Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

ROZPRAWA DOKTORSKA

lek. Katarzyna Kulej-Łyko

Znaczenie odpowiedzi z chemoreceptorów obwodowych w patogenezie duszności wysiłkowej u chorych z rozkurczową niewydolnością serca

The role of peripheral chemoreflexes in pathogenesis of exercise intolerance in patients with heart failure with preserved ejection fraction

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Badania przedstawione w niniejszej rozprawie doktorskiej pt. **„Znaczenie odpowiedzi z chemoreceptorów obwodowych w patogenezie duszności wysiłkowej u chorych z rozkurczową niewydolnością serca”** zostały wykonane w Katedrze i Klinice Chorób Serca, Centrum oraz Instytucie Chorób Serca Uniwersytetu Medycznego im. Piastów Śląskich we Wrocławiu kierowanym przez Pana prof. dr hab. n. med. Piotra Ponikowskiego.

Promotorem rozprawy doktorskiej jest Pan prof. dr hab. n. med. Piotr Ponikowski.

Promotorem pomocniczym rozprawy doktorskiej jest Pan dr n. med. Piotr Niewiński.

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Spis treści

1. WYKAZ PUBLIKACJI STANOWIĄCYCH ROZPRAWĘ DOKTORSKĄ

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Wykaz publikacji stanowiących cykl

Lp.	Tytuł, autorzy, źródło	IF	PK
1.	**Inhibition of peripheral chemoreceptors improves ventilatory efficiency during exercise in heart failure with preserved ejection fraction - a role of tonic activity and acute reflex response. KATARZYNA KULEJ-ŁYKO**, PIOTR NIEWIŃSKI, STANISŁAW TUBEK, MAGDALENA KRAWCZYK, WOJCIECH KOSMALA, PIOTR PONIKOWSKI. *Front.Physiol.* 2022 Vol.13 art.911636 [18 s.], ryc., tab., bibliogr., summ. DOI: 10.3389/fphys.2022.911636	4,755*	100,00
2.	**Contribution of Peripheral Chemoreceptors to Exercise Intolerance in Heart Failure.KULEJ-LYKO K[ATARZYNA]**, NIEWINSKI P, TUBEK S, PONIKOWSKI P. Front Physiol. 2022 Apr 14;13:878363. doi: 10.3389/fphys.2022.878363. PMID: 35492596; PMCID: PMC9046845.	4,755*	100,00
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2. STRESZCZENIE

Niewydolność serca (ang. *heart failure* - HF) jest jednostką chorobową charakteryzującą się niską jakością życia, wysoką częstością hospitalizacji i niekorzystnym rokowaniem. Choroba dotyka ok. 1-2% populacji, a częstość jej występowania systematycznie zwiększa się. Podczas gdy zapadalność na niewydolność serca z obniżoną frakcją wyrzutową lewej komory spada (ang. *heart failure with reduced ejection fraction* - HFrEF), częstość występowania niewydolności serca z zachowaną frakcją wyrzutową lewej komory (ang. *heart failure with preserved ejection fraction* - HFpEF) rośnie i stanowi wyzwanie dla współczesnej kardiologii.

W HF dominującym i najbardziej ograniczającym objawem jest nietolerancja wysiłku fizycznego. Patogeneza tego zjawiska jest wieloczynnikowa i niezbyt dobrze poznana, a nieprawidłowości w zakresie regulacji odruchowej (w tym nadmierna aktywacja układu współczulnego oraz zwiększona wrażliwość chemoreceptorów obwodowych) są elementami tego złożonego procesu.

Główną rolą chemoreceptorów obwodowych (ang. *peripheral chemoreceptors* - PChRs) jest utrzymywanie odpowiedniego stężenia tlenu we krwi obwodowej. W odpowiedzi na hipoksję dochodzi do ich pobudzenia, co w kolejnym etapie stymuluje ośrodki regulatorowe w podwzgórzu i rdzeniu przedłużonym prowadząc do zwiększenia wentylacji minutowej, częstości akcji serca i ciśnienia tętniczego.

Działanie PChRs obejmuje: 1) aktywność toniczną (ang. *tonic activity* - PChT) - spoczynkową aktywność PChRs w warunkach normoksji przy nieobecności czynnika stymulującego oraz 2) aktywność ostrą (ang. *acute sensitivity* - PChS) - będącą odpowiedzią na działający bodziec.

Udział obu składowych w kontroli procesów oddechowych i hemodynamicznych w czasie wysiłku fizycznego w HF jak dotąd nie został dobrze poznany. Dostępne doniesienia naukowe pokazują, że u pacjentów z HFrEF farmakologiczne zablokowanie lub resekcja PChRs prowadziły do poprawy tolerancji wysiłku fizycznego. Dlatego można przypuszczać, że podobne mechanizmy występują również u chorych z HFpEF.

Głównym celem przedstawionych publikacji była analiza złożonych patofizjologicznych mechanizmów odpowiedzialnych za nietolerancję wysiłku fizycznego u chorych z HF oraz weryfikacja hipotezy, że PChRs uczestniczą w patogenezie duszności wysiłkowej u chorych z HFpEF. Kolejną hipotezą było udowodnienie, że farmakologiczne zablokowanie ww. struktur przy pomocy małych dawek dopaminy prowadzi do poprawy tolerancji wysiłku fizycznego w badanej populacji.

W ramach publikacji pt. ***"Contribution of peripheral chemoreceptors to exercise intolerance in heart failure"*** kompleksowo przedstawiono znaczenie PChRs w wywoływaniu duszności wysiłkowej oraz zmęczenia - objawów najbardziej ograniczających tolerancję wysiłku fizycznego i najczęściej zgłaszanych przez pacjentów z HF. Opisano, w jaki sposób PChRs uczestniczą w wywoływaniu hiperwentylacji, dynamicznej hiperinflacji płuc, oddychania cyklicznego oraz jak modulują aktywność metaboreceptorów, prowadząc do wystąpienia i nasilenia duszności wysiłkowej. Ponadto podkreślono znaczenie zmniejszonego rzutu serca, ograniczenia perfuzji oraz strukturalnych i czynnościowych nieprawidłowości jako głównych determinant zmęczenia mięśni szkieletowych.

W ramach publikacji pt. ***"Inhibition of peripheral chemoreceptors improves ventilatory efficiency during exercise in heart failure with preserved ejection fraction – a role of tonic activity and acute reflex response"*** wykazano, że PChRs są zaangażowane w procesy regulujące oddychanie, a ich zahamowanie prowadzi do poprawy efektywności wentylacji w czasie wysiłku fizycznego u chorych z HFpEF. Co więcej, udowodniono, że w tej grupie aktywność PChRs była zwiększona, podobnie jak w HFrEF, pomimo prawidłowej frakcji wyrzutowej lewej komory. Unikatową wartością przedstawionego badania okazała się ocena zarówno aktywności ostrej jak i tonicznej u chorych z HFpEF oraz udział każdej komponenty w patogenezie duszności wysiłkowej. Udowodniono, że wyznacznikiem niskiej efektywności wentylacji definiowanej jako wysoki wskaźnik VE/VCO_2 (stosunek wentylacji minutowej do produkcji dwutlenku węgla) była wysoka PChS. Natomiast PChT odzwierciedlała potencjalną poprawę VE/VCO_2 po farmakologicznym zablokowaniu PChRs.

Zwiększona aktywność chemoreceptorów obwodowych jest udowodnionym czynnikiem odpowiedzialnym za złą tolerancją wysiłku fizycznego u chorych z HFrEF. Liczne interwencje (farmakologiczne i chirurgiczne) w tej grupie chorych prowadziły do poprawy wydolności wysiłkowej. Brak jest podobnych badań w HFpEF. Powyższe publikacje przedstawiają złożony proces regulacji wydolności wysiłkowej w HF, ze szczególnym naciskiem na rolę nadmiernej aktywności PChRs w populacji chorych z HFpEF.
Na podstawie naszych obserwacji można przypuszczać, że pacjenci z wysoką toniczną aktywnością PChRs mogą potencjalnie odnieść korzyści z ich blokady, co przełoży się na poprawę tolerancji wysiłku fizycznego – w zakresie lepszej efektywności wentylacyjnej.

3. SUMMARY

Heart failure (HF) is characterized by worse quality of life, high prevalence of hospitalizations and poor long-term outcomes. HF affects about 1-2% population and the prevalence of the disease is constantly rising. Whereas incidence of heart failure with reduced ejection fraction (HFrEF) is falling, the prevalence of heart failure with preserved ejection fraction (HFpEF) is still growing and has become a challenge for modern cardiology.

Exercise intolerance is dominant and most debilitating syndrome of HF. Its pathogenesis is multifactorial and not clearly understood but disturbances in chemoreflex regulation (including increased sympathetic gain and enhanced peripheral chemoreceptors activation) contribute to this complex mechanism.

The main role of peripheral chemoreceptors (PChRs) is maintaining adequate blood oxygenation in the periphery. Activation of PChRs in response to hypoxia leads to excitation of central chemoreceptors in the hypothalamus and medulla that in turn increases minute ventilation, heart rate and blood pressure.

PChRs activity comprises: 1) tonic activity (PChT) - basal activity under normoxic conditions without any stimulus and 2) acute sensitivity (PChS) - in response to acute stimulation.

The contribution of these two components to ventilatory and hemodynamic regulation during exercise in HF has not been extensively studied. Previous studies indicated that pharmacological blockade or surgical resection of PChRs provoked improvement in exercise tolerance in the HFrEF population. Therefore, we speculate that similar mechanisms may be in play in HFpEF patients.

The main goal of our studies was to investigate the multifactorial pathophysiological mechanisms responsible for exercise intolerance in HF patients and to confirm the hypothesis that PChRs are involved in exertional dyspnoea in the HFpEF population. Moreover, we planned to prove that pharmacological blockade of PChRs with low-dose dopamine leads to improvement in exercise tolerance in studied population.

In the paper: ***"Contribution of peripheral chemoreceptors to exercise intolerance in heart failure"*** we comprehensively described the role of PChRs in provoking dyspnoea and muscular fatigue. These symptoms are most often reported by patients with HF and seem to be main factors limiting exertional capacity. We presented the contribution of PChRs in hyperventilation, dynamic lung hyperinflation, oscillatory ventilation and metaboreceptors activation in skeletal muscles that in aggregate predispose to exertional dyspnoea. Likewise, restriction in blood flow, functional and structural abnormalities in skeletal muscles together with reduced cardiac output determine muscular fatigue.

In the paper: ***"Inhibition of peripheral chemoreceptors improves ventilatory efficiency during exercise in heart failure with preserved ejection fraction – a role of tonic activity and acute reflex response"*** we presented that PChRs were involved in ventilatory control during exercise and their inhibition resulted in improvement in ventilatory efficiency in the HFpEF population. Furthermore, we demonstrated that PChRs' activity was increased similarly to HFrEF population despite preserved ejection fraction of left ventricle. The novelty of our study stems from the assessment of both acute and tonic component

of PChRs functionality with careful evaluation of their individual contribution to the exertional capacity. We demonstrated that high PChS was associated with poor ventilatory efficiency defined as a high VE/VCO_2 (the ratio of minute ventilation to carbon dioxide production). Whereas, augmented PChT reflected the magnitude of the potential improvement in exercise tolerance following pharmacological PChRs deactivation.

Increased peripheral chemoreflex is a well-known factor contributing to exercise intolerance in the HFrEF population. Numerous interventions (pharmacological and surgical) have been shown to improve exercise capacity in the aforementioned group. Nonetheless, similar reports in HFpEF patients are lacking. Our studies presented complex mechanisms contributing to exercise intolerance in HF, particularly concerning augmented PChRs' activity in the HFpEF population. Based on our observations, we speculate that patients with high PChT would benefit from PChRs deactivation that may improve their exertional capacity.

4. WYKAZ STOSOWANYCH SKRÓTÓW:

$EtCO_2$ *(ang. end-tidal carbon dioxide)* – stężenie dwutlenku węgla podczas wydechu
HF (*ang. heart failure*) – niewydolność serca
HFpEF (*ang. heart failure with preserved ejection fraction*) – niewydolność serca z zachowaną frakcją wyrzutową lewej komory
HFrEF (*ang. heart failure with reduced ejection fraction*) – niewydolność serca z obniżoną frakcją wyrzutową lewej komory
$PaCO_2$ *(ang. arterial partial pressure of carbon dioxide)* – ciśnienie parcjalne dwutlenku węgla we krwi tętniczej
PChRs (*ang. peripheral chemoreceptors*) – chemoreceptory obwodowe
PChS (*ang. peripheral acute chemosensitivity*) – ostra aktywność chemoreceptorów obwodowych
PChT (*ang. tonic activity*) – toniczna aktywność chemoreceptorów obwodowych
VE/VCO_2 (*ang. the ratio between ventilation and carbon dioxide production*) – wskaźnik efektywności wentylacji definiowany jako stosunek wentylacji minutowej do produkcji dwutlenku węgla

5. WPROWADZENIE

Niewydolność serca (ang. *heart failure* - HF) jest jednostką chorobową charakteryzującą się niską jakością życia, wysoką częstością hospitalizacji i niekorzystnym rokowaniem (1,2). Choroba dotyka ok. 1-2% populacji, a częstość jej występowania systematycznie zwiększa się (3). Podczas gdy zapadalność na niewydolność serca z obniżoną frakcją wyrzutową lewej komory (ang. *heart failure with reduced ejection fraction* - HFrEF) ulega zmniejszeniu (4), częstość występowania niewydolności serca z zachowaną frakcją wyrzutową lewej komory (ang. *heart failure with preserved ejection fraction* - HFpEF) nadal rośnie (5), co stanowi wyzwanie dla współczesnej kardiologii.

W HF dominującym i najbardziej ograniczającym objawem jest nietolerancja wysiłku fizycznego (4,6). Patogeneza tego procesu jest złożona i nie do końca poznana. Istotną rolę odgrywają zaburzenia wentylacji wysiłkowej (takie jak hiperwentylacja (7,8) i oddychanie cykliczne (9)), zmniejszony rzut serca (10), nieprawidłowa aktywność metaboreceptorów (11), ograniczenie perfuzji mięśni szkieletowych (12), strukturalne i czynnościowe nieprawidłowości w funkcjonowaniu mięśni szkieletowych (13,14) oraz zaburzenia autonomicznych reakcji odruchowych (w tym nadmierna aktywacja układu współczulnego oraz zwiększona aktywność chemoreceptorów obwodowych) (2,15,16). W przypadku pacjentów z HFpEF dodatkowymi mechanizmami odpowiedzialnymi za gorszą wydolność wysiłkową jest nieprawidłowe sprzężenie lewokomorowo-naczyniowe (17), podwyższone wysiłkowe ciśnienie napełniania w lewych jamach serca (18), niewydolność chronotropowa (19), zaburzona rezerwa skurczowa i rozkurczowa lewej komory (20) oraz zmniejszenie uwalniania tlenu w tkankach obwodowych (z powodu dysfunkcji mikrokrążenia i zaburzeń strukturalnych w mięśniach szkieletowych) (21).

Chemoreceptory obwodowe (ang. *peripheral chemoreceptors* - PChRs) są strukturami zlokalizowanymi głównie w okolicy rozwidlenia tętnicy szyjnej wspólnej (kłębki szyjne) oraz wzdłuż łuku aorty (kłębki aortalne) (22). Ich podstawową funkcją jest utrzymywanie odpowiedniego stężenia tlenu we krwi obwodowej. Oprócz hipoksji (23) struktury te są pobudzane przez wiele innych substancji takich jak jony wodorowe (24), dwutlenek węgla (24), glukozę (25), jony potasowe (26) i mleczany (26).

Spadek stężenia tlenu aktywuje PChRs i prowadzi do pobudzenia jądra przykomorowego podwzgórza (27), kompleksu pre-Botzingera (28) i presynaptycznych neuronów dogłowowej brzuszno-bocznej części rdzenia przedłużonego (29). Wynikiem tej stymulacji jest zwiększenie wentylacji minutowej (30), częstości akcji serca i ciśnienia tętniczego (31). Jednoczasowo dochodzi do zahamowania aktywności baroreceptorów obwodowych (32).

Działanie PChRs obejmuje: 1) aktywność toniczną (ang. *tonic activity* - PChT) - spoczynkową aktywność PChRs w warunkach normoksji przy nieobecności czynnika stymulującego oraz 2) aktywność ostrą (ang. *acute sensitivity* - PChS) - będącą odpowiedzią na działający bodziec.

Farmakologiczne zablokowanie lub resekcja PChRs poprawiały tolerancję wysiłku fizycznego w grupie pacjentów z HFrEF (15,33,34). Zmniejszenie aktywności PChRs przy pomocy tlenu prowadziło do wydłużenia czasu trwania wysiłku na cykloergometrze rowerowym (33). Podobnie zablokowanie PChRs dihydrokodeiną spowodowało wydłużenie czasu trwania wysiłku fizycznego, zwiększenie szczytowego zużycia tlenu oraz poprawę efektywności wentylacji definiowanej jako spadek VE/VCO_2 (stosunku wentylacji minutowej

do produkcji dwutlenku węgla) (34). Chirurgiczna resekcja PChRs u pacjentów z HFrEF wydłużała czas trwania wysiłku fizycznego oraz zmniejszała wskaźnik VE/VCO_2 (15). Na podstawie wyników uzyskanych w tej grupie chorych można przypuszczać, że podobne mechanizmy występują również u chorych z HFpEF. Jednak do tej pory nie zostało to dokładnie zbadane. Co więcej, niejasny pozostaje udział zarówno komponenty ostrej jak i tonicznej w kontroli procesów oddechowych i hemodynamicznych w czasie wysiłku fizycznego w HFpEF.

6. CELE BADAŃ

Głównym celem przedstawionych badań była analiza mechanizmów odpowiedzialnych za nietolerancję wysiłku fizycznego (w tym zwiększonej aktywności chemoreceptorów obwodowych) u chorych z niewydolnością serca, ze szczególnym uwzględnieniem HF z zachowaną frakcją wyrzutową lewej komory.

Cele szczegółowe publikacji pt. ***"Contribution of peripheral chemoreceptors to exercise intolerance in heart failure"***:

- przedstawienie roli PChRs w wywoływaniu głównych objawów HF (duszności i zmęczenia mięśni szkieletowych) determinujących gorszą wydolność wysiłkową

Cele szczegółowe publikacji pt. ***"Inhibition of peripheral chemoreceptors improves ventilatory efficiency during exercise in heart failure with preserved ejection fraction – a role of tonic activity and acute reflex response"***:

- ocena aktywności chemoreceptorów obwodowych z uwzględnieniem zarówno komponenty ostrej jak i tonicznej u chorych z HFpEF

- ocena tolerancji wysiłku fizycznego i poszukiwanie czynników determinujących gorszą wydolność wysiłkową w tej grupie chorych

- weryfikacja hipotezy, że zwiększona aktywność PChRs uczestniczy w patogenezie duszności wysiłkowej u chorych z HFpEF

- udowodnienie, że farmakologiczne zablokowanie PChRs prowadzi do poprawy tolerancji wysiłku fizycznego w badanej populacji

7. MATERIAŁ I METODY

Wszystkie badania przedstawione w niniejszym opracowaniu zostały przeprowadzone w Katedrze i Klinice Chorób Serca, Centrum oraz Instytucie Chorób Serca Uniwersytetu Medycznego we Wrocławiu. Zgodę na przeprowadzenie badania opisanego w publikacji pt. ***"Inhibition of peripheral chemoreceptors improves ventilatory efficiency during exercise in heart failure with preserved ejection fraction – a role of tonic activity and acute reflex response"*** wydała Komisja Bioetyczna przy Uniwersytecie Medycznym we Wrocławiu.

W ramach publikacji pt. ***"Contribution of peripheral chemoreceptors to exercise intolerance in heart failure"*** na podstawie dostępnej literatury opisano udział PChRs w wywoływaniu głównych objawów HF (duszności i zmęczenia mięśni szkieletowych) determinujących gorszą tolerancję wysiłku fizycznego (praca poglądowa).

W ramach publikacji pt. ***"Inhibition of peripheral chemoreceptors improves ventilatory efficiency during exercise in heart failure with preserved ejection fraction – a role of tonic activity and acute reflex response"*** przebadano 12 stabilnych pacjentów z rozpoznaniem HFpEF ustalonym na podstawie wytycznych Europejskiego Towarzystwa Kardiologicznego (35,36). Wstępna ocena chorych obejmowała: wywiad lekarski, badanie fizykalne, test 6-minutowego marszu, ocenę jakości życia przy pomocy kwestionariuszy "Minnesota Living With Heart Failure Questionnaire" (37,38) i "Kansas City Cardiomyopathy Questionnaire" (39,40), wykonanie podstawowych badań laboratoryjnych, EKG, spirometrii i badania echokardiograficznego. Następnie wykonywano ocenę chemowrażliwości obwodowej (16,41) w warunkach standardowych i w czasie farmakologicznego zahamowania PChRs przy pomocy małych dawek dopaminy ($3\ \mu g\ kg^{-1}min^{-1}$) (42,43). W kolejnym etapie wykonywano próbę wysiłkową na cykloergometrze rowerowym (44). Test wysiłkowy, podobnie jak badanie chemowrażliwości obwodowej był wykonywany dwukrotnie: w czasie wlewu placebo (rozwór soli fizjologicznej) oraz podczas podawania dopaminy. Badania były podwójnie zaślepione, a kolejność podawania dopaminy / placebo była randomizowana. Szczegółowy opis metody badania chemowrażliwości obwodowej oraz protokół oceny tolerancji wysiłku fizycznego został przedstawiony w publikacji w części „Methods".

Analizę statystyczną przeprowadzono przy pomocy testu kolejności par Wilcoxona, a zmienne zostały przedstawione jako średnia arytmetyczna ± odchylenie standardowe oraz jako średnia arytmetyczna ± błąd standardowy. Do obliczeń korelacji została wykorzystana metoda korelacji Spearmana. Wynik uznano za istotny statystycznie, gdy wartość $p < 0.05$. Obliczenia zostały wykonane przy pomocy programu Statistica 13 (StatSoft Inc., Tulsa, OK, United States).

8. PUBLIKACJE

8.1. Publikacja 1

Kulej-Lyko K, Niewinski P, Tubek S and Ponikowski P (2022)
Contribution of peripheral chemoreceptors to exercise intolerance in heart failure.
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Contribution of Peripheral Chemoreceptors to Exercise Intolerance in Heart Failure

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Peripheral chemoreceptors (PChRs), because of their strategic localization at the bifurcation of the common carotid artery and along the aortic arch, play an important protective role against hypoxia. Stimulation of PChRs evokes hyperventilation and hypertension to maintain adequate oxygenation of critical organs. A relationship between increased sensitivity of PChRs (hyperreflexia) and exercise intolerance (ExIn) in patients with heart failure (HF) has been previously reported. Moreover, some studies employing an acute blockade of PChRs (e.g., using oxygen or opioids) demonstrated improvement in exercise capacity, suggesting that hypertonicity is also involved in the development of ExIn in HF. Nonetheless, the precise mechanisms linking dysfunctional PChRs to ExIn remain unclear. From the clinical perspective, there are two main factors limiting exercise capacity in HF patients: subjective perception of dyspnoea and muscle fatigue. Both have many determinants that might be influenced by abnormal signalling from PChRs, including: exertional hyperventilation, oscillatory ventilation, ergoreceptor oversensitivity, and augmented sympathetic tone. The latter results in reduced muscle perfusion and altered muscle structure. In this review, we intend to present the milieu of abnormalities tied to malfunctioning PChRs and discuss their role in the complex relationships leading, ultimately, to ExIn.

Keywords: peripheral chemoreceptors, carotid bodies, heart failure, exercise intolerance, dyspnoea, muscle fatigue

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INTRODUCTION

Peripheral chemoreceptors (PChRs) play important roles in adapting to hypoxia, physiologically and evolutionarily. In humans, PChRs are represented mainly by carotid bodies (CBs) located close to the bifurcation of the common carotid artery and aortic bodies situated along the aortic arch (Paton et al., 2013). A decrease in arterial blood oxygenation activates CBs and then, *via* a reflex arc involving brain stem nuclei, leads to hyperventilation (Ponikowski and Banasiak, 2001). Similarly, stimulation of PChRs elicits sympathetic excitation and, in turn, increases peripheral resistance (Despas et al., 2009; Despas et al., 2012). Moreover, direct stimulation of aortic bodies and activation of Hering-Breuer reflex (originating from pulmonary stretch receptors) secondary to hyperventilation result in tachycardia (Niewinski et al., 2014; Tubek et al., 2016; Paleczny et al., 2019). Undoubtfully, these reactions are protective in acute settings (e.g., high altitude). On the other hand, elevated tonic activity and exaggerated (concerning the physiological need) acute responses from PChRs may be potentially harmful. This has repeatedly been shown in selected patients with heart failure (HF)—possibly due to enhanced adrenergic tone (Ponikowski et al., 2001a; Floras and Ponikowski, 2015).

Augmented peripheral chemosensitivity characterizes approximately 40% of patients with heart failure with reduced ejection fraction (Chua et al., 1997a; Niewinski et al., 2013). There is a clear relationship between hyperreflexia of PChRs (i.e. increased peripheral chemosensitivity) and exercise intolerance (ExIn) expressed as: 1) higher New York Heart Association (NYHA) functional class or 2) worse cardiopulmonary exercise test indices (Chua et al., 1996a; Chua et al., 1997a). Hyperreflexia of PChRs has been repeatedly linked to the worse clinical profile of HF patients, including a greater degree of neurohormonal derangement (e.g., higher level of NTpro-BNP) (Giannoni et al., 2008). However, in the experimental study employing acute inhibition of PChRs (Chua et al., 1996; Chua et al., 1997) not only oversensitivity chemoreflex but also tonic activity of PChRs have been targeted. In those studies, PChR were blocked with the use of oxygen or opioids, which resulted in improved exercise capacity of HF subjects. Whether such benefit was related to a decrease in acute reflex response to the metabolites of exercising muscles (e.g., lactate) (Torres-Torrelo et al., 2021) or to the dimished tonic activity of PChRs remains unknown.

The limitation of exertional capacity in the HF population emerges from the dyspnoea sensation and/or muscle fatigue. These are the two most common complaints reported at the end of the symptom-limited exercise test by HF patients (Clark et al., 1995). Both can be influenced by a variety of factors related primarily to low cardiac output and secondarily to: pulmonary abnormalities (Wasserman et al., 1997; Schmid et al., 2008), autonomic imbalance (Niewinski et al., 2017), impaired peripheral perfusion (Piepoli et al., 1996), and altered muscle function and structure (Wilson et al., 1993).

DETERMINANTS OF EXERTIONAL DYSPNOEA IN HEART FAILURE

Excessive Hyperventilation During Exercise

Historical studies from the 1960s and 1970s reported a reduction of dyspnoea sensation in patients with severe bronchial asthma and chronic obstructive pulmonary disease following unilateral or bilateral CB resection (Nakayama, 1962; Winter 1973; Stulbarg and Winn, 1989). This supports a relationship between the PChRs' function and the perception of breathing difficulty. Hyperventilation (expressed as an increase in tidal volume and/or respiratory rate) as the primary response to the activation of PChRs may be subjectively identified as shortness of breath (Chua et al., 1997a; Wasserman et al., 1997; Motiejunaite et al., 2021). Inhibition of the tonic PChRs activity (with oxygen, dopamine or dihydrocodeine) (Chua et al., 1996a; Chua et al., 1997b; van de Borne et al., 1998) or CB denervation (Niewinski et al., 2017) decreased the regression slope relating ventilation to carbon dioxide output (VE/VCO_2 slope) in HF patients subjected to cardiopulmonary exercise test indicating diminished ventilatory effort for a given carbon dioxide production. This might translate into a reduced sensation of dyspnoea and thus explain the benefits seen in the former studies on CB resection (Nakayama, 1962; Winter 1973; Stulbarg and Winn, 1989).

A growing body of evidence points to the connection between the functionalities of central and peripheral chemoreceptors. A significant reduction of central chemosensitivity occurring acutely after bilateral CB resection is a piece of obvious evidence for the hyperadditive character of this interaction (Del Rio et al., 2013; Marcus et al., 2014). Thus, in HF, hypertonicity of PChRs enhances exertional hyperventilation not only directly but also indirectly through the augmentation of central respiratory drive.

Due to relatively stable arterial partial pressures of oxygen and carbon dioxide during incremental exercise (Sun et al., 2001; Forster et al., 2012), acute activation of PChRs is debatable in this context. On the other hand, it could be hypothesized that the rising on-exercise concentration of other (than oxygen and carbon dioxide) known CBs stimulants, such as lactate (Torres-Torrelo et al., 2021), potassium (McLoughlin et al., 1995), adenosine (McQueen and Ribeiro, 1981), and catecholamines (Lahiri et al., 1981), could contribute to excessive ventilation due to hyperreflexia of PChRs in HF. According to that notion, not only "tonic" but also "acute" reactivity of CBs would be involved in ExIn in HF patients (Scott et al., 2003). This is supported by the fact that the increase in lactate production during exercise is significantly faster in HF subjects than in healthy controls. Indeed, Scott et. (Scott et al., 2003) demonstrated that local lactate concentrations in the exercising muscles of HF patients were significantly higher than in subjects with normal left ventricular function (2.55 ± 0.2 *vs.* 1.78 ± 0.2 mmol/L).

Restriction of the inspiratory effort ("unsatisfied inspiration") may be perceived as breathlessness limiting exercise capacity (O'Donnell et al., 1999; O'Donnell and Laveneziana, 2006). One of its main reasons is the phenomenon called dynamic lung hyperinflation (DLH), which has been described in HF patients (O'Donnell et al., 1999). DLH is characterized by a progressive rise in end-expiratory lung volume with concomitant fall in dynamic inspiratory capacity relative to the degree of air trapping. The dynamic inspiratory capacity is continuously diminished due to increasing elastic forces affecting respiratory muscles when tidal volumes are operating closer to total lung capacity.

O`Donnell et al. elegantly documented that at a peak work rate of only 41% of predicted value, end-expiratory lung volume was equal to 92% of total lung capacity in a group of stable patients with congestive HF (O'Donnell et al., 1999). DLH emerges from the expiratory flow limitation caused by several factors connected with HF state: mucosal oedema (Duguet et al., 2000), hyperresponsiveness of bronchi (Cabanes et al., 1989), and age-related airways abnormalities (Light, 1983).

Kawachi et al. show that DLH can be experimentally produced by hyperventilation (Kawachi and Fujimoto, 2020). Because hyperventilation during exercise is closely linked to PChRs' overactivity (Chua et al., 1996a), one could expect that such patients are also prone to the development of DLH. Moreover, patients with the augmented activity of PChRs present with increased sympathetic drive (Floras and Ponikowski, 2015),

which generates water and sodium retention (Martin and Schrier, 1997; Schrier, 2006). Thus, it may be speculated that interstitial oedema and inflammation within the airways produced by sympathetically-mediated [including mobilization of the venous reservoir *via* venoconstriction (Bruno et al., 2012)] increase in fluid volume (Miller, 2016) -could participate in the development of the obstructive pattern and consequently further predispose to DLH. However, such a notion would need to be confirmed in experimental studies.

Apart from the phenomena described above resulting in airway obstruction, the role of reduced lung compliance should also be emphasized (Faggiano, 1994). The restrictive pattern in HF patients may be secondary to heart enlargement, pleural effusion, and pulmonary vascular congestion with ensuing interstitial and alveolar edema (Apostolo et al., 2012). The latter results in an impairment of alveolar-capillary gas diffusion (DLCO), reflecting poor gas exchange efficiency (Agostoni et al., 2006).

Metaboreflex Oversensitivity

Overactivity of the muscle ergoreceptors plays an important role in ExIn in HF patients (Piepoli et al., 1996; Piepoli et al., 1999; Ponikowski et al., 2001b). The ergoreceptors conduct neural traffic from the exercising muscles to the ventrolateral medulla and lateral reticular nucleus through the lateral spinothalamic tract of the spinal cord (Nauli et al., 2001). The stimulation of the ventrolateral medulla in an animal model causes a rise in arterial blood pressure, heart rate, and minute ventilation (Bauer et al., 1990). Thus, ergoreceptors are responsible for appropriate ventilation together with adequate blood supply to the working muscles (Perez-Gonzalez, 1981), which ought to be adjusted according to the local demands (Piepoli et al., 1995). Due to many biochemical and structural abnormalities in the skeletal muscles (presented below), ergoreflexes in HF patients are exaggerated, provoking an increase in ventilatory drive, overt peripheral vasoconstriction, and sympathetic excitation.

Ergoreceptors can be divided into metaboreceptors (activated by metabolites of contracting muscles) (Sinoway et al., 1993) and mechanoreceptors (sensitive to mechanical contraction) (Kaufman et al., 1983). As shown by Scott et al., the role of metaboreceptors in the development of ExIn in HF is more evident than the contribution of mechanoreceptors (Scott et al., 2000).

Interestingly, the functionality of metaboreceptors and PChRs is interrelated. Edgell et al. (Edgell and Stickland, 2014) demonstrated that the concurrent activation of metaboreceptors and CBs under hypoxic conditions leads to the augmentation of both ventilation and muscle sympathetic nerve activity (MSNA), which was not higher than the sum of each response separately. It indicates that chemoreflex activation does not increase the sensitivity of metaboreflex and *vice versa*. On the other hand, inhibition of the CBs with hyperoxia diminished sympathetic response (measured with MSNA) when concurrent metaboreflex activation was applied but did not change MSNA when metaboreflex co-activation was absent. This outcome may be explained by the change in central integration of carotid chemoreceptor feedback with metaboreflex activation. This is consistent with the notion of CBs excitation during exercise in the absence of CBs stimuli.

Contrasting results have been provided by Wan et al. (Wan et al., 2020), who presented a case for hyper-additive interaction between metabo- and chemoreflexes under normocapnic hypoxic conditions during exercise. Interestingly, a hypo-additive interaction was reported for leg blood flow and vascular conductance. Consequently, it could be hypothesized that aroused metaboreceptors may contribute to ExIn in HF due to tonic activation and possibly by augmentation of acute reflex response from PChRs. Regardless of somehow discordant results, it should be emphasized that both cited studies were carried out in healthy participants. Therefore, how these might interact in the HF population is unknown.

Exertional Oscillatory Ventilation

Exertional oscillatory ventilation (EOV), according to the American Heart Association, is defined as an oscillatory ventilatory pattern lasting for at least 60% of the exercise duration at amplitude ≥15% of the average resting minute ventilation (Balady et al., 2010). Schmid et al. (Schmid et al., 2008) demonstrated that EOV was related to worse exercise capacity in HF. Patients with heart failure with reduced ejection fraction and EOV were characterized by poor ventilatory efficiency on exertion (higher VE/VCO_2 slope: 38.0 ± 8.3 *vs.* 32.8 ± 6.3) and lower workload at peak exercise (ΔWatts = 5.8 ± 23.0) (Schmid et al., 2008). The potential mechanisms by which EOV attenuates exercise tolerance in HF comprise oscillatory changes of dead space ventilation and unequal lung and muscle perfusion. These disturbances generate a mismatch between ventilation and perfusion and lead to greater respiratory muscles work and higher oxygen consumption (Yajima et al., 1994; Schmid et al., 2008).

The pathophysiology of EOV and periodic breathing in HF is congruous and related to the disturbances within the "control loop" system, which regulates ventilation proportionally to the metabolic demand. These disturbances include increased controller gain (Ponikowski et al., 2001a), increased plant gain (Agostoni et al., 2002), and prolonged loop delay (Leite et al., 2003). Enhanced plant gain emerges from greater carbon dioxide damping due to diminished lung volume (Agostoni et al., 2002). Increased loop delay results from the low cardiac output-hallmark of HF (Yajima et al., 1994). Finally, augmented controller gain results from oversensitive central and peripheral chemoreceptors (Chua et al., 1996b). PChRs, as elegantly presented by Dempsey et al. (Dempsey et al., 2010; Dempsey, 2012; Dempsey et al., 2012), are essential for producing apneas following transient ventilatory overshoot and thus for periodic breathing initiation (Nakayama et al., 2003). Their hyperadditive interplay with central chemoreceptive areas in the brainstem (sensitive to carbon dioxide fluctuations) further perpetuates the oscillatory ventilation pattern.

Apart from the factors mentioned above, an augmented sensitivity of ergoreceptors (to metabolic changes occurring locally in exercising muscles), may play an additional role in generating EOV in the HF population (Dhakal and Lewis, 2016). By exaggerating the ventilatory response to exertion, sensitized

metaboreceptors promote hypocapnia which, in turn, may initiate the periodic pattern of respiration in individuals characterized by abnormal components of the "control loop" (Ponikowski et al., 2001b; Scott et al., 2002).

DETERMINANTS OF MUSCLE FATIGUE IN HF

Limited Muscle Perfusion

According to the Fick principle, oxygen consumption depends on cardiac output (CO) and peripheral oxygen utilization (VO_2 = CO · ΔAVO_2 [arteriovenous oxygen difference]). Consequently, individuals characterized by higher CO present with greater peakVO_2 on exercise. Interestingly, an acute increase in CO (e.g., with catecholamines) does not influence peakVO_2 and exercise capacity (Maskin et al., 1983). This so-called "hemodynamic paradox" can be explained only by the concurrent decline in oxygen consumption in the periphery. This brings the notion of dysfunctional peripheral tissues as the major limiting factor of exercise tolerance in HF. The oxygen consumption decreases peripherally because of: 1) restricted blood perfusion in the skeletal muscles; and 2) functional and structural abnormalities within the skeletal muscles. In healthy subjects, metabolic changes occurring in exercising muscle lead to dilatation of the local vasculature. In HF, this mechanism is limited, which could be seen as a protective mechanism aiming to preserve a minimal degree of perfusion levels for the brain, heart, and respiratory muscles (Poole et al., 2012). It is likely mediated by overactivation of the sympathetic system (a typical feature of advanced HF) (Joyner et al., 1992) combined with diminished capacity for metabolic vasodilatation (due to oxidative stress and endothelial dysfunction) (Landmesser et al., 2002; Sharma and Davidoff, 2002) leading to elevated peripheral vascular resistance (PVR). The link between PVR and tonic activation of PChRs in HF was evaluated by Tubek et al. (Tubek et al., 2021). Under hyperoxic conditions (transient administration of 100% O_2 to inhibit PChRs), PVR decreased in the HF group (1239 ± 380 dyn s cm^{-5} *vs.* 1174 ± 299 dyn s cm^{-5}, $p < 0.05$), whereas in controls there was no significant change (1180 ± 317 dyn s cm^{-5} *vs.* 1242 ± 332 dyn s cm^{-5}, p = NS) reflecting the influence of tonic activation of PChRs over PVR in HF patients but not in healthy controls. An additional piece of evidence linking PChRs and PVR comes from the study by Niewinski et al. (Niewinski et al., 2017), in which CB resection decreased sympathetic tone measured directly with microneurography. While numerically, the decline in muscle sympathetic nerve activity (MSNA) was modest (10 bursts/100 beats at 2 months following surgery); it should be noted that it equated to ~45% of the excess sympathetic activity related to the heart failure state (when compared with healthy volunteers of similar age) (Hart et al., 2009). Furthermore, there are some premises indicating that PChRs contribute to restriction in peripheral (not muscle) blood flow. Marcus et al. (Marcus et al., 2015) demonstrated that in rabbits with congestive heart failure, renal blood flow decreased under hypoxic conditions. This response was abolished after CB resection, confirming the maladaptive role of PChRs hyperreflexia in adequate tissue perfusion.

Intrinsic Muscle Abnormalities

It has been suggested that intrinsic muscle dysfunction might constitute a better determinant of ExIn in the HF population than limited muscle perfusion (Wilson et al., 1993). Intrinsic muscle dysfunction ensues from structural (Wilson et al., 1993) and functional (enzymatic) alterations (Drexler et al., 1992). Among various structural changes observed in HF, a decline in the proportion of energy-efficient slow-twitch fibres (type 1) to fast-twitch fibres (type IIb; relying mostly on glycolytic metabolism) has been commonly reported (Sullivan et al., 1990).

Enzymatic changes in skeletal muscles are characterized by reduced activity of enzymes involved in aerobic metabolism without significant changes in enzymes participating in the glycolytic pathway (Sullivan et al., 1991). The function of enzymes contributing to aerobic processes is dependent on iron supply (Dziegala et al., 2018). Thus, iron deficiency evokes disturbances in the function of mitochondria in myocytes (Cartier et al., 1986), reduction of myoglobin concentration (Hagler et al., 1981), and elevation of lactate production due to impaired mitochondrial oxidative phosphorylation (Finch et al., 1979). Moreover, iron deficiency augments lipid peroxidation, which contributes to myocyte damage (Knutson et al., 2000).

Therefore, iron deficiency/anaemia (which is a common comorbidity in HF) (von Haehling et al., 2017) deteriorates skeletal muscles' function directly (as explained above), but also indirectly–through PChRs, which become tonically activated possibly due to reduced oxygen-carrying capabilities of blood cells. In support of that notion, Franchitto et al. (Franchitto et al., 2010) demonstrated that patients with HF and anaemia are characterized by augmented baseline MSNA when compared to those with HF alone (56.0 ± 3.2 vs. 45.5 ± 3.1 bursts per min; $p < 0.02$). Furthermore, inhibition of PChR by breathing 100% oxygen for 15 min attenuated MSNA in HF patients with anaemia (from 56.0 ± 3.4 to 50.9 ± 3.2 bursts per min; $p < 0.002$) but did not alter MSNA in patients without anaemia.

An excessive sympathetic tone might translate into intrinsic muscle dysfunction by restraining muscular blood flow, increasing inflammatory cytokines production, and deterioration of energy metabolism (Nilsson Jr. et al., 2008). Activation of the β-adrenergic system increases glycogenolysis and lactate production in contracting muscle and enhances the uptake of oxygen and glucose (Richter et al., 1982). These effects tilt the balance between glycogenolysis and gluconeogenesis towards the unfavourable catabolic state (Richter et al., 1982). Furthermore, sympathetic overactivation promotes a surge of inflammatory cytokines–among them: tumour necrosis factor-α, which has known proapoptotic properties (Dalla Libera et al., 2001) and

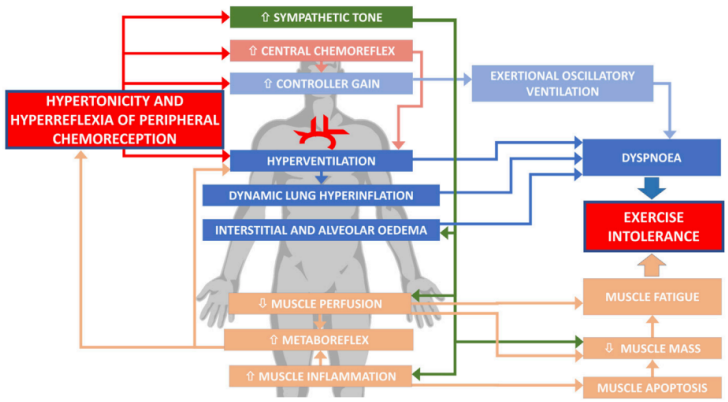

FIGURE 1 | Involvement of abnormal peripheral chemoreception in exercise intolerance in heart failure.

interleukin-6, whose level is inversely related to muscle fibre diameter (Larsen et al., 2002).

Deranged Central Hemodynamics

Central hemodynamics, expressed as a cardiac index or pulmonary artery wedge pressure, do not correlate with exercise tolerance characterized by peakVO_2 in patients with advanced HF (Wilson et al., 1995). On the other hand, there is no doubt that low cardiac output by itself is the primary reason for most of the disturbances (mentioned in the above paragraphs) that finally culminate in the development of ExIn. Interestingly, studies with biventricular cardiac resynchronization therapy, where an acute augmentation of cardiac output improves exercise tolerance, support this concept (Laveneziana et al., 2009; Schlosshan et al., 2009). This beneficial effect of cardiac resynchronization is multifactorial and likely related to several pathways of action: ergoreceptors modulation (Jaussaud et al., 2012), improvement in respiratory muscles' function (improved dynamic inspiratory capacity) (Papazachou et al., 2007), and attenuation of the sympathetic drive (Hamdan et al., 2002).

To date, we are not aware of any published data documenting that cardiac resynchronization therapy or other intervention acutely enhancing cardiac output influences the activity of PChRs. On the other hand, as showed in the rabbit model by Ding et al. (Ding et al., 2011), experimental reduction of CB perfusion (using carotid artery occluders mimicking diminished blood flow as seen in HF state) augments peripheral chemosensitivity. Similarly, Del Rio et al. (Del Rio et al., 2017) demonstrated that in rats with ischaemic HF, augmentation of chemoreflex was related to reduced cardiac output. Interestingly, animals with low cardiac output exhibited a trend towards reduction of Krüppel-like Factor 2 (KLF2) expression in CBs (Del Rio et al., 2017). The downregulation of KLF2 (a shear stress-sensitive transcription factor) leads to oversensitivity of PChRs, increase in renal sympathetic nerve activity, development of oscillatory breathing, and propensity for arrhythmias in rabbits with congestive HF (Marcus et al., 2018). Interestingly, increasing KLF2 expression with simvastatin treatment in rodent model limited the augmentation of peripheral chemosensitivity and improved respiratory variability, periodic breathing and arrhythmia index following coronary ligation (Haack et al., 2014).

The Impact of Exercise Training on Peripheral Chemoreflex Function

Some premises suggest that exercise training (ExT) may normalize the oversensitivity of peripheral chemoreflexes (Schultz et al., 2015). Calegari et al. (Calegari et al., 2016) presented that regular treadmill for 8 weeks (60 min/day, 5 days/week) improved baroreflex sensitivity and the attenuated acute pressor response elicited by potassium cyanide in HF rats. In another study, Li et al. (Li et al., 2008) investigated the impact of ExT on peripheral chemoreflex in rabbits with congestive HF. They found that 4–5 weeks of treadmill training (30–40 min/day, 6 days/week) decreased tonic single-fiber discharge within the CB nerve and reduced the acute response to hypoxia. Furthermore, ExT attenuated elevated angiotensin II levels and increased nitric oxide concentration. Downing and Balady (Downing and Balady, 2011) suggested that restoration of sympatho-vagal balance contributes to improved exercise tolerance seen after regular ExT in HF patients. This beneficial change might be mediated by increased blood flow through CBs occurring during repetitive exercise, which desensitizes PChRs (through upregulation of KLF2) and, in turn, decreases adrenergic tone (Marcus et al., 2018).

SUMMARY

The pathophysiology of ExIn in HF is neither simple nor intuitive. Numerous factors evoking ExIn exceed beyond low cardiac output and are closely interrelated. The impaired function of PChRs–both an augmented tonic activity (hypertonicity) and increased acute sensitivity (hyperreflexia)—presents as an important link in the complex pathophysiology of poor exercise capacity in HF (**Figure 1**). As discussed above, the detrimental role of PChRs is related to both dyspnea sensation and muscle fatigue, with sympathetic overactivation and hyperventilation as the major mediators leading to ExIn.

Therefore, PChRs seem to be an attractive goal for novel therapies aiming to improve exercise tolerance in the HF population. Importantly, such interventions due to the protective role of PChRs against hypoxemia ought to be performed with great caution (Niewinski et al., 2021). Bilateral CB resection might result in profound blood oxygen desaturation and marked variability in saturation levels even during mild hypoxia (Niewinski et al., 2021). One way forward might be to use a pharmacological modulation (e.g., using specific P2X3 inhibitors) instead of an irreversible surgical approach (Pijacka et al., 2016). Recently proposed denervation of the sympathetic ganglioglomerular nerve, which is involved in the tonic activation and sensitization of CB, would also maintain the physiological function of PChRs, thereby minimizing hypoxia-related side effects (Niewinski et al., 2021). Those methods of selective modulation of PChRs, while attractive from a conceptual point of view, have not yet been transferred into human clinical trials. Only by performing randomized and placebo (or sham) controlled studies one could unravel the true role of PChRs in ExIn.

AUTHOR CONTRIBUTIONS

PN, KK, ST, and PP contributed to the conception of the manuscript. KK wrote first version of draft, figure and organized references. PN, ST, PP, and KK reviewed and corrected the manuscript. ST designed and created final version of the figure. All authors read, checked and approved final version of manuscript.

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8.2. Publikacja 2

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Inhibition of peripheral chemoreceptors improves ventilatory efficiency during exercise in heart failure with preserved ejection fraction – a role of tonic activity and acute reflex response

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Peripheral chemoreceptors (PChRs) play a significant role in maintaining adequate oxygenation in the bloodstream. PChRs functionality comprises two components: tonic activity (PChT) which regulates ventilation during normoxia and acute reflex response (peripheral chemosensitivity, PChS), which increases ventilation following a specific stimulus. There is a clear link between augmented PChS and exercise intolerance in patients with heart failure with reduced ejection fraction. It has been also shown that inhibition of PChRs leads to the improvement in exercise capacity. However, it has not been established yet: 1) whether similar mechanisms take part in heart failure with preserved ejection fraction (HFpEF) and 2) which component of PChRs functionality (PChT vs. PChS) is responsible for the benefit seen after the acute experimental blockade. To answer those questions we enrolled 12 stable patients with HFpEF. All participants underwent an assessment of PChT (attenuation of minute ventilation in response to low-dose dopamine infusion), PChS (enhancement of minute ventilation in response to hypoxia) and a symptom-limited cardiopulmonary exercise test on cycle ergometer. All tests were placebo-controlled, double-blinded and performed in a randomized order. Under resting conditions and at normoxia dopamine attenuated minute ventilation and systemic vascular resistance ($p = 0.03$ for both). These changes were not seen with placebo. Dopamine also decreased ventilatory and mean arterial pressure responses to hypoxia ($p < 0.05$ for both). Inhibition of PChRs led to a decrease in VE/VCO_2 comparing to placebo (36 ± 3.6 vs. 34.3 ± 3.7, $p = 0.04$), with no effect on peak oxygen consumption. We found a significant relationship between PChT and the relative decrement of VE/VCO_2 on dopamine comparing to placebo ($R = 0.76$, $p = 0.005$). There was a trend for correlation between PChS (on placebo) and VE/VCO_2 during placebo infusion ($R = 0.56$, $p = 0.059$), but the relative improvement in VE/VCO_2 was

not related to the change in PChS (dopamine vs. placebo). We did not find a significant relationship between PChT and PChS. In conclusion, inhibition of PChRs in HFpEF population improves ventilatory efficiency during exercise. Increased PChS is associated with worse (higher) V_E/V_{CO_2}, whereas PChT predicts an improvement in V_E/V_{CO_2} after PChRs inhibition. This results may be meaningful for patient selection in further clinical trials involving PChRs modulation.

KEYWORDS

peripheral chemosensitivity, heart failure with preserved ejection fraction, exercise tolerance, tonic activity, reflex response

Introduction

Heart failure (HF) became a true epidemy of 21st century with the prevalence of 1-2% (Groenewegen et al., 2020) in developed countries. At least half of HF patients is characterized by preserved ejection fraction of left ventricle (heart failure with preserved ejection fraction, HFpEF) (Bursi et al., 2006). The number of patients with HFpEF is constantly rising (in contrast to patients with HF with reduced ejection fraction, HFrEF) leading to significant increment in hospitalization rates and costly burden on the health care systems (Owan et al., 2006; Steinberg et al., 2012; Tsao et al., 2018).

Clinically HFpEF presents with typical signs and symptoms of HF (McDonagh et al., 2021). Among them exercise intolerance seems to be most debilitating, affecting normal daily activities and being linked to worse outcomes (Owan et al., 2006; Tsao et al., 2018). The mechanism underlying exercise intolerance in HFpEF population is complex and not clearly understood. Previous studies have suggested various explanations for this phenomenon including: abnormal left-ventricle-central vascular coupling (Kosmala et al., 2016), increased left ventricular filling pressure during exercise (Borlaug et al., 2010), chronotropic incompetence (Borlaug et al., 2006), impaired left ventricular systolic and diastolic reserve (Kosmala et al., 2016; Kosmala, Przewlocka-Kosmala and Marwick, 2019), diminished cardiac output on exercise (Abudiab et al., 2013) and blunted oxygen extraction in the periphery (due to microvascular dysfunction and/or intrinsic muscle abnormalities) (Dhakal et al., 2015).

There is some evidence that abnormal reflex control contributes to exercise intolerance in HFrEF (Ponikowski et al., 1997, 2001). This includes an enhanced reflex response from peripheral chemoreceptors (PChRs) (Chua, Ponikowski et al., 1996, 1997). PChRs are multimodal sensors located mainly within the carotid bodies (CBs) close to the bifurcation of the common carotid artery but also within the structures, known as the aortic bodies (ABs), along the aortic arch (Paton, Sobotka et al., 2013). Apart from the ability to detect hypoxemia (O'Regan and Majcherczyk, 1982), PChRs are sensitive to various stimuli including: carbon dioxide (Nye, 1994), hydrogen ions (Nurse, 2009), glucose (Allen, 1998), lactate (Torres-Torrelo et al., 2021), potassium (McLoughlin, Linton and Band, 1995) and angiotensin II (Allen, 1998). Some of these stimuli may be in play during exercise and thus activate PChRs. Excitation of CBs provokes stimulation of the nuclei of the solitary tract with subsequent activation of the paraventricular nucleus of the hypothalamus, pre-Botzinger complex (Ramirez et al., 1998) and pre-sympathetic neurons localized in rostral ventrolateral medulla (RVLM) (Chen, Du and Wang, 2004; Reddy, Patel and Schultz, 2005; Schultz, Li and Ding, 2007). This results in augmentation of the minute ventilation (Ponikowski and Banasiak, 2001), activation of the sympathetic drive (leading to an increase in blood pressure), tachycardia (through the activation of Hering-Breuer reflex and due to direct stimulation of ABs) (Niewinski and Janczak, 2014) and decrease in the barosensitivity (Despas et al., 2012).

Apart from an augmented reflex response (acute sensitivity, PChS), the potential role of heightened tonic activity (tonicity, PChT) of PChRs in exercise intolerance must be acknowledged. Its relation to worse exercise tolerance in HF population has not been extensively studied. Similarly, it is unclear whether the level of tonic activity is related to the sensitivity of acute reflex response in a given individual with HF. It is possible to directly assess the magnitude of tonic activation of PChRs using various approaches including hyperoxia (Tubek et al., 2021) and low-dose dopamine infusion (Niewinski and Tubek, 2014).

The involvement of PChRs in exercise intolerance in HF is supported by the results of experiments with oxygen and opioids (Chua, Ponikowski et al., 1996; Chua, Harrington et al., 1997) and recently by CB resection trial (Niewinski et al., 2017) in which prolongation of exercise time and decrease in slope relating ventilation to carbon dioxide (V_E/V_{CO_2} slope) were observed. Based on these results obtained from HFrEF patients, one could speculate, that similar mechanisms may be in play in HFpEF. Data from some animals models indicate that central but not peripheral chemoreceptors are predominantly responsible for the autonomic imbalance seen in HFpEF (Kristen et al., 2002; Toledo et al., 2017). On the contrary, augmented PChS is often encountered in patients with metabolic disorders (Cunha-Guimaraes et al., 2020) and chronic obstructive pulmonary disease (Stickland et al., 2016),

while exaggerated PChT has been reported in hypertension (Sinski et al., 2014). The above diseases commonly coexist with HFpEF.

We hypothesize, that PChRs play an important role in exercise intolerance in HFpEF population. In order to verify this hypothesis we designed this double-blinded, placebo controlled experiment. The low-dose dopamine infusion, which is known to diminish both PChS and PChT (van de Borne, Oren and Somers, 1998), or placebo were administered during incremental cardiometabolic stress in HFpEF patients. Additionally, to determine which component of PChRs functionality is responsible for exercise intolerance, the separate measurements of individual PChS (employing intermittent hypoxia method) and PChT (expressed as the magnitude of the change in minute ventilation following low-dose dopamine infusion initiation) were performed in resting conditions and compared with the results of cardiometabolic stress tests.

Methods

Studied population

Twelve patients (three men, nine women) with a diagnosis of HFpEF in NYHA (New York Heart Association) II or III functional class were enrolled into the study after signing an informed consent. All subjects had to be clinically stable and optimally treated for at least 12 weeks before the study entry. The diagnosis of HFpEF, according to the current European Society of Cardiology guidelines criteria, was verified at initial evaluation and was based on the presence of signs and symptoms of HF, results of blood sampling, spirometry, electrocardiography and echocardiography (Ponikowski et al., 2016; McDonagh et al., 2021). The presence of a severe untreated or treated valvular heart disease, severe pulmonary hypertension, symptomatic asthma or chronic obstructive pulmonary disease, uncontrolled hypertension, severe renal impairment (estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2 using Cockcroft-Gault formula) (Cockcroft and Gault, 1976), serious anaemia, or severe physical disability precluding exercise test on cycle ergometer were considered as exclusion criteria.

The study was performed in accordance with the Helsinki Declaration and was approved by the local Institutional Ethics Committee (The Bioethics Committee at the Wroclaw Medical University).

Study protocol

Following initial evaluation all patients filled in the quality of life questionnaires, namely Minnesota Living With Heart Failure Questionnaire (MLWHFQ) (Rector, Kubo and Cohn, 1987; Garin et al., 2014) and Kansas City Cardiomyopathy Questionnaire (KCCQ) (Green et al., 2000; Joseph et al., 2013) and underwent exercise capacity assessment with 6-min walking test. During subsequent visits at an interval of 1-7 days patients were subjected to: 1) testing of the function of PChRs during low-dose dopamine infusion, 2) testing of the function of PChRs during placebo infusion, 3) symptom-limited cardiopulmonary exercise test during low-dose dopamine infusion and 4) symptom-limited cardiopulmonary exercise test during placebo infusion. Tests were performed in randomized, double-blinded fashion in a silent, air-conditioned room at an ambient temperature of 22°C. During one visit no more than one test of each type took place. The solutions were administered through the venous catheter placed into cephalic vein with the use of an infusion pump (Perfusor Space, B. Braun, Germany). Dopamine was administered at the dose of 3 $\mu g\,kg^{-1}\,min^{-1}$, which is known to effectively inhibit PChRs (Horwitz, Fox and Goldberg, 1962; Heistad et al., 1972). The same volume of normal saline solution was used as a placebo. Before each test patients were asked to take their usual medications in the morning, stay fasting and avoid caffeine or nicotine intake for at least 12 h prior to the visit.

Echocardiography

Echocardiographic imaging was performed according to recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging (Lang et al., 2015; Nagueh et al., 2016) using standard equipment (Vivid S70N, General Electric Medical Systems, Milwaukee, Wisconsin).

Assessment of peripheral chemoreflex

Peripheral chemoreceptors function testing was performed twice in each subject—during an infusion of low-dose dopamine and during the placebo infusion in a supine position. After adjusting silicone nasofacial mask (Hans Rudolph, Inc, Shawnee, Kansas) patients were connected to a one-way open breathing circuit. A spirometry set (flowhead—MTL3000L, and pressure transducer—FE141 Spirometer, ADInstruments, Sydney, Australia) was attached to the expiratory arm of the circuit for continuous measurements of tidal volume (TV) and breathing rate (BR) from which minute ventilation (MV) was calculated. End-tidal CO_2 ($EtCO_2$) was sampled from the expiratory arm of the circuit and measured with capnograph (Capstar 100; CWE, Ardmore, Pennsylvania). The inspiratory arm of the circuit was connected to the electric valve allowing for the silent switching between 100% nitrogen gas and room air. Hemodynamic parameters including: mean blood pressure (MAP), heart rate (HR), cardiac output (CO) and systemic vascular resistance (SVR) were continuously, non-invasively measured using Nexfin device (BMEYE B.V. Amsterdam, Netherlands). Oxygen saturation (SpO_2) was collected with a pulse oximeter (Radical-7; Masimo Corp., Irvine, CA,

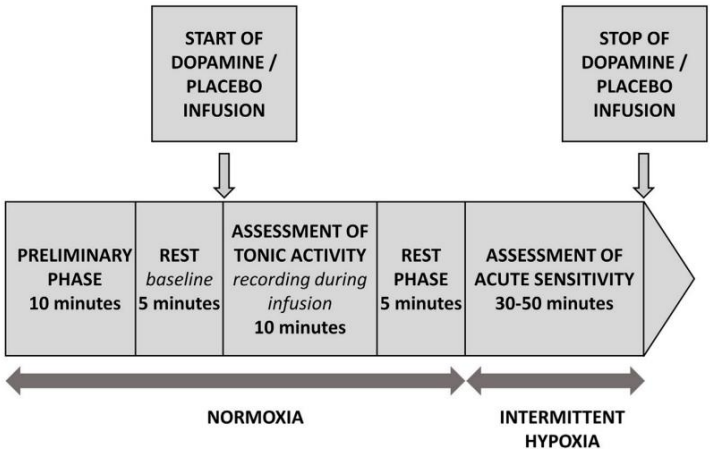

FIGURE 1
Study protocol.

United States) using a lightweight probe attached to the earlobe. All the parameters were processed with PowerLab (ADInstruments, Sydney, Australia) and recorded on a laptop computer (Dell Inc., Round Rock, TX, United States).

All patients were tested according to the same protocol depicted on Figure 1. Briefly, following the first 10 min necessary for the subject`s familiarization with the study environment (not included into the analysis), 5 min of *baseline* was recorded. Subsequently, the infusion of dopamine or placebo was initiated and continued for 10 min. This period was defined as "recording during infusion". Next, after 5 min of rest, an analysis of acute sensitivity commenced which consisted of several (5-7) administrations of pure nitrogen gas (each for 2-20 s), which resulted in minimal values of SpO_2 in a range between 90% and 65%. Length and order of hypoxic exposures was random and they were separated by 3-4 min of breathing with room air which allowed for the normalization of recorded parameters. Finally, the infusion of dopamine or placebo was withdrawn and the test ended.

Assessment of PChS and hemodynamic response to hypoxia

PChS was assessed using well-described transient hypoxia method (Rebuck and Campbell, 1974; Chua and Coats, 1995). Subjects were silently switched from breathing room air to breathing N_2 gas for time period lasting between 2 s and 20 s. This procedure was repeated 5–7 times per study participant which resulted in minimal SpO_2 between 90% and 65%. After each N_2 administration subjects were allowed to rest for 5 min breathing room air. A ventilatory response was averaged from the three largest consecutive breaths following the end of N_2 administration and plotted against the associated nadir of SpO_2 providing Point 1. Baseline values of MV and SpO_2 were averaged from a 90 s period preceding each N_2 administration. Then, baseline MV was plotted against baseline SpO_2 providing Point 2. The slope of the regression line linking Point 1 and Point 2 was found for each N_2 exposure. Arithmetic average of values of the slopes for all N_2 administrations (Prasad et al., 2020) was taken as a measure of PChS (l min^{-1} $\%^{-1}$) (Figure 2A).

The hemodynamic responses to hypoxia were calculated in the analogous way as PChS. Hemodynamic data were smoothed by a moving average (10 s window) in order to eliminate the effect of fluctuations in HR caused by respiratory sinus arrythmia or atrial fibrillation. The slope of linear regression describing the relation between the peak values of HR and MAP after nitrogen administrations and corresponding SpO_2 nadirs was calculated (HR slope and MAP slope respectively) to express the magnitude of acute hypoxic reactivity of a given hemodynamic variable.

Assessment of PChT

PChT (l min^{-1}) was defined as the absolute decrease in MV following initiation of dopamine infusion. MV was averaged from the last 2 min of steady *baseline* recording and from the 2 min of *recording during infusion*, when changes in ventilatory and hemodynamic parameters stabilized following initiation of dopamine infusion (Figure 1 and Figure 2B).

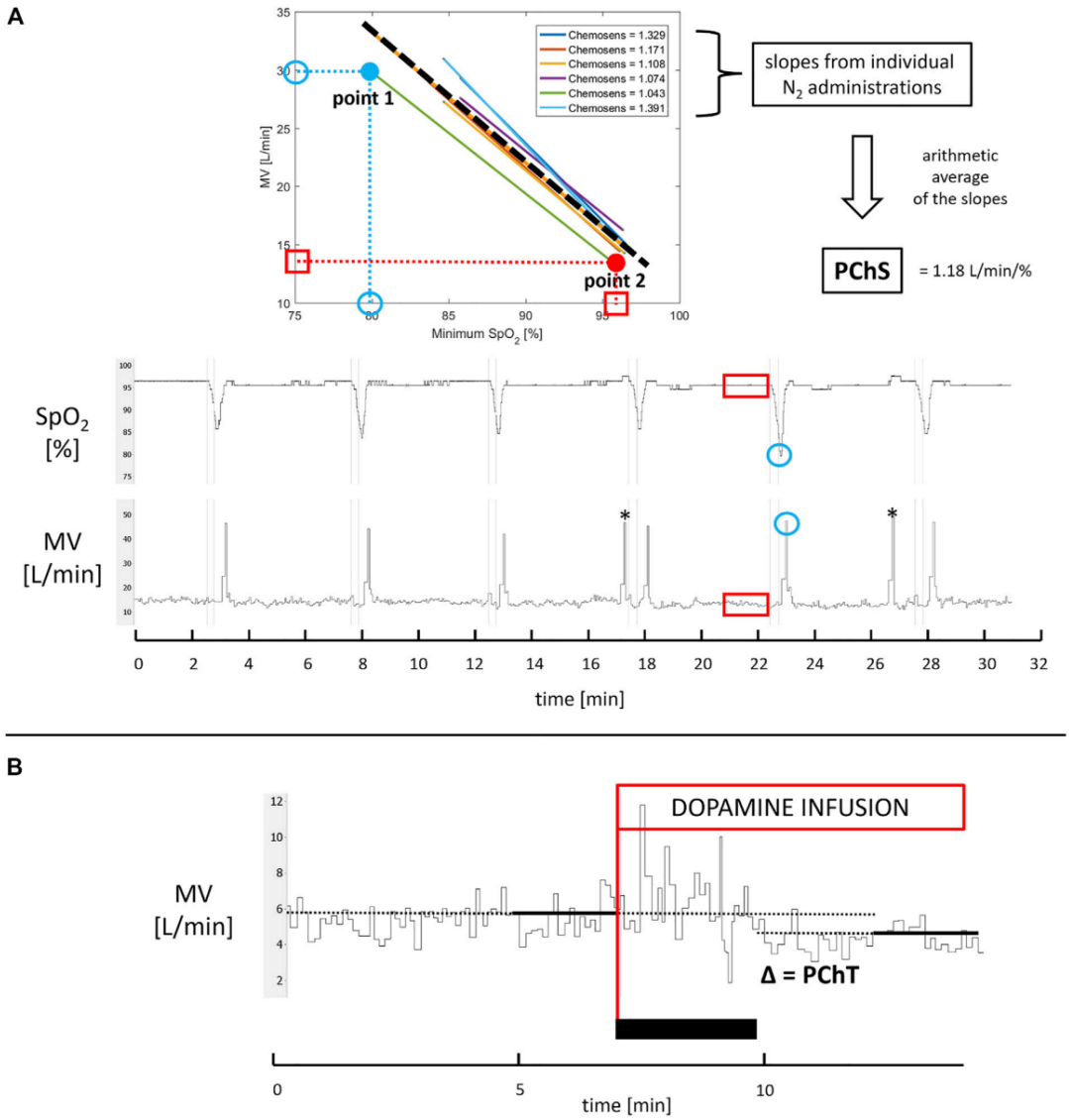

FIGURE 2
Assessment of PChS and PChT. Panel **(A)** For each N_2 administration (thin vertical lines marking start and stop of N_2 exposures) minimal SpO_2 and corresponding maximal minute ventilation (MV) averaged from three consecutive breaths were identified (blue circles; note that MV tracing is recorded breath-by-breath) to provide point 1. Next, 90 s recordings of SpO_2 and MV directly preceding N_2 administration were averaged to provide point 2 (red squares and rectangles). The slope of regression function linking point 1 and point 2 was calculated for each N_2 exposure. The average of all slopes (dashed thick line) constitutes PChS. * indicates incidental gasps ignored in PChS assessment. Panel **(B)** PChT was calculated as an absolute difference between MV averaged from 2 min directly preceding initiation of low-dose dopamine infusion (red line) and MV obtained from 2 min of recording during dopamine infusion when ventilatory and hemodynamic parameters stabilized (the black rectangle indicates stabilization phase when dopamine does not exert its full action yet).

Assessment of exercise capacity

Symptom-limited cardiopulmonary exercise test using cycle ergometer (Ergoselect 5, Ergoline GmbH, Germany) was performed in the upright seated position twice in each subject—during an infusion of low-dose dopamine and on saline. During the tests ventilatory parameters, end-tidal CO_2 and end-tidal oxygen were collected with pneumotachometer (Ergoflow, Reynolds Medical, Poland). ECG was continuously monitored during the stress test (Amedtec ECG, Reynolds Medical, Poland). The cardiopulmonary exercise tests begun with a 5-min long resting phase to allow for familiarization with the equipment. Following the resting phase workload was set at 20 W and increased by 10 W every minute until maximal tolerated level of exertion was achieved (Borlaug et al., 2011). The subjects were instructed to pedal with a constant cadence of 60 ± 5 revolutions per minute (rpm). Exercise phase was followed by a 5-min long recovery phase.

The following variables were automatically collected and calculated from the last 30 s of the cardiopulmonary exercise test (Blue Cherry, Reynolds Medical, Poland): peak oxygen uptake (peak VO_2), peak carbon dioxide production (peak VCO_2), slope relating ventilation to oxygen uptake (VE/VO_2 slope), slope relating ventilation to carbon dioxide production (VE/VCO_2 slope), respiratory exchange ratio (RER) (Glaab and Taube, 2022), and peak workload (Watts). We also recorded total exercise time (s) and reported VE/VCO_2 nadir defined as the lowest VE/VCO_2 before the respiratory compensation point. Nadir VE/VCO_2 is believed to be the most accurate tool in estimation of ventilatory efficiency because it is independent of exercise workload, hyperventilation and metabolic acidosis at peak exercise (Whipp and Ward, 1982; Phillips, Collins and Stickland, 2020).

Data and statistical analysis

LabChart 8 (ADInstruments, Sydney, Australia), MATLAB (MathWorks, Natick, MA, United States) and Statistica 13 (StatSoft Inc., Tulsa, OK, United States) were used for analyzing the data. The data were blinded for the researchers responsible for PChS and PChT calculations. The statistical analysis was performed with the Wilcoxon matched pairs test and variables were presented as mean and standard deviation (SD) or mean and standard error of the mean (SEM). Spearman rank method was used for correlation calculation. P value < 0.05 was assumed as statistically significant.

Results

Baseline characteristics of the study population

The baseline clinical and physiological characteristics of the study population (n = 12) are presented in Table 1 and Table 2 respectively. We did not find differences between baseline hemodynamic and ventilatory parameters recorded before dopamine and placebo infusions.

Assessment of PChT

Under normoxic resting conditions dopamine administration significantly attenuated MV (10.0 ± 4.0 vs. 9.2 ± 3.1 L/min, Δ = 6.2%, p = 0.03), SpO_2 (95 ± 2 vs. 93 ± 3%, Δ = 1.8%, p = 0.005), SVR (1429 ± 406 vs. 1318 ± 375 dyn s cm^{-5}, Δ = 7.3% p = 0.03) but increased HR (62 ± 5 vs. 64 ± 7 beats per minute, Δ = 3.6%, p = 0.02) and CO (5.0 ± 1.1 vs. 5.2 ± 1.1 L min^{-1}, Δ = 3.6%, p = 0.02) (Figure 3). We also noted a trend for decrease in MAP after initiation of dopamine (81 ± 8 vs. 78 ± 7 mmHg, Δ = 3.6%, p = 0.07) and a trend for increase in $EtCO_2$ (37.1 ± 3.5 vs. 38.1 ± 3.8 mmHg, Δ = 2.7%, p = 0.07). After placebo infusion a fall in SpO_2 (95 ± 2 vs. 94 ± 3%, Δ = 1.2%, p = 0.02) and increase in MAP (82 ± 12 mmHg vs. 84 ± 11 mmHg, Δ = 2.2%, p = 0.03) were observed while other ventilatory and hemodynamic parameters remained unaffected.

Assessment of PChS on/off dopamine

The mean PChS measured during placebo infusion was -0.6 ± 0.7 L min^{-1} $\%^{-1}$ comparing to -0.4 ± 0.4 L min^{-1} $\%^{-1}$ (Δ = 35.1%) on dopamine. This difference was statistically significant (p = 0.0096). Additionally, dopamine infusion decreased MAP slope (-0.4 ± 0.2 vs. -0.3 ± 0.2 mmHg $\%^{-1}$, Δ = 10.1%, p = 0.049) with no effect on HR slope (-0.3 ± 0.2 vs. -0.3 ± 0.2 b.p.m $\%^{-1}$, Δ = 2.5%, p = NS) (Figure 4). There was a significant decrease in $EtCO_2$ when baseline values were compared to minimal $EtCO_2$ following nitrogen administration (38.4 ± 4.3 vs. 33.1 ± 4.6 mmHg, Δ = 13.8%, and 38.2 ± 4.0 vs. 33.8 ± 4.1 mmHg, Δ = 13.3%, for placebo and dopamine respectively; p = 0.005 for both).

Relation between PChS, PChT and exercise tolerance

We did not find a relation between PChS (when measured on placebo) and PChT (p = 0.24). There was a trend for a correlation between PChS on placebo and VE/VCO_2 slope on placebo (R = 0.56, p = 0.059). Hemodynamic slopes on placebo (HR slope, MAP slope) did not correlate with peak exercise indices (p = NS for all).

Interestingly, significant positive relation was found between PChT and exercise time (R = 0.73, p = 0.007) and between PChT and peak workload (R = 0.58, p = 0.048). No other correlations were found between PChS, PChT and exercise-derived parameters.

TABLE 1 Clinical characteristics of the study population.

Clinical variables	
Age [years]	73 ± 7
Gender [female/male]	9/3
BMI [kg/m^2]	32.2 ± 6
NYHA class (II/III) [%]	83.3/16.7
Smoking [yes, %]	8
6MWT [m]	398 ± 129
Peak $V'O_2$ [ml kg^{-1}min^{-1}]	14.8 ± 3.4
MLHFQ [points]	35 ± 23
KCCQ [points]	88 ± 21
Echocardiographic parameters	
LVEF [%]	58 ± 3
LVMI [g m^{-2}]	116 ± 29
Left ventricular hypertrophy [%]	75
LAVI [ml m^{-2}]	49 ± 22
E/e'	14 ± 3
TRPG [mmHg]	26 ± 6
Spirometry	
FEV_1/FVC [%]	105 ± 12
Blood tests measurements	
NTproBNP [pg/mL]	712 ± 688
Haemoglobin [g/dL]	13.3 ± 1.3
eGFR ml/min/1.73 m^2	70.1 ± 28.2
Comorbidities	
Hypertension [%]	100
Atrial fibrillation [%]	50
Ischaemic heart disease [%]	33.3
Dyslipidemia [%]	83.3
Diabetes mellitus [%]	25
Chronic kidney disease defined as eGFR <60 ml min/1.73 m^2 [%]	50
Treatment	
Loop diuretics [%]	50
Thiazide diuretics [%]	17
Beta-blockers [%]	92
ACEI/ARB [%]	92
Aldosterone antagonists [%]	33

Values are presented as mean ± SD.
BMI- body mass index, NYHA- New York Heart Association, 6MWT- 6-minutes walking test, peak $V'O_2$- peak oxygen consumption, MLHFQ- Minnesota Living With Heart Failure Questionnaire, KCCQ- The Kansas City Cardiomyopathy Questionnaire, LVEF- left ventricular ejection fraction, LVMI- left ventricular mass index, LAVI- left atrial volume index, E/e'- ratio of mitral peak velocity of early filling (E) to early averaged diastolic mitral annular velocity (e'), TRPG- tricuspid regurgitation peak gradient, FEV_1/FVC (Tiffeneau index)- ratio between forced expiration in the first second (FEV_1) and forced vital capacity (FVC), NTproBNP- N-terminal pro-B type natriuretic peptide, eGFR- estimated glomerular filtration rate with Cockcroft-Gault formula, ACEI- angiotensin-converting enzyme inhibitors, ARB- angiotensin receptor blockers.

The impact of PChRs inhibition on exercise tolerance

The peak exercise values of the ventilatory and hemodynamic parameters are presented in Table 3. Dopamine decreased VE/VCO_2 slope (36 ± 3.6 vs. 34.3 ± 3.7, p = 0.04) and increased $EtCO_2$ (33.7 ± 3.0 vs. 35.3 ± 3.8 mmHg, p = 0.02) but had no effect on other reported peak exercise parameters (p = NS for all). Furthermore, dopamine improved ventilatory efficiency by reducing VE/VCO_2 nadir (32 ± 3.4 vs. 30.8 ± 3.7, p = 0.03).

We found that both relative and absolute improvement in VE/VCO_2 slope was related to PChT (R = 0.76, p = 0.005 and

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TABLE 2 Baseline ventilatory and hemodynamic indices.

Baseline ventilatory and hemodynamic parameters	Pre- placebo infusion	Pre- dopamine infusion
BR [breaths min^{-1}]	16 ± 4	17 ± 4
MV [l min^{-1}]	9.6 ± 3.2	10 ± 4
TV [l]	0.6 ± 0.2	0.6 ± 0.3
$EtCO_2$ [mmHg]	38.2 ± 3.7	37.1 ± 3.5
SpO_2 [%]	95 ± 2	95 ± 2
SVR [dyn s cm^{-5}]	1578 ± 667	1429 ± 406
HR [beats $minute^{-1}$]	60 ± 5	62 ± 5
CO [l min^{-1}]	4.8 ± 1.2	5.0 ± 1.1
MAP [mmHg]	82 ± 12	81 ± 8

Values are presented as mean ± SD.
All p = not significant.
BR- breathing rate, MV- minute ventilation, TV- tidal volume, $EtCO_2$- end-tidal carbon dioxide, SpO_2- oxygen saturation, SVR- systemic vascular resistance, HR- heart rate, CO- cardiac output, MAP- mean arterial pressure.

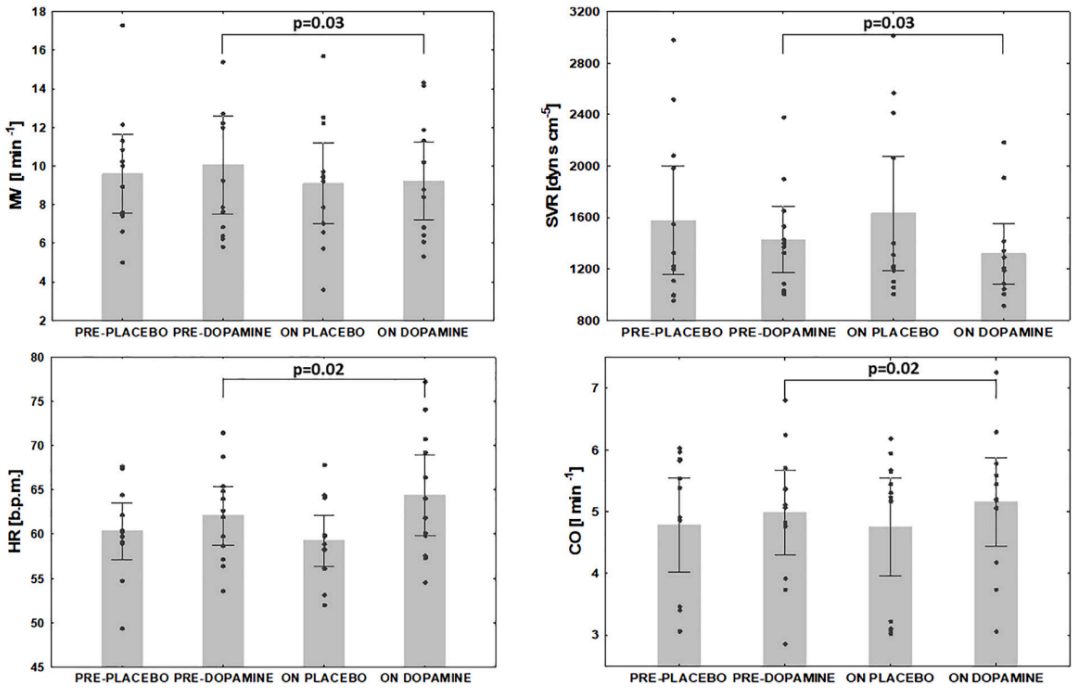

FIGURE 3
The effect of dopamine infusion on ventilation and hemodynamic indices under normoxia. MV- minute ventilation, SVR- systemic vascular resistance, HR- heart rate, CO- cardiac output.

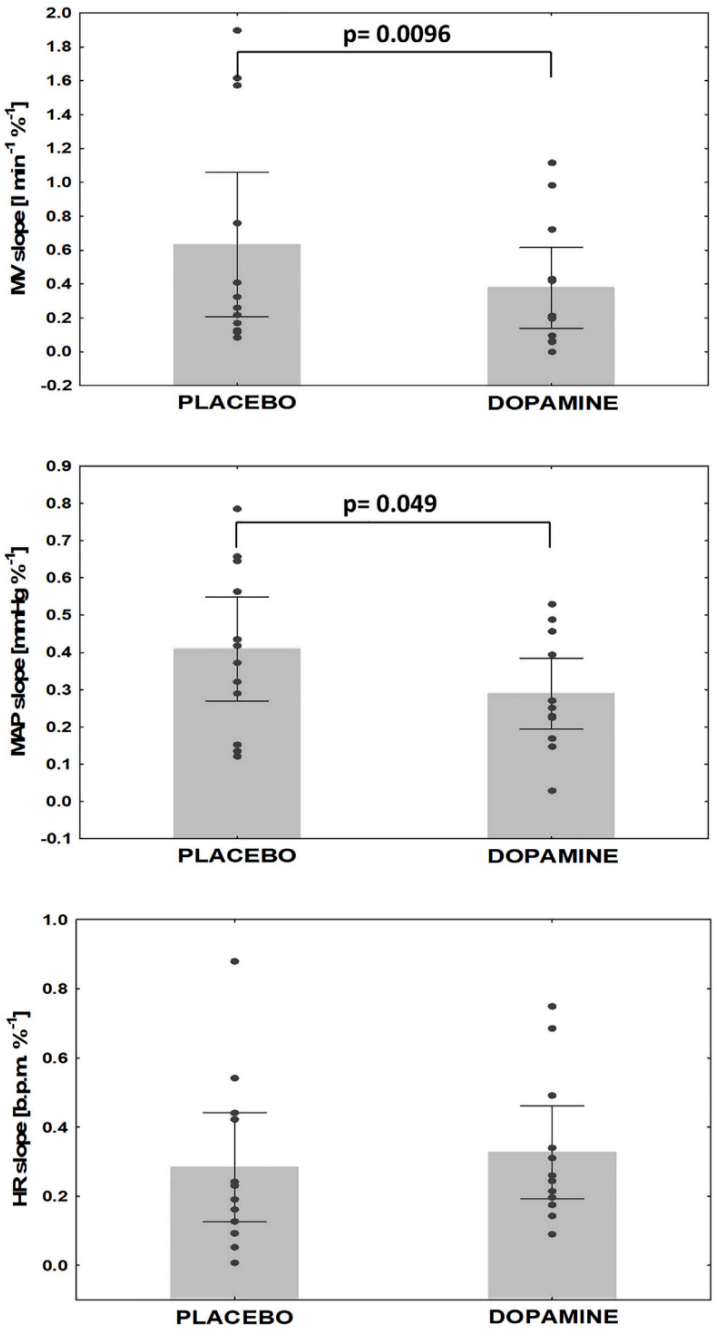

FIGURE 4
Changes in hypoxic reactivity on dopamine vs. placebo. MV- minute ventilation, MAP- mean arterial pressure, HR- heart rate.

TABLE 3 The effect of dopamine on peak exercise parameters.

Peak exercise parameters	Placebo	Dopamine
VO_2 [ml kg^{-1} min^{-1}]	14.8 ± 3.4	15.3 ± 3.9
VCO_2 [l min^{-1}]	1342.1 ± 491.8	1399.7 ± 634.4
VE/VO_2	39.2 ± 3.9	37.7 ± 4.4
VE/VCO_2	36.0 ± 3.6	34.3 ± 3.7*
TV [l]	1.52 ± 0.45	1.51 ± 0.47
BF [min^{-1}]	35 ± 6	33 ± 5
$EtCO_2$ [mmHg]	33.7 ± 3.0	35.3 ± 3.8*
RER	1.1 ± 0.1	1.1 ± 0.1
SBP [mmHg]	153 ± 21	153 ± 20
DBP [mmHg]	74 ± 9	74 ± 12
HR [beats $minute^{-1}$]	106 ± 22	106 ± 16
Exercise duration [s]	498 ± 233	480 ± 223
Workload [Watt]	96.7 ± 38.9	95.8 ± 35.8

Values are presented as mean ± SD.
*$p < 0.05$ for dopamine vs. placebo.
VO_2- oxygen consumption, VCO_2- carbon dioxide production, VE/VO_2- the ratio between ventilation and oxygen consumption, VE/VCO_2- the ratio between ventilation and carbon dioxide production, TV- tidal volume, BF- breathing frequency, $EtCO_2$- end-tidal CO_2, RER- respiratory exchange ratio, SBP- systolic blood pressure, DBP- diastolic blood pressure, HR- heart rate.

R = 0.73, $p = 0.007$ respectively) (Figure 5). Such correlation was found neither for PChS on placebo nor for the change in PChS (relative and absolute) following dopamine infusion (p = NS for all).

Discussion

To the best of our knowledge, this is the first double-blinded, placebo controlled study investigating the role of PChRs in diminished exercise capacity in patients with HFpEF. The major finding of our study is the improvement in ventilatory efficiency during exercise (decrease in VE/VCO_2 slope) following inhibition of PChRs with low-dose dopamine. We also present the inhibitory effect of dopamine on ventilatory response to hypoxia, and on resting minute ventilation. Using a novel approach based on the separate assessment of two components of PChRs functionality (Figure 2) we showed that the magnitude of this benefit depends on tonic activity of PChRs, whereas hyperreflexia constitutes a marker of poor exercise tolerance, but has no bearing on the response to the inhibitory maneuver.

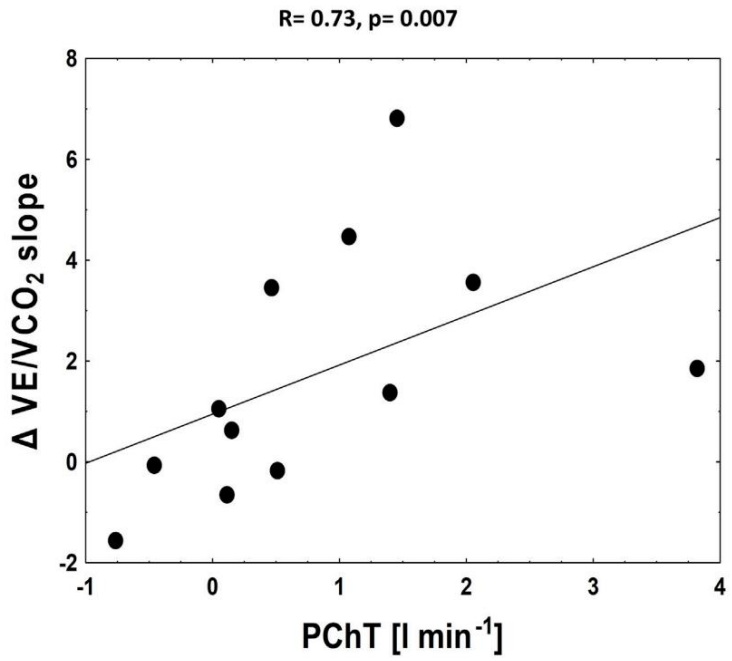

FIGURE 5
The correlation between absolute improvement in VE/VCO_2 slope and PChT (tonic activity).

The mechanism of exercise intolerance in the HFpEF population

Exercise intolerance is a cardinal manifestation of heart failure with preserved ejection fraction. Pathogenesis of this syndrome is multifactorial and involves cardiac, pulmonary, muscular, peripheral and autonomic abnormalities (Nayor et al., 2020). The HFpEF patients, despite preserved ejection fraction of left ventricle, present significant impaired of exercise capacity similar to those with reduced ejection fraction. Chronotropic incompetence (Borlaug et al., 2006), reduced systolic and diastolic left ventricular capacity (Kosmala, Przewlocka-Kosmala and Marwick, 2019), abnormal left-ventricle systemic vascular coupling (Kosmala et al., 2016), reduced function of left atrium (Reddy et al., 2017), right ventricle and pulmonary vascular dysfunction (Del Buono et al., 2019) limit the left ventricular capacity in increasing cardiac output during exercise which provokes significant rise in pulmonary capillary arterial pressure on exertion. Another reason of reduced physical capacity in the HFpEF population is the lung dysfunction: mismatch between ventilation and perfusion (Olson, Johnson and Borlaug, 2016), unfavourable pulmonary vascular remodelling and limited lung compliance (Malhotra et al., 2016). Additionally, skeletal muscular myopathy (structural and functional) (Drexler et al., 1992; Wilson, Mancini and Dunkman, 1993) with peripheral endothelial dysfunction (Dhakal et al., 2015) disrupt oxygen utilization in the periphery and attenuate exertional capacity. Finally, enhanced sympathetic activity exaggerated by increased peripheral and central chemoreceptors (Ponikowski and Banasiak, 2001), with diminished function of baroreceptors (Ponikowski et al., 1997) and abnormal signalling from muscular ergoreceptors (Piepoli et al., 1996) modify the circulatory and ventilatory response to exercise. In our study, we focused on the role of chemoreflex (arising from carotid bodies) and tonic activity of PChRs in the ventilatory and hemodynamic control during exercise.

Mechanisms of altered PChRs' function in HFpEF

Our study population included mainly elderly women with preserved ejection fraction of the left ventricle and high prevalence of various co-morbidities typical for HFpEF (hypertension, obesity, atrial fibrillation) (Table 1). The study population was characterized by moderate to good quality of life and moderate worsening of physical endurance based on 6-minutes walking test and cardiopulmonary exercise test indices when measured on placebo.

Interestingly, the PChS in the studied HFpEF population was similar to that observed by Niewinski et al. in patients with HFrEF (0.63 L min^{-1} $\%^{-1}$ vs. 0.58 L min^{-1} $\%^{-1}$) (Niewinski et al., 2013). This is particularly surprising, since described HFrEF population clearly presented with more advanced disease (higher level of natriuretic peptides and NYHA class) comparing to currently investigated HFpEF cohort. We hypothesise that this finding could be explained by higher prevalence of the co-morbidities (especially obesity and impaired glucose metabolism) which may have additional impact on PChS.

Two-thirds of the study population suffered from diabetes mellitus or impaired glucose tolerance. There are some premises suggesting that PChRs contribute to the control of glucose metabolism (Ward, Voter and Karan, 2007; Wehrwein et al., 2010). Ribeiro et al. demonstrated augmented CBs activity in rats which developed insulin resistance and hypertension after 3-4 weeks of hypercaloric diet (Ribeiro et al., 2013). Importantly, bilateral CBs resection abolished these diet-induced disturbances.

Visceral obesity was also present in most patients investigated in our study. Obesity often coexists with obstructive sleep apnea syndrome where repetitive apnea/hypopnea episodes augment CBs sensitivity and increase sympathetic gain (Paton, Sobotka et al., 2013; Iturriaga, Andrade and Del Rio, 2014). Furthermore, obese patients are characterized by exaggerated production of leptin which leads to sympathoexcitation (Eikelis et al., 2003). Leptin and leptin receptors were observed in human and rat type I glomus cells within CBs (Porzionato et al., 2011) and intravenous injection of leptin resulted in CBs activation (Messenger, Moreau and Ciriello, 2012).

Moreover, all patients in our population suffered from hypertension which has been previously linked to PChRs' oversensitivity (Prabhakar and Peng, 2004) and hypertonicity. The latter was elegantly showed by Sinski et al. who used 100% oxygen to block PChRs in a group of hypertensive males, what led to significant reduction in both blood pressure and muscle sympathetic nerve activity (Sinski et al., 2014). This was not observed in normotensive peers.

The interpretation of PChS level in our work is limited by the lack of control group of age- and sex-matched healthy individuals. In the previous studies, where identical methodology of PChS assessment was employed (Chua and Coats, 1995; Niewinski et al., 2013; Paleczny et al., 2014; Tubek et al., 2018) consistently lower levels of PChS had been reported in healthy controls (0.2-0.39 L min^{-1} $\%^{-1}$). However, all those groups were characterized by considerably lower age than currently studied HFpEF population.

The effects of low-dose dopamine on resting parameters (tonicity)

In the current study we used dopamine in a dose of 3 μg kg^{-1} min^{-1} in order to activate selectively D_2 presynaptic receptors (Niewinski and Tubek, 2014; Limberg et al., 2016) on glomus type I cells (Lehmann, Briley and Langer, 1983), that results in

decreased release of neurotransmitters and thus leads to diminished discharge rate within sinus nerves (González et al., 1995). On the contrary, dopamine in high doses stimulates both pre-synaptic D_2 and post-synaptic type 1 dopamine receptors (D_1) resulting finally in the augmentation of the neural traffic from CBs with subsequent hyperventilation, due to relative domination of D_1 receptors (Welsh, Heistad and Abboud, 1978; González et al., 1995).

We observed that dopamine administration reduced resting MV with a concomitant decrease in SpO_2. These changes are solely related to the direct blockade of D_2 receptors in PChRs since the blockade of β-receptors and stimulation of α-receptors does not influence this response (Welsh, Heistad and Abboud, 1978). Our results are concordant with previous studies where dopamine diminished normocapnic ventilation in patients with HFrEF, but not in age-matched healthy volunteers (Welsh, Heistad and Abboud, 1978; van de Borne, Oren and Somers, 1998). These findings underline the significant role of PChT in the breathing control in whole HF population. Another possible explanation by which dopamine might reduce MV is the effect on pulmonary J receptors. One could hypothesize that dopamine by increasing CO leads to lung decongestion and thus diminishes activation of pulmonary J receptors involved in hyperventilation in HF (van de Borne, Oren and Somers, 1998). We believe that such possibility is rather unlikely, as the time course of changes in MV (minutes) following dopamine introduction precludes significant decongestion.

Another important observation related to the initiation of low-dose dopamine was a fall in SVR. As previously shown low-dose dopamine leads to a decrease in blood pressure, systemic peripheral resistance and renal vascular resistance in an experimental animal model (Setler, Pendleton and Finlay, 1975). Dopamine in dogs with congestive HF provoked vasodilatory response and improved hindlimb flow and conductance at rest and during exercise (Stickland et al., 2007). Edgell et al. presented data indicating that dopamine attenuated ventilation and total peripheral resistance index at rest in HF with no impact on these parameters in healthy peers (Edgell et al., 2015).

The drop in SVR was observed also in studies employing hyperoxia as PChRs inhibitor—in both HFrEF (Tubek et al., 2021) and hypertensive patients (Sinski et al., 2014). Thus, it could be speculated that decline of SVR seen in our study was at least partially due to the inhibition of PChRs with subsequent reduction in sympathetic neural traffic to systemic vasculature. However, we cannot exclude direct vasodilatory effect related to the stimulation of D_2 receptors within peripheral vessels (Overgaard and Džavík, 2008). This has to be confirmed in the future studies employing microneurography recordings.

We also reported an augmentation of HR and CO following dopamine infusion. One plausible explanation of this effect would be a direct stimulation of β_1-receptors. Dopamine at medium doses (3-10 $\mu g\, kg^{-1}\, min^{-1}$) shows an affinity to β_1-receptors which may lead to mild positive inotropic and chronotropic effects (Overgaard and Džavík, 2008). On the other hand, one could hypothesize that increase in CO and HR may be a compensatory mechanism (possibly baroreflex-mediated) in order to maintain adequate blood supply when SVR is falling. This is further supported by the fact that inhibition of PChRs results in improved baroreflex sensitivity as documented by Ponikowski et al. (Ponikowski et al., 1997).

The effects of low-dose dopamine on acute peripheral chemoreflex sensitivity

Apart from resting parameters during normoxia (PChT), low-dose dopamine infusion also diminished the ventilatory response to hypoxia (PChS) and MAP slope, but did not influence HR slope when compared to placebo. This observations are in line with the results of our previous studies performed in healthy individuals (Niewinski and Tubek, 2014). The dissociation regarding the influence of low-dose dopamine on the particular components of hemodynamic response to acute PChRs stimulation may be explained by the dualism of HR response. The cardiovascular reflex from PChRs includes primary and secondary components (Paton, Ratcliffe et al., 2013). The primary response to hypoxia from CBs is a vagally-mediated bradycardia, while an excitation of ABs results in tachycardia (Daly and Scott, 1962; Tubek et al., 2016). The secondary response is initiated by hyperventilation, and subsequent activation of pulmonary stretch receptors (Hering-Breuer reflex), which promotes tachycardia (Kumar, 2009). Therefore, the final result of non-selective PChRs stimulation (tachycardia vs. bradycardia) depends on the strength of the ventilatory reactivity, and the predominance of the aforementioned primary vs. secondary mechanisms. We speculate that dopamine may inhibit both types of the responses. Thus, on the one hand primary responses arising from CBs and ABs become limited, and on the other hand the magnitude of Hering-Breuer reflex, which promotes tachycardia, is reduced (due to decreased hypoxic ventilatory reactivity) resulting in an unchanged HR response to hypoxia.

The effects of low-dose dopamine on exercise tolerance

We showed that inhibition of PChRs with low-dose dopamine results in an improvement (decrease) of VE/VCO_2 slope. The decline in VE/VCO_2 was modest but still statistically significant. Our results are supported by the fact that dopamine infusion did also significantly decrease nadir VE/VCO_2 (32 ± 3.4 vs. 30.8 ± 3.7, $p = 0.03$). Furthermore, our findings correspond well with previous papers reporting numerically modest but statistically significant improvements in ventilatory efficiency

(reflected by VE/VCO_2 slope) following various interventions. In the paper by Chua et al. blockade of peripheral chemoreceptors with dihydrocodeine led to decrease in VE/VCO_2 slope from 34.19 ± 2.35 to 30.85 ± 1.91 ($p = 0.01$) (Chua, Harrington et al., 1997). Modulation of peripheral chemoreflex with cardiac resynchronization therapy (4-6 months after device implantation) led to decline in VE/VCO_2 from 44 ± 10 to 40 ± 8, $p < 0.01$ (Cundrle et al., 2015). Treatment with carvedilol was also associated with numerically small difference in VE/VCO_2 slope when compared to patients taking bisoprolol (29.7 ± 0.4 vs. 31.6 ± 0.5, $p = 0.023$) (Agostoni et al., 2010). Finally, initiation of sacubitril-valsartan was related to a decline in VE/VCO_2 of only 2.4 (from 34.1 ± 6.3 to 31.7 ± 6.1; $p = 0.006$) as recently reported by Vitale et al. (Vitale et al., 2019).

VE/VCO_2 is an index of ventilatory effectiveness on exertion. Higher level of this parameter reflects increased ventilatory drive and is a well-recognized marker of poor prognosis (Francis, 2000; Arena et al., 2008). Shen et al. demonstrated that VE/VCO_2 slope ≥39.3 was related to increased cardiac mortality, whereas VE/VCO_2 slope ≥32.9 was linked to elevated risk of cardiac-related hospitalizations in HFrEF patients (Shen et al., 2015). There are many factors responsible for elevated VE/VCO_2 slope in the HF population: enlarged physiological (Kleber et al., 2000) and anatomical dead space (Buller and Poole-Wilson, 1990), impaired pulmonary vascular hemodynamics (Metra et al., 1992), ventilation-perfusion mismatch (Uren et al., 1993) and abnormal ventilatory reflex control (Chua, Clark et al., 1996; Ponikowski et al., 2001). The latter was demonstrated by Ponikowski et al. who showed that increased PChS is related to higher VE/VCO_2 slope in congestive HF ($r = 0.27$, $p = 0.015$) (Ponikowski et al., 2001). Similar findings were reported by Giannoni et al. ($r = 0.42$, $p < 0.001$) (Giannoni et al., 2008).

Mathematically a decrease in VE/VCO_2 slope could be a result of either diminished ventilation or increased production of CO_2. As we did not find a significant difference in peak VCO_2 between stress tests performed on placebo and dopamine, it should be assumed that the attenuation of ventilation during exercise is mostly responsible for this benefit. An inhibition of PChRs with dopamine diminishes ventilation at rest and we assume that this effect is also in operation during whole exercise. This is further supported by the fact that the degree of improvement (decrease) in VE/VCO_2 slope was proportional to the magnitude of MV attenuation following dopamine initiation (PChT). A decrease in tonic respiratory drive from PChRs might be further aggravated by a concomitant decrease in central respiratory drive, as a hyperadditive interaction between PChRs and central chemoreceptors has been previously described (O'Regan and Majcherczyk, 1982; Gonzalez et al., 1994). Interestingly, in the study by Collins et al. dopamine administration (in similar dose of 2 $\mu g\,kg^{-1}\,min^{-1}$) caused improvement in vascular conductance and oxygen delivery with no changes in ventilation (Collins et al., 2020). This difference may be explained by the divergent group of patients studied in the current paper (exclusively HFpEF vs. primarily HFrEF). Additionally, patients studied by Collins et al., presented with considerably better exercise tolerance and ventilatory efficiency at the baseline (reflected by mean peak VO_2 of 25 ml kg^{-1} min^{-1} and VE/VCO_2 of 31.7). Therefore, we speculate that due to possibly low PChT in this apparently mildly affected population low-dose dopamine could not exert its ventilatory benefits as seen in our study.

Reduction in VE/VCO_2 slope has important clinical consequences. Attenuation of excessive ventilation on exertion reduces the subjective sensation of dyspnoea (Nakayama, 1962; Stulbarg and Winn, 1989), decreases the propensity for dynamic lung hyperinflation and potentially reduces the fatigue of respiratory muscles (O'Donnell et al., 1999). A rise in end-tidal CO_2 and arterial CO_2 partial pressure during exercise is another consequence of diminished ventilation following PChRs inhibition (Welsh, Heistad and Abboud, 1978; Chua and Harrington, 1997; van de Borne, Oren and Somers, 1998). As observed by Huckauf et al. with dopamine infusion (Huckauf, Ramdohr and Schröder, 1976) and following bilateral CBs resection (Niewinski et al., 2013) an increase in arterial CO_2 partial pressure related to the blockade of PChRs is mild, and as such is unlikely to exert untoward effects from the clinical point of view. On the contrary, mild hypercapnia might reduce the risk for periodic breathing and thus for exercise oscillatory ventilation (Yajima et al., 1994), which is known to be related to poor exercise tolerance in HF (Schmid et al., 2008).

The unique protocol employed in our study allowed for the separate assessment of the involvement of PChS and PChT in the ventilatory efficiency during exercise. In the study by Chua (Chua, Ponikowski et al., 1996) inhibition of PChRs with oxygen prolonged exercise duration and improved ventilatory efficiency. In another study, administration of dihydrocodeine decreased hypoxic and hypercapnic ventilatory responses and improved exercise time, peak VO_2 and VE/VCO_2 slope (decrease from 34.19 ± 2.35 to 30.85 ± 1.91, $p = 0.01$) (Chua and Harrington, 1997). CB resection in HFrEF resulted in attenuation of PChS (Niewinski et al., 2017) and better exercise tolerance expressed as a prolongation of exercise duration and a fall in VE/VCO_2 slope at 2 months (36.4 ± 3.0 vs. 32.8 ± 3.2, $p = 0.03$). It should be noted that in all mentioned studies (including our work) the improvement in VE/VCO_2 occurred following the inhibition of both components of PChRs functionality.

Interestingly, we found that only PChT reflected the magnitude of improvement in exercise tolerance. In the study by Stickland et al. (Stickland et al., 2007) dopamine during mild-intensity exercise improved blood flow in the periphery (assessed as an increase in hindlimb conduction). Moreover, the vasodilatory effect observed after alpha-adrenergic blockade confirmed that sympathetic activation limited the blood flow

in skeletal muscles. Interestingly, PChT was responsible for only one-third of the total sympathetic restraint in muscular blood flow pointing out other factors involved in cardiorespiratory control during exercise (such as central chemoreceptors, muscle ergoreceptors and baroreceptors) (Rowell and O'Leary, 1990).

On the other hand, a decrease in PChS following PChRs deactivation did not correlate with the relative (and absolute) reduction in VE/VCO_2 slope. This can be explained by the following mechanisms. First, it is possible that the degree of inhibition of acute responsiveness arising from PChRs achieved with low-dose dopamine is not sufficient to translate into meaningful decrease in ventilation on exertion. Second, keeping in mind that the partial pressure of O_2 remains fairly stable during exercise (Forster, Haouzi and Dempsey, 2012), it could be speculated that the inhibition of hypoxic response is not equal to the inhibition of the acute responsiveness to the metabolites of exertion (e.g. lactate). The latter explanation suggests that PChS is not directly involved in the ventilatory response to exercise in HF patients. If this is the case, than how should we interpret the positive relation between PChS and VE/VCO_2 slope (during placebo infusions) seen in our and in numerous previous studies? We believe that high PChS ought to be seen more as a marker of advanced HF (in fact of the worse perfusion through CBs (Ding, Li and Schultz, 2011), where number of different factors could be contributing to the ineffective ventilation on exertion (e.g. pulmonary congestion, increased dead space, augmented sensitivity of metaboreceptors).

Although dopamine reduced VE/VCO_2 slope in our study, it did not improve exercise tolerance as reflected by unchanged peak VO_2. Thus, the exercise tolerance in HFpEF is likely determined by factors other than dysfunctional PChRs. For example, Toledo et al. demonstrated overactivation of central but not peripheral chemoreceptors in rats with HFpEF. Furthermore, acute stimulation of central chemoreceptors provoked increase in sympathetic gain, abnormalities in cardiac function and induced cardiac arrhythmogenesis (Toledo et al., 2017). Structural and functional muscular abnormalities must be also taken into consideration regarding limited exercise capacity in the HFpEF population (Haykowsky et al., 2014; Kitzman et al., 2014). In the study by Haykowsky et al. elderly patients with HFpEF were characterized by greater intermuscular fat area and higher ratio of intermuscular fat to skeletal muscle compared to age-matched healthy controls. Furthermore, both intrinsic muscle abnormalities were found to be predictors of low peak VO_2 (Haykowsky et al., 2014).

The inhibition of PChRs presents as a promising approach for alleviating debilitating symptoms of HF. However, the safety aspects of such maneuver should be taken into consideration—especially the risk of profound hypoxemia due to diminished ventilatory responsiveness, which may be seen even during exposure to mild hypoxia (e.g. at high altitude or during long-haul air travels) (Niewinski et al., 2021). This aspect of PChRs modulation was not directly assessed in our study as the prolonged hypoxia was not a part of the experimental protocol.

Several study limitations should be acknowledged. First, the sample size was small, which precluded multivariable modeling, and was a likely reason of failure to evidence the significance of some associations. Due to small sample size our work should be seen as a pilot study. Thus, presented correlations ought to be interpreted with caution. Second, the majority of patients were women. In such population, we cannot exclude the plausible impact of sex hormones on PChRs function (Regensteiner et al., 1989; Prabhakar and Peng, 2004; Kumar and Prabhakar, 2012). In order to minimalize this effect, only postmenopausal women were enrolled into the study. Third, we did not have a control group, thus we cannot compare our result with the healthy peers. We should also emphasize, that PChS is only a putative determinant of PChRs' sensitivity to the metabolites of exercise. We did not measure the lactate concentration during exercise which would definitely shed more light on the matter. Particularly, increase in lactate production in muscles during exercise was significantly faster in HF subjects compared to healthy controls (Scott et al., 2003). Further, we did not maintain isocapnic conditions when analyzing the PChRs response to acute hypoxia. Therefore, we cannot eliminate the effect of concomitant hypocapnia which might lead to underestimation of the reflex response (Keir, Duffin and Floras, 2020). However, the method used in the study, has been previously validated and accepted as a reliable tool in the assessment of PChS in human subjects (Chua and Coats, 1995; Niewinski et al., 2013), where it better simulates environmental or disease-related conditions, and was further found to have prognostic significance (Ponikowski et al., 2001). Also we did not take into consideration the inter-individual variability in the ideal dose of IV dopamine (Limberg et al., 2016). Establishing the most effective dose of dopamine for each individual subject would have been an optimal approach, however it would considerably prolong already busy study protocol. Nonetheless, a dose of 3 $\mu g\ kg^{-1}\ min^{-1}$ employed in our work has been shown to effectively inhibit both acute and tonic activity of PChRs (Limberg et al., 2016).

Finally, our study was not a clinical trial and the power calculation was not conducted. However, as an exploratory physiological experiment, we rather intended to reveal the potential mechanisms involved in exercise intolerance in the patients with HFpEF. Further studies incorporating considerably larger populations are needed to fully address the effect of PChRs inhibition on the clinical end-points.

Conclusion

This study demonstrated an exaggerated PChRs response to hypoxia (PChS) in HFpEF, the magnitude of which was similar to

that previously reported in HFrEF (Niewinski et al., 2013). Our protocol allowed for the identification of two different determinants of the PChRs functionality: while PChS tended to correlate with worse exercise tolerance in basic conditions, the degree of exercise capacity improvement following the inhibition of PChRs with dopamine was associated only with PChT. Confirmation of our results in larger clinical trials, would give opportunity to modulate CBs in HFpEF patients. The profile of eligibility for this kind of treatment (by means of CBs denervation or pharmacological modulation of PChRs) should consider the level of PChT rather than the magnitude of PChS.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by The Bioethics Committee at the Wroclaw Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

KK-L, PN, ST, PP contributed to conception and design of the experiment. KK-L, ST, and MK were responsible for collection data. KK-L, PN, ST, and MK were responsible for analysis of the data. KK organized the database and wrote the first draft of the manuscript. KK-L, PN, ST, WK, and PP were responsible for interpretation of the data. KK-L and PN were responsible for preparation of tables and figures. PN, WK, and PP were responsible for revision of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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9. PODSUMOWANIE I WNIOSKI

W przedstawionych badaniach udowodniono, że nietolerancja wysiłku fizycznego jest uwarunkowana licznymi, często nakładającymi się procesami, w których istotną rolę odgrywa dysfunkcja chemoreceptorów obwodowych. Co więcej, farmakologiczne lub chirurgiczne zablokowanie ich funkcji może wiązać się z poprawą wydolności wysiłkowej u chorych z HF.

W publikacji pt.***"Contribution of peripheral chemoreceptors to exercise intolerance in heart failure"*** na podstawie dostępnych danych literaturowych wykazano, że nieprawidłowa zwiększona aktywność PChRs dotyka dużego odsetka populacji chorych z HFrEF i jest związana z gorszą tolerancją wysiłku fizycznego (1,16). Co więcej, zablokowanie PChRs przy pomocy tlenu lub dihydrokodeiny (33,34), jak również chirurgiczna resekcja kłębków szyjnych (15) wpływała pozytywnie na poprawę tolerancji wysiłku fizycznego w tej grupie chorych. Nadaktywność PChRs nasilała poczucie duszności oraz zmęczenie mięśni szkieletowych - objawy najczęściej zgłaszane i ograniczające tolerancję wysiłku fizycznego u chorych z HF. W publikacji przedstawiono argumenty sugerujące, że zwiększona aktywność PChRs prowadzi do hiperwentylacji (7), nasila zjawisko dynamicznej hiperinflacji płuc (45,46) oraz oddychania cyklicznego w czasie wysiłku fizycznego (9,47). Ponadto PChRs poprzez hyperaddytywne oddziaływanie na centralne ośrodki oddechowe w ośrodkowym układzie nerwowym zwiększają (w sposób nieadekwatny w stosunku do potrzeb metabolicznych) napęd oddechowy (48,49). Odrębnym mechanizmem odpowiedzialnym za gorszą tolerancję wysiłku fizycznego u chorych z HF jest zwiększona aktywność metaboreceptorów mięśni szkieletowych (11,50), które poprzez stymulację ośrodków w rdzeniu przedłużonym (51,52), podobnie jak PChRs, zwiększają wentylację minutową potęgując zjawisko hiperwentylacji i duszności wysiłkowej.
W publikacji opisano także czynniki wywołujące zmęczenie mięśni szkieletowych, które jest istotnym elementem gorszej wydolności fizycznej (53). Przedstawiono, że zmniejszenie perfuzji tkanek obwodowych na skutek wzmożonej stymulacji adrenergicznej (54) oraz czynnościowe i strukturalne nieprawidłowości mięśni szkieletowych (13,14) prowadzą do ograniczenia perfuzji mięśniowej w czasie wysiłku, czego efektem jest ich szybsze zmęczenie. Nie można również pominąć zmniejszonego rzutu serca jako bezpośredniej przyczyny gorszej tolerancji wysiłku u pacjentów z HF. Dowodem tego może być terapia resynchronizująca, która poprzez zwiększenie indeksu sercowego wpływa na poprawę tolerancji wysiłku fizycznego (55,56).

W publikacji pt. "***Inhibition of peripheral chemoreceptors improves ventilatory efficiency during exercise in heart failure with preserved ejection fraction – a role of tonic activity and acute reflex response"*** przedstawiono znaczenie PChRs w patogenezie nietolerancji wysiłku fizycznego u chorych z HFpEF. Pokazano, że zablokowanie PChRs małymi dawkami dopaminy spowodowało poprawę efektywności wentylacji w czasie wysiłku fizycznego. W protokole badawczym uwzględniono ocenę zarówno aktywności ostrej jak i tonicznej - co jest unikalnym walorem tego badania. Pokazano, że wysoka aktywność ostra korelowała z gorszą tolerancją wysiłku fizycznego (wyrażoną wyższym VE/VCO_2), natomiast aktywność toniczna odzwierciedlała wielkość potencjalnej poprawy efektywności wentylacji po zablokowaniu PChRs dopaminą. Ponadto przedstawiono, że dopamina zmniejszała wentylację minutową i opór obwodowy z jednoczesnym zwiększeniem rzutu oraz częstości akcji serca w warunkach normoksji. W odpowiedzi na hipoksję po podaniu dopaminy obserwowano zmniejszenie odpowiedzi wentylacyjnej i hemodynamicznej (spadek wentylacji minutowej i średniego ciśnienia tętniczego) bez wpływu na częstość akcji serca.

Badana populacja w naszym projekcie obejmowała głównie kobiety w starszym wieku z licznymi chorobami typowymi dla fenotypu HFpEF takimi jak nadciśnienie tętnicze, migotanie przedsionków, otyłość, zaburzenia gospodarki węglowodanowej. Pomimo zachowanej frakcji wyrzutowej lewej komory wielkość PChS była podobna do pacjentów z HFrEF (16), co jest zaskakujące w kontekście bardziej zaawansowanych objawów i wyższych wartości peptydów natriuretycznych u chorych z obniżoną frakcją wyrzutową lewej komory obserwowanych w poprzednich badaniach (16,33). Spekulujemy, że jest to prawdopodobnie wynik schorzeń współistniejących, które mają wpływ na funkcję PChRs. Zwiększoną aktywność PChRs obserwowano bowiem u osób otyłych (57), z nadciśnieniem tętniczym (58), z cukrzycą lub nieprawidłową tolerancją glukozy (59,60).

W badaniu będącym przedmiotem niniejszej rozprawy w celu zahamowania PChRs użyto małych dawek dopaminy (3 $\mu g\ kg^{-1}\ min^{-1}$). Taka dawka pozwalała na selektywną aktywację presynaptycznych receptorów D_2 w kłębkach szyjnych prowadząc do ich blokady (61) bez wpływu na receptory D_1, które zwiększają wentylację i aktywację współczulną. Ta selektywna inhibicja wyjaśnia fakt zmniejszenia wentylacji minutowej oraz saturacji w warunkach normoksji w naszym badaniu. Otrzymane wyniki były zgodne z poprzednio opublikowanymi danymi, gdzie dopamina zmniejszała wentylację minutową u chorych z HFrEF, ale nie w grupie kontrolnej (62,63).

Przedstawiono również, że dopamina podana w warunkach spoczynkowych powodowała spadek oporu obwodowego, co można wyjaśnić zarówno wpływem na receptory D_2 w kłębkach szyjnych (co prowadzi do zmniejszenia aktywacji współczulnej), jak również bezpośrednim wpływem wazodylatacyjnym na receptory D_2 w ścianie naczyń obwodowych (64). Obserwowany wzrost rzutu i częstości akcji serca po podaniu dopaminy w warunkach normoksji wynikał prawdopodobnie z bezpośredniego wpływu leku na receptory β_1. Dopamina w dawkach 3-10 $\mu g\ kg^{-1}\ min^{-1}$ wykazuje powinowactwo do receptorów β_1 wywołując niewielki pozytywny efekt inotropowy i chronotropowy (64). Nie można również wykluczyć reakcji kompensacyjnej (ze strony baroreceptorów) w odpowiedzi na spadek oporu obwodowego w celu utrzymania odpowiedniego zaopatrzenia w tlen i substancje odżywcze tkanek obwodowych.

W przypadku ostrej aktywności PChRs w czasie wlewu dopaminy obserwowano spadek odpowiedzi wentylacyjnej oraz ciśnieniowej na hipoksję (w stosunku do badania podczas wlewu placebo), ale bez wpływu na odpowiedź w zakresie akcji serca. Taki wynik można wytłumaczyć dwoistością reakcji chronotropowej. Odruch z PChRs składa się z komponenty pierwotnej i wtórnej (65). Pierwotna reakcja w odpowiedzi na hipoksję obejmuje stymulację kłębków szyjnych - co wywołuje bradykardię (poprzez aktywację nerwu błędnego); oraz tachykardię w odpowiedzi na stymulację kłębków aortalnych (66,67). Wtórna reakcja z PChRs wiąże się z hiperwentylacją, która następnie stymuluje receptory zlokalizowane w mięśniach gładkich dróg oddechowych (ang. *pulmonary stretch receptors*) prowadząc do przyśpieszenia akcji serca (68). Ostateczna odpowiedź wynikająca z tej nieselektywnej stymulacji zależy od przewagi jednej z wymienionych komponent, a ponieważ dopamina hamuje wszystkie odpowiedzi, wynikiem może być brak zmian w częstości akcji serca w odpowiedzi na hipoksję.

Kolejnym interesującym wynikiem opisanym w publikacji było przedstawienie, że zablokowanie PChRs poprawiało efektywność wentylacji definiowaną jako zmniejszenie stosunku wentylacji minutowej do produkcji dwutlenku węgla (VE/VCO_2). Wysoka wartość VE/VCO_2 jest związana ze złym rokowaniem (69,70) oraz ze zwiększoną PChS u chorych

z HFrEF (2,71). W naszej pracy nie wykazano wpływu dopaminy na produkcję dwutlenku węgla na szczycie wysiłku, wobec tego należy uznać, że samo zmniejszenie wentylacji minutowej odpowiadało za redukcję VE/VCO_2. Ponieważ dopamina zahamowała również wentylację w spoczynku w warunkach normoksji (PChT), uważamy, że podobny efekt występuje podczas wysiłku fizycznego. Wielkość poprawy wentylacji wysiłkowej była proporcjonalna do wielkości zahamowania wentylacji minutowej po rozpoczęciu wlewu dopaminy, co dodatkowo potwierdza naszą hipotezę, Co więcej, ten mechanizm może być nasilany współistniejącym zmniejszeniem aktywności chemoreceptorów ośrodkowych ze względu na ich synergistycznie działanie (23,72).

Zmniejszenie stosunku VE/VCO_2 implikuje wiele ważnych konsekwencji: zmniejsza odczucie duszności (73), redukuje ryzyko wystąpienia zjawiska dynamicznej hiperinflacji płuc oraz zmęczenie mięśni oddechowych (45). Zablokowanie PChRs dodatkowo zwiększa stężenie dwutlenku węgla w czasie wydechu ($EtCO_2$) i ciśnienie parcjalne dwutlenku węgla we krwi tętniczej ($PaCO_2$) (62,63), co zmniejsza ryzyko oddychania cyklicznego w czasie wysiłku (47).

W naszej pracy udowodniliśmy, że jedynie PChT (ale nie PChS) była związana z poprawą efektywności wentylacji podczas wysiłku fizycznego po zablokowaniu PChRs dopaminą. W związku z tym, wysoka PChS wskazuje raczej na stopień zaawansowania HF, w której oprócz nieprawidłowej aktywności odruchowej szereg innych czynników odgrywa ważną rolę w nieefektywnej wentylacji w czasie wysiłku fizycznego (np. zastój w krążeniu płucnym, zwiększenie czynnościowej przestrzeni martwej płuc, nadaktywność metaboreceptorów).

W publikacji nie udowodniono również, że zahamowanie PChRs przekładało się na wzrost zużycia tlenu na szczycie wysiłku fizycznego. Świadczy to o obecności innych patomechanizmów uczestniczących w regulacji procesów oddechowo-krążeniowych w czasie wysiłku fizycznego takich jak nadmierna aktywność chemoreceptorów centralnych (74) oraz strukturalne i czynnościowe zaburzenia mięśni szkieletowych (75,76).

Podsumowując, zablokowanie PChRs może być w przyszłości obiecującą metodą leczenia objawów nietolerancji wysiłku fizycznego u chorych z HFpEF, choć potrzebne są dalsze badania kliniczne potwierdzające tą hipotezę. Nasz unikatowy protokół umożliwił ocenę dwóch różnych składowych aktywności PChRs. Pokazaliśmy, że aktywność ostra korelowała z gorszą efektywnością wentylacji, natomiast wielkość jej poprawy po zablokowaniu PChRs była związana jedynie z aktywnością toniczną. W związku z tym, kryterium doboru pacjentów, którzy mogliby odnieść korzyść z blokady PChRs w przyszłości powinno opierać się na ocenie aktywności tonicznej, a nie ostrej.

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Severe Chronic Obstructive Pulmonary Disease. Chest [Internet]. 1989 May;95(5):1123–8.

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11. ZAŁĄCZNIKI

11.1. DOROBEK NAUKOWY DOKTORANTA

Wykaz publikacji

KATARZYNA KULEJ-ŁYKO

1.1 Publikacje w czasopiśmie naukowym posiadającym Impact Factor

Lp	Opis bibliograficzny	IF	PK
1.	**Zastosowanie lewosimendanu u chorych z ostrą niewydolnością serca z objawami małego rzutu minutowego serca: opis serii przypadków (Application of levosimendan in acute heart failure patients with symptoms of low cardiac output: case series report).** JAN BIEGUS, ROBERT ZYMLIŃSKI, KATARZYNA KULEJ, JOANNA SZACHNIEWICZ, WALDEMAR BANASIAK, EWA ANITA JANKOWSKA, PIOTR PONIKOWSKI. *Kardiol.Pol.* 2013 T.71 nr 3 s.275-278, ryc., tab., bibliogr. 12 poz., summ. DOI: 10.5603/KP.2013.0041	0,519	15,00
2.	**Could gonadal and adrenal androgen deficiencies contribute to the depressive symptoms in men with systolic heart failure?. KATARZYNA KULEJ-ŁYKO**, JACEK MAJDA, STEPHAN VON HAEHLING, WOLFRAM DOEHNER, MONIKA ŁOPUSZAŃSKA, ALICJA SZKLARSKA, WALDEMAR BANASIAK, STEFAN D. ANKER, PIOTR PONIKOWSKI, EWA A. JANKOWSKA. *Aging Male* 2016 Vol.19 no.4 s.221-230, ryc., tab., bibliogr. 85 poz., summ. DOI: 10.1080/13685538.2016.1208166	2,108	20,00
3.	**Phrenic nerve stimulation in patients with central sleep apnea: a single-center experience from pilot and pivotal trials evaluating the remede System.** DARIUSZ JAGIELSKI, ADAM KOŁODZIEJ, RANDY WESTLUND, BARTOSZ BIEL, KRZYSZTOF NOWAK, IWONA SZEMPLIŃSKA, IRENA FLINTA, MAGDALENA KRAWCZYK, KATARZYNA KULEJ, BARTOSZ KRAKOWIAK, ROBIN GERMANY, ANTONIS PANTELEON, SCOTT MCKANE, WALDEMAR BANASIAK, WILLIAM T. ABRAHAM, PIOTR PONIKOWSKI. *Kardiol.Pol.* 2019 Vol.77 no.5 s.553-560, ryc., tab., bibliogr. 26 poz., summ. DOI: 10.5603/KP.a2019.0061	1,874	100,00
4.	**Pathophysiology of advanced heart failure: what knowledge is needed for clinical management?.** JAN BIEGUS, PIOTR NIEWIŃSKI, KRYSTIAN JOSIAK, KATARZYNA KULEJ, BARBARA PONIKOWSKA, KRZYSZTOF NOWAK, ROBERT ZYMLIŃSKI, [AUT. KORESP.] PIOTR PONIKOWSKI. *Heart Fail.Clin.* 2021 Vol.17 no.4 s.519-531, ryc., tab., bibliogr. 90 poz., summ. DOI: 10.1016/j.hfc.2021.06.001	2,828	70,00
5.	**Inhibition of peripheral chemoreceptors improves ventilatory efficiency during exercise in heart failure with preserved ejection fraction - a role of tonic activity and acute reflex response. KATARZYNA KULEJ-ŁYKO**, PIOTR NIEWIŃSKI, STANISŁAW TUBEK, MAGDALENA KRAWCZYK, WOJCIECH KOSMALA, PIOTR PONIKOWSKI. *Front.Physiol.* 2022 Vol.13 art.911636 [18 s.], ryc., tab., bibliogr., summ. DOI: 10.3389/fphys.2022.911636	4,755*	100,00
6.	**Contribution of Peripheral Chemoreceptors to Exercise Intolerance in Heart Failure.KULEJ-LYKO K[ATARZYNA]**, NIEWINSKI P, TUBEK S, PONIKOWSKI P. *Front Physiol.* 2022 Apr 14;13:878363. doi: 10.3389/fphys.2022.878363.	4,755*	100,00
		16,839	405,00

**IF 2021*

1.2 Publikacja w czasopiśmie naukowym nieposiadającym IF

Lp	Opis bibliograficzny	PK
1.	**Ostry zespół wieńcowy indukowany stresem - trudności diagnostyczne w rozpoznaniu zespołu tako-tsubo.** PIOTR TRĄBKA, KATARZYNA KULEJ, ELŻBIETA KALICIŃSKA, DOROTA KUSTRZYCKA-KRATOCHWIL, MAŁGORZATA SUKIENNIK-KUJAWA, EWA A. JANKOWSKA, PIOTR PONIKOWSKI, WALDEMAR BANASIAK. *Folia Cardiol.Excerpta* 2012 T.7 nr 3 s.164-169, tab., bibliogr. 47 poz., streszcz.	5,00
2.	**Problemy w diagnostyce i leczeniu chorych z niewydolnością serca i z chorobami współistniejącymi. Odcinek 8: Niewydolność serca a dna moczanowa.** KATARZYNA KULEJ, WALDEMAR BANASIAK, PIOTR PONIKOWSKI, EWA A. JANKOWSKA. *Med.Prakt.* 2014 nr 7-8(281-282) s.45-51, tab., bibliogr. 88 poz.	4,00
		9,00

2. Monografie naukowe i skrypty

2.1 Autorstwo monografii naukowej -

2.2 Autorstwo rozdziału w monografii naukowej

Lp	Opis bibliograficzny	PK
1.	**Kardioendokrynologia.** EWA ANITA JANKOWSKA, IDA KINALSKA, PIOTR PONIKOWSKI, WALDEMAR BANASIAK, MARCIN DROZD, ANDRZEJ JANUSZEWICZ, KRYSTIAN JOSIAK, IRINA KOWALSKA, **KATARZYNA KULEJ-ŁYKO**, JANUSZ MYŚLIWIEC, PIOTR NIEWIŃSKI, MACIEJ OWECKI, MARIOLA PĘCZKOWSKA, ALEKSANDER PREJBISZ, MICHAŁ TKACZYSZYN, STANISŁAW TUBEK. W: Endokrynologia kliniczna 2017 : praca zbiorowa [e-book] Wrocław 2017, Polskie Towarzystwo Endokrynologiczne, rozdział 12 Wyd.2 uaktual., 978-83-935526-3-4.	0,00
		0,00

3. Streszczenia zjazdowe

Lp	Opis bibliograficzny
1.	**Czynniki determinujące śmiertelność 30- i 180-dniową u 326 kolejnych pacjentów hospitalizowanych z powodu ostrej niewydolności serca w jednym ośrodku kardiologicznym.** JAN BIEGUS, MATEUSZ SOKOLSKI, ROBERT ZYMLIŃSKI, KATARZYNA KULEJ, JOANNA SZACHNIEWICZ, PAWEŁ SIWOŁOWSKI, SYLWIA NAWROCKA, WALDEMAR BANASIAK, EWA A. JANKOWSKA, PIOTR PONIKOWSKI. W: XV Międzynarodowy Kongres Polskiego Towarzystwa Kardiologicznego. Wrocław, 6-8. 10. 2011 r. Abstrakty [CD-ROM], poz.031.
2.	**Hipogonadyzm i zaawansowanie niewydolności serca jako główne czynniki ryzyka rozwoju zaburzeń depresyjnych u mężczyzn ze skurczową niewydolnością serca (Hypogonadism and heart failure severity as principal risk factors of development of depressive symptoms in men with systolic heart failure).** KATARZYNA KULEJ, BEATA PONIKOWSKA, MONIKA ŁOPUSZAŃSKA, ALICJA SZKLARSKA, JACEK MAJDA, WALDEMAR BANASIAK, PIOTR PONIKOWSKI, EWA JANKOWSKA. *Kardiol.Pol.* 2013 T.71 supl.6 [CD-ROM] s.245-246, tab, XVII Międzynarodowy Kongres Polskiego Towarzystwa Kardiologicznego. Wrocław, 26-28 września 2013. Streszczenia.

3.	**Deficiencies in gonadal and adrenal androgens and depression in men with systolic heart failure: are they linked?.** KATARZYNA KULEJ, J. MAJDA, M. ŁOPUSZAŃSKA, A. SZKLARSKA, S. VON HAEHLING, W. DOEHNER, W. BANASIAK, S.D. ANKER, P[IOTR] PONIKOWSKI, E[WA] A. JANKOWSKA. *Eur.J.Heart Fail.* 2014 Vol.16 suppl.2 s.335 poz.P1685, Heart Failure Congress 2014 and the 1st World Congress on Acute Heart Failure. Athens (Greece), 17-20th May 2014. Abstracts.
4.	**Iron deficiency is associated with neurohormonal activation in acute myocarditis.** PAWEŁ FRANCZUK, MARCIN DROZD, **KATARZYNA KULEJ-ŁYKO**, MICHAŁ TKACZYSZYN, NATALIA SIDOROWICZ, IRENA FLINTA, PAWEŁ GAĆ, WALDEMAR BANASIAK, PIOTR PONIKOWSKI, EWA JANKOWSKA. *Kardiol.Pol.* 2018 T.76 supl.1 s.315-316, XXII Międzynarodowy Kongres Polskiego Towarzystwa Kardiologicznego. Kraków, 13-15 września 2018. Streszczenia.
5.	**Iron deficiency relates to neurohormonal activation in acute myocarditis.** P[AWEŁ] FRANCZUK, **K[ATARZYNA] KULEJ-ŁYKO**, M[ARCIN] DROZD, M[ICHAŁ] TKACZYSZYN, N. SIDOROWICZ, I[RENA] FLINTA, P[AWEŁ] GAĆ, W[ALDEMAR] BANASIAK, P[IOTR] PONIKOWSKI, EWA A[NITA] JANKOWSKA. *Eur.J.Heart Fail.* 2018 Vol.20 suppl.1 s.132 poz.P516, Heart Failure 2018 and the World Congress on Acute Heart Failure. Vienna, Austria, 26-29 May 2018. Abstracts. DOI: 10.1002/ejhf.1197
6.	**Biomarkers of iron status (transferrin saturation, serum ferritin) in the course of acute myocarditis: relations with neurohormonal activation, cardiac dysfunction and clinical recovery.** P[AWEŁ] FRANCZUK, A[NETA] KOSIOREK, M[ICHAŁ] TKACZYSZYN, M[ARCIN] DROZD, A[NNA] ZAPOLSKA, T[OMASZ] WALCZAK, **K[ATARZYNA] KULEJ-ŁYKO**, N. SIDOROWICZ, A[LICJA] SOŁTOWSKA, W[ALDEMAR] BANASIAK, J[OANNA] JAROCH, P[IOTR] PONIKOWSKI, E[WA] A. JANKOWSKA. *Eur.J.Heart Fail.* 2019 Vol.21 suppl.1 s.279-280 poz.P1143, Heart Failure 2019 and the World Congress on Acute Heart Failure. Athens, Greece, 25-28 May 2019. Abstracts. DOI: 10.1002/ejhf.1488
7.	**Depleted iron stores are associated with decreased exercise capacity in patients with non-ischaemic cardiomyopathy.** M[ARCIN] DROZD, M[ICHAŁ] TKACZYSZYN, A[NNA] ZAPOLSKA, T[OMASZ] WALCZAK, J. TOBISZEWSKI, P[AWEŁ] FRANCZUK, A[NETA] KOSIOREK, I[RENA] FLINTA, J[OANNA] JAROCH, A[LICJA] SOŁTOWSKA, **K[ATARZYNA] KULEJ-ŁYKO**, W[ALDEMAR] BANASIAK, P[IOTR] PONIKOWSKI, E[WA] A. JANKOWSKA. *Eur.J.Heart Fail.* 2019 Vol.21 suppl.1 s.101 poz.P437, Heart Failure 2019 and the World Congress on Acute Heart Failure. Athens, Greece, 25-28 May 2019. Abstracts. DOI: 10.1002/ejhf.1488
8.	**HFWM: Sera from myocarditis patients caused iron depletion in cultured human cardiomyocytes.** KAMIL ALEKSANDER KOBAK, J. SCHUBERT, M[AGDALENA] DZIĘGAŁA, M[ONIKA] KASZTURA, P[AWEŁ] FRANCZUK, M[ARCIN] DROZD, **K[ATARZYNA] KULEJ-ŁYKO**, J. BANIA, P[IOTR] PONIKOWSKI, E[WA] A. JANKOWSKA. *Eur.J.Heart Fail.* 2019 Vol.21 suppl.1 s.475 poz.P1874, Heart Failure 2019 and the World Congress on Acute Heart Failure. Athens, Greece, 25-28 May 2019. Abstracts. DOI: 10.1002/ejhf.1488
9.	**High circulating ferritin predicts oedema and fibrosis assessed in cardiac magnetic resonance in patients with acute myocarditis.** A[NETA] KOSIOREK, P[AWEŁ] FRANCZUK, P[AWEŁ] GAĆ, M[ARCIN] DROZD, M[ICHAŁ] TKACZYSZYN, T[OMASZ] WALCZAK, A[NNA] ZAPOLSKA, **K[ATARZYNA] KULEJ-ŁYKO**, N. SIDOROWICZ, A[LICJA] SOŁTOWSKA, W[ALDEMAR] BANASIAK, J[OANNA] JAROCH, P[IOTR] PONIKOWSKI, E[WA] A. JANKOWSKA. *Eur.J.Heart Fail.* 2019 Vol.21 suppl.1 s.458 poz.P1812, Heart Failure 2019 and the World Congress on Acute Heart Failure. Athens, Greece, 25-28 May 2019. Abstracts. DOI: 10.1002/ejhf.1488

10.	**High circulating ferritin reflects myocardial injury assessed in cardiac magnetic resonance in patients with acute myocarditis.** ANETA KOSIOREK, PAWEŁ FRANCZUK, PAWEŁ GAĆ, MARCIN DROZD, MICHAŁ TKACZYSZYN, TOMASZ WALCZAK, ANNA ZAPOLSKA, **KATARZYNA KULEJ-ŁYKO**, NATALIA SIDOROWICZ, ALICJA SOŁTOWSKA, WALDEMAR BANASIAK, JOANNA JAROCH, PIOTR PONIKOWSKI, EWA JANKOWSKA. *Kardiol.Pol.* 2019 Vol.77 suppl.1 s.124-125, The 23rd International Congress of the Polish Cardiac Society. Katowice, Poland, September 26-28, 2019. Abstract proceedings. DOI: 10.33963/KP.15080
11.	**Indicators of iron status (serum ferritin, transferrin saturation) in the course of acute myocarditis: relations with cardiac dysfunction, neurohormonal activation and clinical recovery.** PAWEŁ FRANCZUK, ANETA KOSIOREK, MICHAŁ TKACZYSZYN, MARCIN DROZD, ANNA ZAPOLSKA, TOMASZ WALCZAK, **KATARZYNA KULEJ-ŁYKO**, NATALIA SIDOROWICZ, ALICJA SOLTOWSKA, WALDEMAR BANASIAK, WOJCIECH KOSMALA, MONIKA PRZEWŁOCKA-KOSMALA, JOANNA JAROCH, PIOTR PONIKOWSKI, EWA JANKOWSKA. *Kardiol.Pol.* 2019 Vol.77 suppl.1 s.132-133, The 23rd International Congress of the Polish Cardiac Society. Katowice, Poland, September 26-28, 2019. Abstract proceedings. DOI: 10.33963/KP.15080
12.	**Iron depletion in human cardiomyocytes cultured with sera from myocarditis patients.** K[AMIL] A. KOBAK, J. SCHUBERT, M[ONIKA] KASZTURA, P[AWEŁ] FRANCZUK, M[AGDALENA] DZIĘGAŁA, M[ARCIN] DROZD, M[ICHAŁ] TKACZYSZYN, **K[ATARZYNA] KULEJ-ŁYKO**, J. BANIA, W. BANASIAK, P[IOTR] PONIKOWSKI, E[WA] A. JANKOWSKA. *Eur.Heart J.* 2019 Vol.40 suppl. s.3955 poz.P6353, ESC Congress 2019 together with World Congress of Cardiology. Paris (France), 31 August - 4 September 2019. DOI: 10.1093/eurheartj/ehz746.0949
13.	**Iron status indices (transferrin saturation, serum ferritin) in the course of acute myocarditis: relations with neurohormonal activation, cardiac dysfunction and clinical recovery.** P[AWEŁ] FRANCZUK, A[NETA] KOSIOREK, M[ICHAŁ] TKACZYSZYN, M[ARCIN] DROZD, A[NNA] ZAPOLSKA, T[OMASZ] WALCZAK, **K[ATARZYNA] KULEJ-ŁYKO**, N. SIDOROWICZ, A[LICJA] SOŁTOWSKA, W[ALDEMAR] BANASIAK, W[OJCIECH] KOSMALA, M[ONIKA] PRZEWŁOCKA-KOSMALA, J[OANNA] JAROCH, P[IOTR] PONIKOWSKI, E[WA] A. JANKOWSKA. *Eur.Heart J.* 2019 Vol.40 suppl. s.358 poz.P754, ESC Congress 2019 together with World Congress of Cardiology. Paris (France), 31 August - 4 September 2019. DOI: 10.1093/eurheartj/ehz747.0356
14.	**Inhibition of peripheral chemoreceptors improves ventilatory efficacy during exercise in heart failure with preserved ejection fraction. K[ATARZYNA] KULEJ-ŁYKO**, P[IOTR] NIEWIŃSKI, S[TANISŁAW] TUBEK, P[IOTR] PONIKOWSKI. *Eur.J.Heart Fail.* 2022 Vol.24 suppl.2 s.30-31, The Heart Failure 2022 and the World Congress on Acute Heart Failure. Madrid, Spain, 21-24 May 2022. Abstracts.
15.	**Low-dose dopamine improves ventilatory efficiency during exercise in heart failure with preserved ejection fraction through inhibition of tonic activity of peripheral chemoreceptors KULEJ-ŁYKO KATARZYNA,** NIEWIŃSKI PIOTR, TUBEK STANISŁAW, PONIKOWSKI PIOTR. European Heart Journal, 2022, vol. 43, nr suppl.2, s. 761, [ESC Congress 2022. Barcelona, Spain, 26-29 August 2022], DOI:10.1093/eurheartj/ehac544.761

Sumaryczny impact factor: 16,839

	Punktacja MNiSW
do roku 2018	**44,0**
od roku 2019	**370,0**
Razem:	**414,0**

18.10.22 r. Beata Magryś

Uniwersytet Medyczny we Wrocławiu
Biblioteka Główna
DZIAŁ BIBLIOGRAFII I BIBLIOMETRII
ul. Marcinkowskiego 2-6, 50-368 Wrocław
tel. 71 784 19 25, faks 71 784 19 31

11.2. ZGODA KOMISJI BIOETYCZNEJ

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

OPINIA KOMISJI BIOETYCZNEJ Nr KB – 782/2017

Komisja Bioetyczna przy Uniwersytecie Medycznym we Wrocławiu, powołana zarządzeniem Rektora Uniwersytetu Medycznego we Wrocławiu nr 78/XV R/2014 z dnia 26 listopada 2014 r. oraz działająca w trybie przewidzianym rozporządzeniem Ministra Zdrowia i Opieki Społecznej z dnia 11 maja 1999 r. (Dz.U. nr 47, poz. 480) na podstawie ustawy o zawodzie lekarza z dnia 5 grudnia 1996 r. (Dz.U. nr 28 z 1997 r. poz. 152 z późniejszymi zmianami) w składzie:

prof. dr hab. Maciej Bagłaj (chirurgia, pediatria)
prof. dr hab. Karol Bal (filozofia)
dr hab. Jacek Daroszewski (endokrynologia, diabetologia)
prof. dr hab. Krzysztof Grabowski (chirurgia)
dr Henryk Kaczkowski (chirurgia szczękowa, chirurgia stomatologiczna)
mgr Irena Knabel-Krzyszowska (farmacja)
prof. dr hab. Jerzy Liebhart (choroby wewnętrzne, alergologia)
ks. dr hab. Piotr Mrzygłód (duchowny)
mgr Luiza Müller (prawo)
prof. dr hab. Krystyna Orzechowska-Juzwenko (farmakologia kliniczna, choroby wewnętrzne)
prof. dr hab. Zbigniew Rudkowski (pediatria)
dr hab. Sławomir Sidorowicz (psychiatria)
Danuta Tarkowska (położnictwo)
dr hab. Andrzej Wojnar (histopatologia, dermatologia) przedstawiciel Dolnośląskiej Izby Lekarskiej)

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

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

„Znaczenie odpowiedzi z chemoreceptrow obwodowych w patogenezie duszności wysiłkowej u chorych z rozkurczową niewydolnością serca"

zgłoszonym przez **lek. Katarzynę Kulej-Łyko** zatrudnioną w Katedrze i Klinice Chorób Serca Wydziału Nauk o Zdrowiu Uniwersytetu Medycznego we Wrocławiu oraz złożonymi wraz z wnioskiem dokumentami, w tajnym głosowaniu postanowiła **wyrazić zgodę** na przeprowadzenie badania w Katedrze i Klinice Chorób Serca Wydziału Nauk o Zdrowiu Uniwersytetu Medycznego we Wrocławiu oraz Ośrodku Chorób Serca 4 Wojskowego Szpitala Klinicznego we Wrocławiu **pod warunkiem zachowania anonimowości uzyskanych danych**.

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

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

Opinia powyższa dotyczy projektu badawczego finansowanego przez Narodowe Centrum Nauki – „Preludium 12"

Wrocław, dnia 28 grudnia 2017 r.

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

11.3. OŚWIADCZENIA O WSPÓŁAUTORSTWIE

Wrocław, 13.11.2022

Lek. Katarzyna Kulej-Łyko
Klinika Kardiologii
Instytut Chorób Serca
Uniwersytecki Szpital Kliniczny
we Wrocławiu

OŚWIADCZENIE O WSPÓŁAUTORSTWIE

Oświadczam, że w przygotowaniu publikacji:

1) Kulej-Lyko K, Niewinski P, Tubek S and Ponikowski P (2022)
Contribution of peripheral chemoreceptors to exercise intolerance in heart failure.
Front. Physiol. 13:878363. doi: 10.3389/fphys.2022.878363

2) Kulej-Lyko K, Niewinski P, Tubek S, Krawczyk M, Kosmala W, Ponikowski P (2022)
Inhibition of peripheral chemoreceptors improves ventilatory efficiency during exercise in heart failure with preserved ejection fraction – a role of tonic activity and acute reflex response.
Front. Physiol. doi: 10.3389/fphys.2022.911636

mój udział polegał na:

PUBLIKACJA 1:
- sformułowaniu problemów i hipotez badawczych
- analizie i doborze odpowiedniej literatury pod kątem wybranego tematu
- przygotowaniu manuskryptu
- nadzorowaniu procesu recenzji i nanoszeniu wymaganych przez recenzentów poprawek

PUBLIKACJA 2:
- stworzeniu koncepcji i projektu badania, uzyskaniu jego finansowania
- rekrutacji pacjentów oraz wykonywaniu zadań projektowych zgodnie z protokołem
- opracowaniu wyników oraz tworzeniu bazy danych
- analizie statystycznej wyników i ich interpretacji w świetle danych literaturowych
- przygotowaniu treści manuskryptu
- nanoszeniu krytycznych poprawek do treści manuskryptu
- nadzorowaniu procesu recenzji i nanoszeniu wymaganych przez recenzentów poprawek

Katarzyna Kulej-Łyko

Wrocław, 17.11.2022

Dr n. med. Piotr Niewiński
Klinika Kardiologii
Instytut Chorób Serca
Uniwersytet Medyczny
we Wrocławiu

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mój udział polegał na:

PUBLIKACJA 1:
- sformułowaniu problemów i hipotez badawczych
- pomocy w analizie i doborze odpowiedniej literatury pod kątem wybranego tematu
- redagowaniu i tworzeniu treści manuskryptu
- nadzorowaniu procesu recenzji i nanoszenia wymaganych przez recenzentów poprawek

PUBLIKACJA 2:
- stworzeniu koncepcji i projektu badania
- wykonywaniu niektórych zadań projektowych (zaślepianiu roztworów, pomocy technicznej w czasie testów oceny chemowrażliwości)
- analizie statystycznej wyników i ich interpretacji w świetle danych literaturowych
- przygotowaniu i redagowaniu treści manuskryptu
- nadzorowaniu procesu recenzji i nanoszenia wymaganych przez recenzentów poprawek

Oświadczenie jest składane celem przedłożenia z rozprawą doktorską
lek. Katarzyny Kulej-Łyko, na którą w ramach cyklu publikacji składają się wymienione powyżej prace.

Wrocław, 22.11.2022

Dr n. med. Stanisław Tubek
Klinika Kardiologii
Instytut Chorób Serca
Uniwersytet Medyczny
we Wrocławiu

OŚWIADCZENIE O WSPÓŁAUTORSTWIE

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- interpretacji wyników w świetle danych literaturowych

PUBLIKACJA 2:
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- opracowaniu otrzymanych wyników
- przygotowaniu i redagowaniu treści manuskryptu
- interpretacji wyników w świetle danych literaturowych

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Wrocław, 17.11.2022

Lek. Magdalena Krawczyk
Klinika Kardiologii
Instytut Chorób Serca
Uniwersytecki Szpital Kliniczny
we Wrocławiu

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Front. Physiol. doi: 10.3389/fphys.2022.911636

mój udział polegał na:

- pomocy w rekrutacji pacjentów oraz wykonywaniu badań echokardiograficznych przezklatkowych w grupie badanej

Oświadczenie jest składane celem przedłożenia z rozprawą doktorską
lek. Katarzyny Kulej-Łyko, na którą w ramach cyklu publikacji składa się wymieniona powyżej praca oryginalna.

Magdalena Krawczyk

Wrocław, 28.11.2022

Prof. dr hab. Wojciech Kosmala
Kierownik
Zakładu Obrazowania Układu Sercowo-Naczyniowego
Instytut Chorób Serca
Uniwersytet Medyczny
we Wrocławiu

OŚWIADCZENIE O WSPÓŁAUTORSTWIE

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Front. Physiol. doi: 10.3389/fphys.2022.911636

mój udział polegał na:

- interpretacji wyników w świetle danych literaturowych
- krytycznych poprawkach w ostatecznej wersji manuskryptu
- nadzorowaniu procesu recenzji

Oświadczenie jest składane celem przedłożenia z rozprawą doktorską
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Wrocław, 28.11.2022

Prof. dr hab. Piotr Ponikowski
Dyrektor
Instytutu Chorób Serca
Uniwersytet Medyczny
we Wrocławiu

OŚWIADCZENIE O WSPÓŁAUTORSTWIE

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