iwona Jannasz, Tadeusz Sondej, Tomasz Targowski, Małgorzata Mańczak, Karolina Obiała, Andrzej Piotr Dobrowolski, Robert Olszewski; mój wkład merytoryczny w przygotowanie publikacji polegał na:

1. analizie statystycznej

Oceniam swój wkład procentowy w publikację na poziomie 3 %. Wyrażam zgodę na przedłożenie powyższej publikacji przez lek Iwonę Jannasz jako część rozprawy doktorskiej w formie spójnego cyklu artykułów naukowych opublikowanych w recenzowanych czasopismach naukowych. Jednocześnie oświadczam, iż samodzielna i możliwa do wyodrębnienia część powyższej publikacji wykazuje indywidualny wkład lek. Iwony Jannasz przy tworzeniu koncepcji pracy, postawieniu hipotez, zaplanowaniu badań, wyborze metodyki, prowadzeniu badań, zbieraniu danych, analizie statystycznej, pisaniu pracy, graficznym przedstawieniu wyników, zbieraniu piśmiennictwa, korekcie pracy przed złożeniem do druku oraz interpretacji wyników i wniosków tej pracy.

Z poważaniem,

M Mańczak

.....
(podpis oświadczającego)

Warszawa, 07.10.2024r.

Karolina Obiała

Oświadczenie

Oświadczam, że w pracy pod tytułem: **Relationship between the Central and Regional Pulse Wave Velocity in the Assessment of Arterial Stiffness Depending on Gender in the Geriatric Population.** opublikowanej w Sensors. 2023; 23(13):5823. doi.org/10.3390/s23135823; autorstwa :
Iwona Jannasz, Tadeusz Sondej, Tomasz Targowski, Małgorzata Mańczak, Karolina Obiała, Andrzej Piotr Dobrowolski, Robert Olszewski; mój wkład merytoryczny w przygotowanie publikacji polegał na:

1 Zbieraniu danych

Oceniam swój wkład procentowy w publikację na poziomie 1 %. Wyrażam zgodę na przedłożenie powyższej publikacji przez lek Iwonę Jannasz jako część rozprawy doktorskiej w formie spójnego cyklu artykułów naukowych opublikowanych w recenzowanych czasopismach naukowych. Jednocześnie oświadczam, iż samodzielna i możliwa do wyodrębnienia część powyższej publikacji wykazuje indywidualny wkład lek. Iwony Jannasz przy tworzeniu koncepcji pracy, postawieniu hipotez, zaplanowaniu badań, wyborze metodyki, prowadzeniu badań, zbieraniu danych, analizie statystycznej, pisaniu pracy, graficznym przedstawieniu wyników, zbieraniu piśmiennictwa, korekcie pracy przed złożeniem do druku oraz interpretacji wyników i wniosków tej pracy.

Z poważaniem,

Karolina Obiała

(podpis oświadczającego)

Warszawa, 07.10.2024 r.

prof. dr hab. inż. Andrzej Dobrowolski
Wydział Elektroniki
Wojskowa Akademia Techniczna im. Jarosława Dąbrowskiego
ul. gen. Sylwestra Kaliskiego 2, 00-908 Warszawa

Oświadczenie

Oświadczam, że w pracy pod tytułem: **Relationship between the Central and Regional Pulse Wave Velocity in the Assessment of Arterial Stiffness Depending on Gender in the Geriatric Population.** opublikowanej w Sensors. 2023; 23(13):5823. doi.org/10.3390/s23135823; autorstwa :
Iwona Jannasz, Tadeusz Sondej, Tomasz Targowski, Małgorzata Mańczak, Karolina Obiała, Andrzej Piotr Dobrowolski, Robert Olszewski; mój wkład merytoryczny w przygotowanie publikacji polegał na:

1 Zaplanowaniu badan, wyborze metodyki badań
2 konsultacji i opiece merytorycznej
3 zdobywaniu środków finansowych

Oceniam swój wkład procentowy w publikację na poziomie 3%. Wyrażam zgodę na przedłożenie powyższej publikacji przez lek Iwonę Jannasz jako część rozprawy doktorskiej w formie spójnego cyklu artykułów naukowych opublikowanych w recenzowanych czasopismach naukowych. Jednocześnie oświadczam, iż samodzielna i możliwa do wyodrębnienia część powyższej publikacji wykazuje indywidualny wkład lek. Iwony Jannasz przy tworzeniu koncepcji pracy, postawieniu hipotez, zaplanowaniu badań, wyborze metodyki, prowadzeniu badań, zbieraniu danych, analizie statystycznej, pisaniu pracy, graficznym przedstawieniu wyników, zbieraniu piśmiennictwa, korekcie pracy przed złożeniem do druku oraz interpretacji wyników i wniosków tej pracy.

Z poważaniem,

(podpis oświadczającego)

Warszawa, 07.10.2024r.

dr hab. n. med. Robert Olszewski, Profesor NIGRiR,
Kierownik Zakładu
Gerontologii, Zdrowia Publicznego i Dydaktyki
Narodowy Instytut Geriatrii Reumatologii i Rehabilitacji.
Spartańska 1, 02-637 Warszawa

Instytut Podstawowych Problemów Techniki
Zakład Ultradźwięków
Polska Akademia Nauk
Pawińskiego 5B, 02-106 Warszawa

Oświadczenie

Oświadczam, że w pracy pod tytułem: **Relationship between the Central and Regional Pulse Wave Velocity in the Assessment of Arterial Stiffness Depending on Gender in the Geriatric Population.** opublikowanej w Sensors. 2023; 23(13):5823. doi.org/10.3390/s23135823; autorstwa: Iwona Jannasz, Tadeusz Sondej, Tomasz Targowski, Małgorzata Mańczak, Karolina Obiała, Andrzej Piotr Dobrowolski, Robert Olszewski; mój wkład merytoryczny w przygotowanie publikacji polegał na:

1. koncepcji pracy, postawieniu hipotez
2. zaplanowaniu badań, wyborze metodyki badań
3. konsultacji i opiece

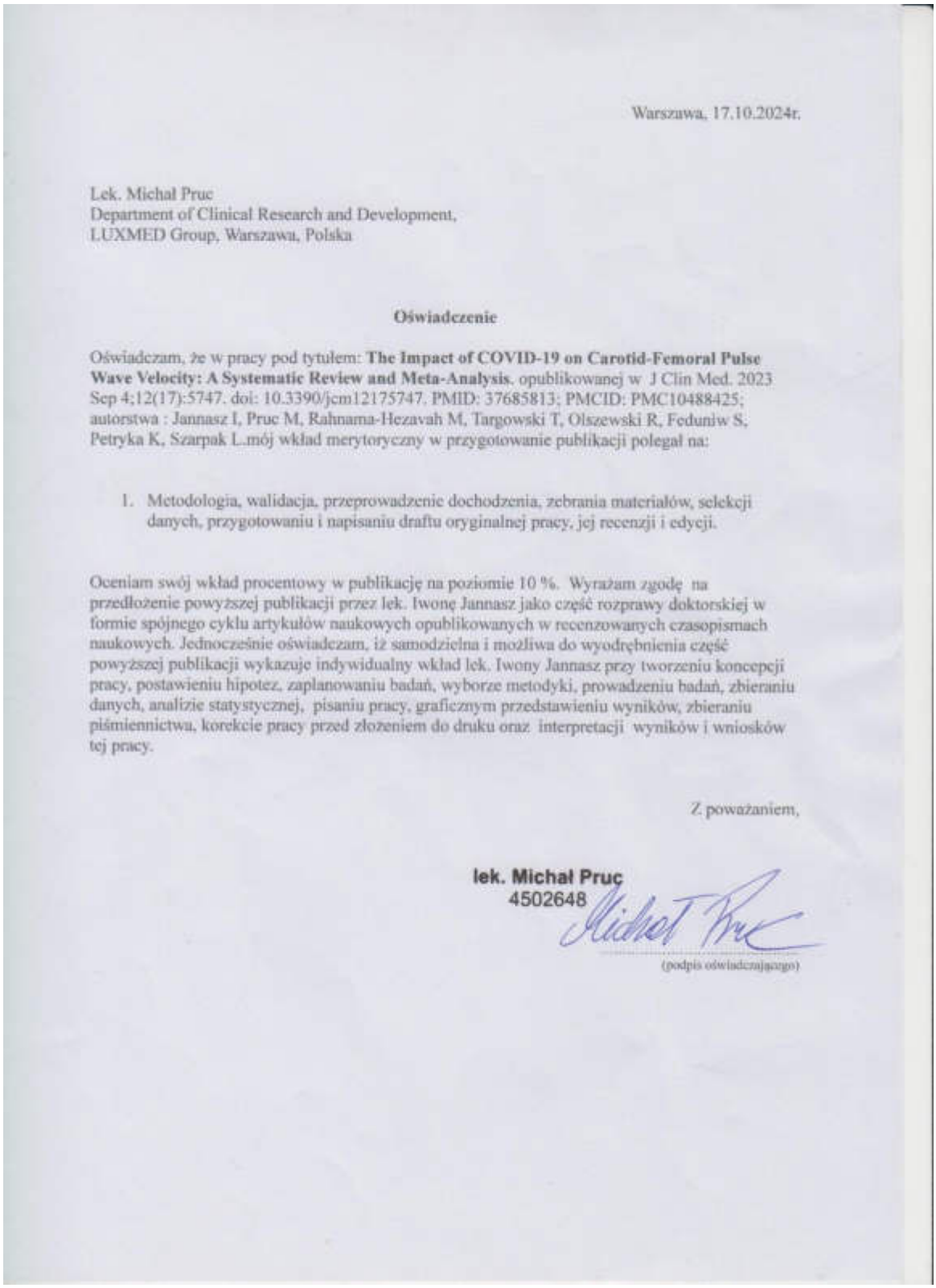
Oceniam swój wkład procentowy w publikację na poziomie 3 %. Wyrażam zgodę na przedłożenie powyższej publikacji przez lek Iwonę Jannasz jako część rozprawy doktorskiej w formie spójnego cyklu artykułów naukowych opublikowanych w recenzowanych czasopismach naukowych. Jednocześnie oświadczam, iż samodzielna i możliwa do wyodrębnienia część powyższej publikacji wykazuje indywidualny wkład lek. Iwony Jannasz przy tworzeniu koncepcji pracy, postawieniu hipotez, zaplanowaniu badań, wyborze metodyki, prowadzeniu badań, zbieraniu danych, analizie statystycznej, pisaniu pracy, graficznym przedstawieniu wyników, zbieraniu piśmiennictwa, korekcie pracy przed złożeniem do druku oraz interpretacji wyników i wniosków tej pracy.

Z poważaniem,

p.o. KIEROWNIK
Zakład Gerontologii, Zdrowia Publicznego i Dydaktyki
Narodowy Instytut Geriatrii, Reumatologii i Rehabilitacji w Warszawie
Dr hab. n. med. Robert Olszewski, Prof. NIGRiR

.....
(podpis oświadczającego)

Publikacja 3: **The Impact of COVID-19 on Carotid-Femoral Pulse Wave Velocity: A Systematic Review and Meta-Analysis**. Jannasz Iwona, Pruc Michał, Rahnama-Hezavah Mansur, Targowski Tomasz, Olszewski Robert, Feduniw Stepan, Petryka Karolina, Szarpak Łukasz. J Clin Med. 2023 Sep 4;12(17):5747. doi: 10.3390/jcm12175747. PMID: 37685813; PMCID: PMC10488425.



Warszawa, 17.10.2024r.

Lek. Michał Pruc
Department of Clinical Research and Development,
LUXMED Group, Warszawa, Polska

Oświadczenie

Oświadczam, że w pracy pod tytułem: **The Impact of COVID-19 on Carotid-Femoral Pulse Wave Velocity: A Systematic Review and Meta-Analysis**. opublikowanej w J Clin Med. 2023 Sep 4;12(17):5747. doi: 10.3390/jcm12175747. PMID: 37685813; PMCID: PMC10488425; autorstwa : Jannasz I, Pruc M, Rahnama-Hezavah M, Targowski T, Olszewski R, Feduniw S, Petryka K, Szarpak L.mój wkład merytoryczny w przygotowanie publikacji polegał na:

1. Metodologia, walidacja, przeprowadzenie dochodzenia, zebrania materiałów, selekcji danych, przygotowaniu i napisaniu draftu oryginalnej pracy, jej recenzji i edycji.

Oceniam swój wkład procentowy w publikację na poziomie 10 %. Wyrażam zgodę na przedłożenie powyższej publikacji przez lek. Iwonę Jannasz jako część rozprawy doktorskiej w formie spójnego cyklu artykułów naukowych opublikowanych w recenzowanych czasopismach naukowych. Jednocześnie oświadczam, iż samodzielna i możliwa do wyodrębnienia część powyższej publikacji wykazuje indywidualny wkład lek. Iwony Jannasz przy tworzeniu koncepcji pracy, postawieniu hipotez, zaplanowaniu badań, wyborze metodyki, prowadzeniu badań, zbieraniu danych, analizie statystycznej, pisaniu pracy, graficznym przedstawieniu wyników, zbieraniu piśmiennictwa, korekcie pracy przed złożeniem do druku oraz interpretacji wyników i wniosków tej pracy.

Z poważaniem,

lek. Michał Pruc
4502648

(podpis oświadczającego)

Warszawa, 17.10.2024r.

Prof. dr hab., dr h.c. Mansur Rahnama-Hezavah
Katedra i Zakład Chirurgii Stomatologicznej
Uniwersytet Medyczny w Lublinie, 20-093 Lublin, Polska

Oświadczenie

Oświadczam, że w pracy pod tytułem: **The Impact of COVID-19 on Carotid-Femoral Pulse Wave Velocity: A Systematic Review and Meta-Analysis**. opublikowanej w J Clin Med. 2023 Sep 4;12(17):5747. doi: 10.3390/jcm12175747. PMID: 37685813; PMCID: PMC10488425;
autorstwa : Jannasz I, Pruc M, Rahnama-Hezavah M, Targowski T, Olszewski R, Feduniw S, Petryka K, Szarpak L.mój wkład merytoryczny w przygotowanie publikacji polegał na:

- Walidacji, recenzji oraz edycji.

Oceniam swój wkład procentowy w publikację na poziomie 5 %. Wyrażam zgodę na przedłożenie powyższej publikacji przez lek. Iwonę Jannasz jako część rozprawy doktorskiej w formie spójnego cyklu artykułów naukowych opublikowanych w recenzowanych czasopismach naukowych. Jednocześnie oświadczam, iż samodzielna i możliwa do wyodrębnienia część powyższej publikacji wykazuje indywidualny wkład lek. Iwony Jannasz przy tworzeniu koncepcji pracy, postawieniu hipotez, zaplanowaniu badań, wyborze metodyki, prowadzeniu badań, zbieraniu danych, analizie statystycznej, pisaniu pracy, graficznym przedstawieniu wyników, zbieraniu piśmiennictwa, korekcie pracy przed złożeniem do druku oraz interpretacji wyników i wniosków tej pracy.

Z poważaniem,

Signed by / Podpisano przez:
Mansur Rahnama-Hezavah
Date / Data: 2024-10-17 13:05

.....
(podpis oświadczającego)

Warszawa, 11.10.2024r.

Prof. dr hab. n. med. Tomasz Targowski
Kierownik Kliniki i Polikliniki Geriatrii
Narodowy Instytut Geriatrii, Reumatologii i Rehabilitacji
Krajowy konsultant w dziedzinie geriatrii
ul. Spartańska 1, 02-637 Warszawa

Oświadczenie

Oświadczam, że w pracy pod tytułem: **The Impact of COVID-19 on Carotid-Femoral Pulse Wave Velocity: A Systematic Review and Meta-Analysis**. opublikowanej w J Clin Med. 2023 Sep 4;12(17):5747. doi: 10.3390/jcm12175747. PMID: 37685813; PMCID: PMC10488425; autorstwa :Jannasz I, Pruc M, Rahnama-Hezavah M, Targowski T, Olszewski R, Feduniw S, Petryka K, Szarpak L.mój wkład merytoryczny w przygotowanie publikacji polegał na:

1. konsultacji i opiece merytorycznej

Oceniam swój wkład procentowy w publikację na poziomie 5 %. Wyrażam zgodę na przedłożenie powyższej publikacji przez lek Iwonę Jannasz jako część rozprawy doktorskiej w formie spójnego cyklu artykułów naukowych opublikowanych w recenzowanych czasopismach naukowych. Jednocześnie oświadczam, iż samodzielna i możliwa do wyodrębnienia część powyższej publikacji wykazuje indywidualny wkład lek. Iwony Jannasz przy tworzeniu koncepcji pracy, postawieniu hipotez, zaplanowaniu badań, wyborze metodyki, prowadzeniu badań, zbieraniu danych, analizie statystycznej, pisaniu pracy, graficznym przedstawieniu wyników, zbieraniu piśmiennictwa, korekcie pracy przed złożeniem do druku oraz interpretacji wyników i wniosków tej pracy.

Z poważaniem,

KIEROWNIK
KLINIKI I POLIKLINIKI GERIATRII
Narodowy Instytut Geriatrii, Reumatologii
i Rehabilitacji w Warszawie ul. Spartańska 1
prof. dr hab. n. med. Tomasz Targowski
(podpis oświadczającego)

Warszawa, 11.10.2024r.

dr hab. n. med. Robert Olszewski, Profesor NIGRiR,
Kierownik Zakładu
Gerontologii, Zdrowia Publicznego i Dydaktyki
Narodowy Instytut Geriatrii Reumatologii i Rehabilitacji.
Spartańska 1, 02-637 Warszawa

Instytut Podstawowych Problemów Techniki
Zakład Ultradźwięków
Polska Akademia Nauk
Pawińskiego 5B, 02-106 Warszawa

Oświadczenie

Oświadczam, że w pracy pod tytułem: **The Impact of COVID-19 on Carotid-Femoral Pulse Wave Velocity: A Systematic Review and Meta-Analysis**. opublikowanej w J Clin Med. 2023 Sep 4;12(17):5747. doi: 10.3390/jcm12175747. PMID: 37685813; PMCID: PMC10488425; autorstwa :Jannasz I, Pruc M, Rahnama-Hezavah M, Targowski T, Olszewski R, Feduniw S, Petryka K, Szarpak L.mój wkład merytoryczny w przygotowanie publikacji polegał na:

1. konsultacji i opiece merytorycznej

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Z poważaniem,

Robert Olszewski

(podpis oświadczającego)

Warszawa, 17.10.2024r.

Dr n. med. Stepan Feduniw
Oddział Ginekologii i Położnictwa,
Szpital Uniwersytecki w Zurychu, 8091 Zurych, Szwajcaria

Oświadczenie

Oświadczam, że w pracy pod tytułem: **The Impact of COVID-19 on Carotid-Femoral Pulse Wave Velocity: A Systematic Review and Meta-Analysis**. opublikowanej w J Clin Med. 2023 Sep 4;12(17):5747. doi: 10.3390/jcm12175747. PMID: 37685813; PMCID: PMC10488425; autorstwa : Jannasz I, Pruc M, Rahnama-Hezavah M, Targowski T, Olszewski R, Feduniw S, Petryka K, Szarpak L.mój wkład merytoryczny w przygotowanie publikacji polegał na:

1. Przygotowaniu oryginalnego draftu manuskryptu, jego recenzji i edycji oraz selekcji danych niezbędnych do przeprowadzenia badania.

Oceniam swój wkład procentowy w publikację na poziomie 5 %. Wyrażam zgodę na przedłożenie powyższej publikacji przez lek. Iwonę Jannasz jako część rozprawy doktorskiej w formie spójnego cyklu artykułów naukowych opublikowanych w recenzowanych czasopismach naukowych. Jednocześnie oświadczam, iż samodzielna i możliwa do wyodrębnienia część powyższej publikacji wykazuje indywidualny wkład lek. Iwony Jannasz przy tworzeniu koncepcji pracy, postawieniu hipotez, zaplanowaniu badań, wyborze metodyki, prowadzeniu badań, zbieraniu danych, analizie statystycznej, pisaniu pracy, graficznym przedstawieniu wyników, zbieraniu piśmiennictwa, korekcie pracy przed złożeniem do druku oraz interpretacji wyników i wniosków tej pracy.

Z poważaniem,

Stepan Feduniw

(podpis oświadczającego)

Karolina Petryka **Warszawa, 9.09.2023**

/imię i nazwisko/

Oświadczenie

Jako współautor pracy:

Iwona Jannasz, Michal Pruc, Mansur Rahnama-Hezavah, Tomasz Targowski, Robert Olszewski, Stepan Feduniw, Karolina Petryka, Lukasz Szarpak. The Impact of COVID-19 on Carotid–Femoral Pulse Wave Velocity: A Systematic Review and Meta-Analysis. J. Clin. Med. 2023, 12(17), 5747; DOI: 10.3390/jcm12175747

Oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi współudział w: redakcji i edycji finalnej wersji manuskryptu. Mój udział procentowy w przygotowanie publikacji określam jako 5%. Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako części rozprawy doktorskiej Iwony Jannasz.

Karolina Petryka

(podpis oświadczającego)

Warszawa, 17.10.2024r.

Prof. dr hab. n. med. dr h.c. multi Łukasz Szarpak, FERC

Department of Clinical Research and Development,
LUXMED Group, Warszawa, Polska

Henry JN Taub Department of Emergency Medicine,
Baylor College of Medicine, Houston, TX 77030, USA

Oświadczenie

Oświadczam, że w pracy pod tytułem: **The Impact of COVID-19 on Carotid-Femoral Pulse Wave Velocity: A Systematic Review and Meta-Analysis**. opublikowanej w J Clin Med. 2023 Sep 4;12(17):5747. doi: 10.3390/jcm12175747. PMID: 37685813; PMCID: PMC10488425; autorstwa : Jannasz I, Pruc M, Rahnama-Hezavah M, Targowski T, Olszewski R, Feduniw S, Petryka K, Szarpak L.mój wkład merytoryczny w przygotowanie publikacji polegał na:

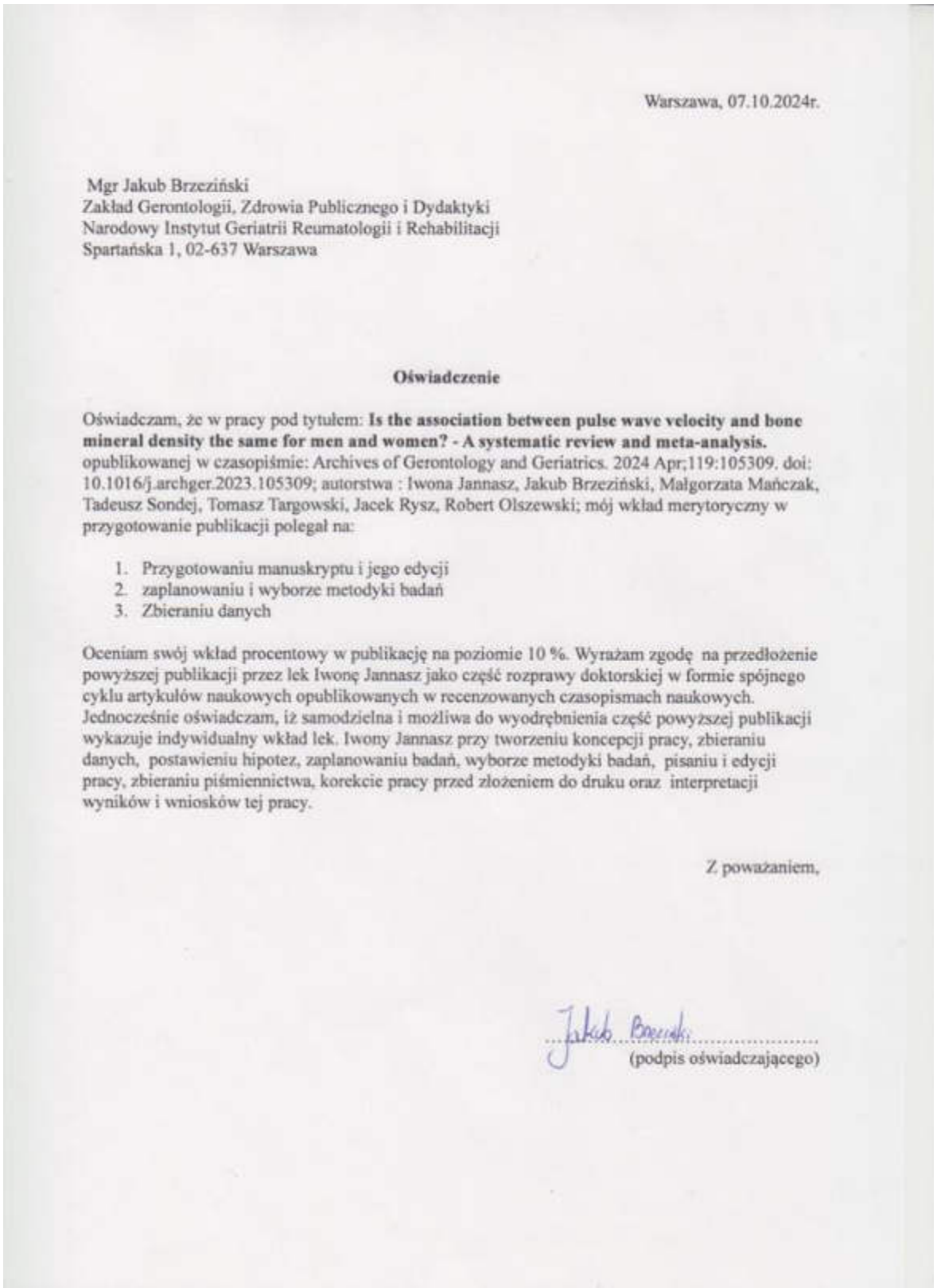
1. Metodologia, oprogramowanie, analiza formalna, przeprowadzenie dochodzenia, zebrania materiałów, selekcji danych, recenzja i edycja, nadzór nad całym projektem.

Oceniam swój wkład procentowy w publikację na poziomie 10 %. Wyrażam zgodę na przedłożenie powyższej publikacji przez lek. Iwonę Jannasz jako część rozprawy doktorskiej w formie spójnego cyklu artykułów naukowych opublikowanych w recenzowanych czasopismach naukowych. Jednocześnie oświadczam, iż samodzielna i możliwa do wyodrębnienia część powyższej publikacji wykazuje indywidualny wkład lek. Iwony Jannasz przy tworzeniu koncepcji pracy, postawieniu hipotez, zaplanowaniu badań, wyborze metodyki, prowadzeniu badań, zbieraniu danych, analizie statystycznej, pisaniu pracy, graficznym przedstawieniu wyników, zbieraniu piśmiennictwa, korekcie pracy przed złożeniem do druku oraz interpretacji wyników i wniosków tej pracy.

Z poważaniem,

.....
(podpis oświadczającego)

Publikacja 4: **Is the association between pulse wave velocity and bone mineral density the same for men and women?** - A systematic review and meta-analysis. Jannasz Iwona, Brzeziński Jakub, Mańczak Małgorzata, Sondej Tadeusz, Targowski Tomasz, Rysz Jacek, Olszewski Robert. Arch Gerontol Geriatr. 2024 Apr; 119:105309. doi: 10.1016/j.archger.2023.105309. Epub 2023 Dec 11. PMID: 38171030.



Warszawa, 07.10.2024r.

Mgr Jakub Brzeziński
Zakład Gerontologii, Zdrowia Publicznego i Dydaktyki
Narodowy Instytut Geriatrii Reumatologii i Rehabilitacji
Spartańska 1, 02-637 Warszawa

Oświadczenie

Oświadczam, że w pracy pod tytułem: **Is the association between pulse wave velocity and bone mineral density the same for men and women? - A systematic review and meta-analysis.** opublikowanej w czasopiśmie: Archives of Gerontology and Geriatrics. 2024 Apr;119:105309. doi: 10.1016/j.archger.2023.105309; autorstwa : Iwona Jannasz, Jakub Brzeziński, Małgorzata Mańczak, Tadeusz Sondej, Tomasz Targowski, Jacek Rysz, Robert Olszewski; mój wkład merytoryczny w przygotowanie publikacji polegał na:

1. Przygotowaniu manuskryptu i jego edycji
2. zaplanowaniu i wyborze metodyki badań
3. Zbieraniu danych

Oceniam swój wkład procentowy w publikację na poziomie 10 %. Wyrażam zgodę na przedłożenie powyższej publikacji przez lek Iwonę Jannasz jako część rozprawy doktorskiej w formie spójnego cyklu artykułów naukowych opublikowanych w recenzowanych czasopismach naukowych. Jednocześnie oświadczam, iż samodzielna i możliwa do wyodrębnienia część powyższej publikacji wykazuje indywidualny wkład lek. Iwony Jannasz przy tworzeniu koncepcji pracy, zbieraniu danych, postawieniu hipotez, zaplanowaniu badań, wyborze metodyki badań, pisaniu i edycji pracy, zbieraniu piśmiennictwa, korekcie pracy przed złożeniem do druku oraz interpretacji wyników i wniosków tej pracy.

Z poważaniem,

Jakub Brzeziński
(podpis oświadczającego)

Warszawa, 07.10.2024r.

Dr n. med. Małgorzata Mańczak
Zakład Gerontologii, Zdrowia Publicznego i Dydaktyki
Narodowy Instytut Geriatrii Reumatologii i Rehabilitacji.
Spartańska 1, 02-637 Warszawa

Oświadczenie

Oświadczam, że w pracy pod tytułem: **Is the association between pulse wave velocity and bone mineral density the same for men and women? - A systematic review and meta-analysis.** opublikowanej w czasopiśmie: Archives of Gerontology and Geriatrics. 2024 Apr;119:105309. doi: 10.1016/j.archger.2023.105309; autorstwa : Iwona Jannasz, Jakub Brzeziński , Małgorzata Manczak, Tadeusz Sondej, Tomasz Targowski, Jacek Rysz, Robert Olszewski, mój wkład merytoryczny w przygotowanie publikacji polegał na:

1. Wyborze metodyki badań
2. zabieraniu danych
3. analizie statystycznej

Oceniam swój wkład procentowy w publikację na poziomie 5 %. Wyrażam zgodę na przedłożenie powyższej publikacji przez lek Iwonę Jannasz jako część rozprawy doktorskiej w formie spójnego cyklu artykułów naukowych opublikowanych w recenzowanych czasopismach naukowych. Jednocześnie oświadczam, iż samodzielna i możliwa do wyodrębnienia część powyższej publikacji wykazuje indywidualny wkład lek. Iwony Jannasz przy tworzeniu koncepcji pracy, postawieniu hipotez, zaplanowaniu badań, wyborze metodyki badań, prowadzeniu badań, zbieraniu danych, pisaniu pracy, zbieraniu piśmiennictwa, korekcie pracy przed złożeniem do druku oraz interpretacji wyników i wniosków tej pracy.

Z poważaniem,

M. Mańczak

(podpis oświadczającego)

Warszawa, 07.10.2024 r.

dr hab. inż. Tadeusz Sondej, prof. WAT
Prodziekan ds. naukowych
Wydział Elektroniki WAT
Wojskowa Akademia Techniczna im. Jarosława Dąbrowskiego
ul. gen. Sylwestra Kaliskiego 2, 00-908 Warszawa

Oświadczenie

Oświadczam, że w pracy pod tytułem: **Is the association between pulse wave velocity and bone mineral density the same for men and women? - A systematic review and meta-analysis.** opublikowanej w czasopiśmie: Archives of Gerontology and Geriatrics. 2024 Apr;119:105309. doi: 10.1016/j.archger.2023.105309; autorstwa : Iwona Jannasz, Jakub Brzeziński , Małgorzata Manczak, Tadeusz Sondej, Tomasz Targowski, Jacek Rysz, Robert Olszewski, mój wkład merytoryczny w przygotowanie publikacji polegał na:

1. zaplanowaniu badań
2. opiece merytorycznej

Oceniam swój wkład procentowy w publikację na poziomie 5%. Wyrażam zgodę na przedłożenie powyższej publikacji przez lek. Iwonę Jannasz jako część rozprawy doktorskiej w formie spójnego cyklu artykułów naukowych opublikowanych w recenzowanych czasopismach naukowych. Jednocześnie oświadczam, iż samodzielna i możliwa do wyodrębnienia część powyższej publikacji wykazuje indywidualny wkład lek. Iwony Jannasz przy tworzeniu koncepcji pracy, postawieniu hipotez, zaplanowaniu badań, wyborze metodyki badań, prowadzeniu badań, zbieraniu danych, pisaniu pracy, zbieraniu piśmiennictwa, korekcie pracy przed złożeniem do druku oraz interpretacji wyników i wniosków tej pracy.

Z poważaniem,

.....
(podpis oświadczającego)

Warszawa, 07.10.2024r.

Prof. dr hab. n. med. Tomasz Targowski
Kierownik Kliniki i Polikliniki Geriatrii
Narodowy Instytut Geriatrii, Reumatologii i Rehabilitacji
Krajowy konsultant w dziedzinie geriatrii
ul. Spartańska 1, 02-637 Warszawa

Oświadczenie

Oświadczam, że w pracy pod tytułem: **Is the association between pulse wave velocity and bone mineral density the same for men and women? - A systematic review and meta-analysis.** opublikowanej w czasopiśmie: Archives of Gerontology and Geriatrics. 2024 Apr;119:105309. doi: 10.1016/j.archger.2023.105309; autorstwa : Iwona Jannasz, Jakub Brzeziński , Małgorzata Manczak, Tadeusz Sondej, Tomasz Targowski, Jacek Rysz, Robert Olszewski, mój wkład merytoryczny w przygotowanie publikacji polegał na:

1. koncepcji pracy, postawieniu hipotez
2. opiece merytorycznej
3. edycji manuskryptu

Oceniam swój wkład procentowy w publikację na poziomie 5 %. Wyrażam zgodę na przedłożenie powyższej publikacji przez lek Iwonę Jannasz jako część rozprawy doktorskiej w formie spójnego cyklu artykułów naukowych opublikowanych w recenzowanych czasopismach naukowych. Jednocześnie oświadczam, iż samodzielna i możliwa do wyodrębnienia część powyższej publikacji wykazuje indywidualny wkład lek. Iwony Jannasz przy tworzeniu koncepcji pracy, postawieniu hipotez, zaplanowaniu badań, wyborze metodyki badań, prowadzeniu badań, zbieraniu danych, pisaniu pracy, zbieraniu piśmiennictwa, korekcie pracy przed złożeniem do druku oraz interpretacji wyników i wniosków tej pracy.

Z poważaniem,

KIEROWNIK
KLINIKI I POLIKLINIKI GERIATRII
Narodowy Instytut Geriatrii, Reumatologii
i Rehabilitacji w Warszawie ul. Spartańska 1
prof. dr hab. n. med. Tomasz Targowski

.....
(podpis oświadczającego)

Warszawa, 07.10.2024r.

Prof. dr hab. n. med. Jacek Rysz
Kierownik Katedry
Nefrologii, Nadciśnienia Tętniczego i Medycyny Rodzinnej
Uniwersytet Medyczny w Łodzi
90-549 Łódź, ul. Żeromskiego 113

Oświadczenie

Oświadczam, że w pracy pod tytułem: **Is the association between pulse wave velocity and bone mineral density the same for men and women? - A systematic review and meta-analysis.** opublikowanej w czasopiśmie: Archives of Gerontology and Geriatrics. 2024 Apr;119:105309. doi: 10.1016/j.archger.2023.105309; autorstwa : Iwona Jannasz, Jakub Brzeziński , Małgorzata Manczak, Tadeusz Sondej, Tomasz Targowski, Jacek Rysz, Robert Olszewski, mój wkład merytoryczny w przygotowanie publikacji polegał na:

1. zbieraniu danych
2. opiece merytorycznej

Oceniam swój wkład procentowy w publikację na poziomie 5 %. Wyrażam zgodę na przedłożenie powyższej publikacji przez lek Iwonę Jannasz jako część rozprawy doktorskiej w formie spójnego cyklu artykułów naukowych opublikowanych w recenzowanych czasopismach naukowych. Jednocześnie oświadczam, iż samodzielna i możliwa do wyodrębnienia część powyższej publikacji wykazuje indywidualny wkład lek. Iwony Jannasz przy tworzeniu koncepcji pracy, postawieniu hipotez, zaplanowaniu badań, wyborze metodyki badań, prowadzeniu badań, zbieraniu danych, pisaniu pracy, zbieraniu piśmiennictwa, korekcie pracy przed złożeniem do druku oraz interpretacji wyników i wniosków tej pracy.

Z poważaniem,

(podpis oświadczającego)

Warszawa, 07.10.2024r.

Dr hab. n. med. Robert Olszewski, Profesor NIGRiR,
Kierownik Zakładu
Gerontologii, Zdrowia Publicznego i Dydaktyki
Narodowy Instytut Geriatrii Reumatologii i Rehabilitacji.
Spartańska 1, 02- 637 Warszawa

Instytut Podstawowych Problemów Techniki
Zakład Ultradźwięków
Polska Akademia Nauk
Pawińskiego 5B, 02-106 Warszawa

Oświadczenie

Oświadczam, że w pracy pod tytułem: **Is the association between pulse wave velocity and bone mineral density the same for men and women? - A systematic review and meta-analysis.** opublikowanej w czasopiśmie: Archives of Gerontology and Geriatrics. 2024 Apr;119:105309. doi: 10.1016/j.archger.2023.105309; autorstwa : Iwona Jannasz, Jakub Brzeziński , Małgorzata Manczak, Tadeusz Sondej, Tomasz Targowski, Jacek Rysz, Robert Olszewski, mój wkład merytoryczny w przygotowanie publikacji polegał na:

1. koncepcji pracy, postawieniu hipotez
2. zaplanowaniu badań
3. opiece merytorycznej
4. edycji manuskryptu

Oceniam swój wkład procentowy w publikację na poziomie 5%. Wyrażam zgodę na przedłożenie powyższej publikacji przez lek Iwonę Jannasz jako część rozprawy doktorskiej w formie spójnego cyklu artykułów naukowych opublikowanych w recenzowanych czasopismach naukowych. Jednocześnie oświadczam, iż samodzielna i możliwa do wyodrębnienia część powyższej publikacji wykazuje indywidualny wkład lek. Iwony Jannasz przy tworzeniu koncepcji pracy, postawieniu hipotez, zaplanowaniu badań, wyborze metodyki badań, prowadzeniu badań, zbieraniu danych, pisaniu pracy, zbieraniu piśmiennictwa, korekcie pracy przed złożeniem do druku oraz interpretacji wyników i wniosków tej pracy.

Z poważaniem,

p/o KIEROWNIK
Zakładu Gerontologii, Zdrowia Publicznego i Dydaktyki
Narodowy Instytut Geriatrii Reumatologii
i Rehabilitacji w Warszawie

Dr hab. n. med. Robert Olszewski, prof. NIGRiR

(podpis oświadczającego)

13. Piśmiennictwo

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