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Ocena interakcji pomiędzy odpowiedzią z mechanoreceptorów i metaboreceptorów mięśni szkieletowych u osób zdrowych

Rozprawa doktorska

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Składam najserdeczniejsze podziękowania Promotorowi mojej pracy,

Pani Profesor Beacie Ponikowskiej,

za nieocenioną pomoc, życzliwość i motywację do działania.

Pragnę również podziękować Panu dr. hab. Bartłomiejowi Palecznemu

za wsparcie merytoryczne przy tworzeniu niniejszej rozprawy.

Paulinie…

Spis treści:

1. WYKAZ PUBLIKACJI STANOWIĄCYCH ROZPRAWĘ DOKTORSKĄ:

a) **Passive bilateral leg cycling with concomitant regional circulatory occlusion for testing mechanoreflex-metaboreflex interactions in humans**

Adrian Lis, Wojciech Łopusiewicz, Massimo F. Piepoli, Beata Ponikowska, Bartłomiej Paleczny

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b) **Understanding mechanoreflex and metaboreflex interactions – a great challenge**

Adrian Lis, Bartłomiej Paleczny, Beata Ponikowska

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2. STRESZCZENIE

Wstęp: Wysiłkowy odruch presyjny, na który składa się odpowiedź z mechanoreceptorów i metaboreceptorów mięśni szkieletowych, odgrywa niebagatelną rolę w fizjologii wysiłku. Uszkodzenie tego mechanizmu przyczynia się do rozwoju niektórych chorób sercowo-naczyniowych, takich jak niewydolność serca. Pomimo ich kluczowego znaczenia zarówno fizjologicznego jak i klinicznego, interakcje pomiędzy odpowiedzią z mechanoreceptorów i metaboreceptorów mięśni szkieletowych nie doczekały się wielu badań, częściowo z powodu trudności metodologicznych. Wyniki dostępnych prac są ograniczone i często rozbieżne.

Cel: Celem niniejszej pracy jest kompleksowe podsumowanie dostępnej wiedzy naukowej o interakcjach pomiędzy odpowiedzią z mechanoreceptorów i metaboreceptorów mięśni szkieletowych; wskazanie przyczyny rozbieżności w wynikach poprzednich badań; ukazanie rzeczywistych interakcji pomiędzy odpowiedzią z mechanoreceptorów i metaboreceptorów mięśni szkieletowych przy użyciu nowatorskiej, efektywnej metody badania; zaproponowanie potencjalnych kierunków przyszłych badań, z uwzględnieniem znaczenia klinicznego wysiłkowego odruchu presyjnego.

Materiał i metody: Trzydziestu czterech zdrowych uczestników (średnia wieku: 24±4 lata; 22 mężczyzn) wzięło udział w badaniu opisanym w publikacji *„Passive bilateral leg cycling with concomitant regional circulatory occlusion for testing mechanoreflex-metaboreflex interactions in humans.* Po 5 minutach spoczynku następowało 5 minut biernego pedałowania (PC) na automatycznym cykloergometrze [stymulacja mechanoreceptorów], po którym napompowane zostały obustronne mankiety udowe, by na 3 minuty doprowadzić do miejscowego zatrzymania krążenia (CO) w kończynach dolnych [stymulacja metaboreceptorów]. Po zwolnieniu ucisku następował 5-minutowy okres PC, a następnie 5 minut odpoczynku. Badanie kontrolne obejmowało 5 minut zapisu spoczynkowego, po którym następowały 3 minuty CO, a następnie 5 minut odpoczynku. Parametry hemodynamiczne i oddechowe były zapisywane w sposób ciągły.

Do przygotowania artykułu *„Understanding mechanoreflex and metaboreflex interactions – a great challenge”* przeszukano bazy danych Pubmed, Scopus i Google Scholar przy użyciu następujących słów kluczowych: metaboreceptors, mechanoreceptors, interactions, effects, exercise pressor reflex, mechanoreflex, metaboreflex, chemoreceptors, baroreceptors,

chemoreflex and baroreflex. Kryteria wyłączenia z analizy obejmowały: język publikacji inny niż angielski, nieprawidłowa metodologa badania, czasopismo nieuwzględnione na liście "InCites Journal Citation Reports" oraz nieistotne wyniki i wnioski.

Wyniki: W badaniu opublikowanym w artykule *„Passive bilateral leg cycling with concomitant regional circulatory occlusion for testing mechanoreflex-metaboreflex interactions in humans"* średnie ciśnienie tętnicze (MAP) i wentylacja minutowa (MV) istotnie wzrosły podczas PC (z 90±9.3 do 95±9.7 mmHg dla MAP, z 11.5±2.5 do 13.5±2.9 L/min dla MV; obydwa $p<0.05$) i ponownie gdy do PC dodano CO (MAP wzrosło z 95±9.7 do 101±11.0 mmHg, MV wzrosła z 13.5±2.9 do 14.8±3.8 L/min; obydwa $p<0.05$). W badaniu kontrolnym nie obserwowano zmian w parametrach oddechowych, odnotowano natomiast niewielki wzrost MAP podczas izolowanego CO (z 92±10.5 do 94±10.0 mmHg; $p<0.05$). Częstość akcji serca nie zmieniła się w odpowiedzi na izolowane PC i CO, jednak wzrosła podczas PC z jednoczesnym CO (z 76±11.2 do 81±13.6 ud/min; $p<0.05$).

Wstępnie rozważano ponad trzysta artykułów do włączenia do artykułu poglądowego *„Understanding mechanoreflex and metaboreflex interactions – a great challenge"*. Po ostatecznej selekcji do przygotowania publikacji przeanalizowano 78 prac oryginalnych, 13 artykułów poglądowych, 3 listy do redakcji, 2 edytoriale, 2 opublikowane raporty z sympozjum i 1 „wymianę poglądów" (ang. *„exchange of views"*).

Wnioski: Obustronne PC z jednoczesnym CO jest nowoczesną, prostą, skuteczną i bezpieczną metodą badania interakcji pomiędzy odpowiedzią z mechanoreceptorów i metaboreceptorów mięśni szkieletowych u ludzi. Przy jej pomocy pokazano, że pobudzenie mechanoreceptorów mięśni szkieletowych wywołuje wzrost MAP i MV, a dodanie do tego odpowiedzi z metaboreceptorów skutkuje dalszym wzrostem MAP i MV. Wykazano także istnienie hiperaddytywnej interakcji pomiędzy obydwiema składowymi wysiłkowego odruchu presyjnego w kontekście częstości akcji serca.

Ponadto, wykonując kompleksowy przegląd literatury dotyczącej tej tematyki, dokonano podsumowania obecnego stanu wiedzy o interakcjach wysiłkowego odruchu presyjnego i ukazano luki w danych naukowych. Podkreślono także kliniczne i praktyczne znaczenie przyszłych badań interakcji pomiędzy odpowiedzią z mechanoreceptorów i metaboreceptorów mięśni szkieletowych u pacjentów z chorobami sercowo-naczyniowymi.

Wiedza pochodząca z tych badań umożliwi z pewnością wprowadzenie nowoczesnych metod leczenia, ukierunkowanych na modulację receptorów i pozostałych komponent powyższych odruchów, których dysfunkcję obserwuje się w schorzeniach układu krążenia.

3. ABSTRACT

Introduction: The exercise pressor reflex, consisting of the responses from the muscle mechano- and metaboreceptors, plays an essential role in exercise physiology. The deterioration of this mechanism contributes to development of certain cardiovascular diseases, such as heart failure. Despite their fundamental physiological and clinical significance, the interactions between muscle mechanoreflex and metaboreflex have not been studied much, partially due to some methodological issues. The results from the previous studies are scarce and mainly discordant.

Aim: The purpose of this contribution is to comprehensively summarize data on the muscle mechano- and metaboreceptors' interactions; identify notional causes of the discrepancies in the previous studies' results; display the actual interactions between the response from muscle mechanoreceptors and metaboreceptors using a novel effective method; propose potential directions for future research, regarding the clinical importance of the exercise pressor reflex.

Material and methods: Thirty-four healthy participants (mean age: 24±4 years, 22 males) were recruited to the study published as *„Passive bilateral leg cycling with concomitant regional circulatory occlusion for testing mechanoreflex-metaboreflex interactions in humans"*. A 5-minute rest was followed by 5 minutes of passive cycling (PC) on an automated cycle ergometer [mechanoreceptors' stimulation], after which tourniquet cuffs located bilaterally on the upper thighs were inflated for 3 minutes to induce regional circulatory occlusion (CO) during PC [metaboreceptors' stimulation]. Deflation was followed by 5 minutes of PC and a 5-minute recovery. The control test comprised a 5-minute rest, followed by 3 minutes of CO only and a 5-minute recovery. Ventilatory and hemodynamic parameters were continuously recorded.

To prepare the review article *„Understanding mechanoreflex and metaboreflex interactions – a great challenge"* Pubmed, Scopus and Google Scholar databases have been searched using following keywords: metaboreceptors, mechanoreceptors, interactions, effects, exercise pressor reflex, mechanoreflex, metaboreflex, chemoreceptors, baroreceptors, chemoreflex and baroreflex. The exclusion criteria included: language other than English, misguided

methodology, journal not included in the "InCites Journal Citation Reports" list and irrelevant results or conclusions.

Results: In the experiment described in the article *„Passive bilateral leg cycling with concomitant regional circulatory occlusion for testing mechanoreflex-metaboreflex interactions in humans"* the mean blood pressure (MAP) and minute ventilation (MV) increased considerably during PC (from 90±9.3 to 95±9.7 mmHg for MAP, from 11.5±2.5 to 13.5±2.9 L/min for MV; both $p<0.05$) and again when CO was added (MAP increased from 95±9.7 to 101±11.0 mmHg, MV increased from 13.5±2.9 to 14.8±3.8 L/min; both $p<0.05$). Minor increase in MAP during CO (from 92±10.5 to 94±10.0 mmHg; $p<0.05$) and no changes in the ventilatory parameters were found in the control test. Heart rate was not changed by isolated PC or CO, but increased during PC with concomitant CO (from 76±11.2 to 81±13.6 bpm; $p<0.05$).

Initially, more than three hundred publications have been considered to include into the review *„Understanding mechanoreflex and metaboreflex interactions – a great challenge"*. After the final selection 78 original research articles, 13 review articles, 3 letters to the editor, 2 editorials, 2 symposium reports and 1 exchange of views were analyzed to prepare this article.

Conclusions: Bilateral leg PC with concomitant CO proved to be a novel, simple, effective and safe method for testing muscle mechanoreflex-metaboreflex interactions in humans. It was found that (i) the response from the muscle mechanoreceptors is expressed by an increase of MAP and MV; (ii) addition of the response from the muscle metaboreceptors to activated mechanoreflex evokes further increases of MAP and MV; (iii) muscle mechanoreflex and metaboreflex work in a hyperadditive manner regarding heart rate.

Moreover, a comprehensive review of the data on the exercise pressor reflex interactions enabled to summarize the state of art and identify scientific gaps. It also underlined the clinical and practical importance of the future research in the area of the relations between the response from muscle mechanoreceptors and metaboreceptors in patients with heart failure and other cardiovascular diseases. The knowledge obtained from such studies will certainly enable development of the novel methods of treatment targeted at modulating the receptors

and other components of the aforementioned reflexes, the dysfunction of which is observed in cardiovascular conditions.

4. WSTĘP

Podczas wysiłku fizycznego u ludzi dochodzi do znacznych zmian w czynności autonomicznego układu nerwowego, wyrażonych głównie poprzez przyspieszenie częstości akcji serca (ang. heart rate - HR), wzrost kurczliwości serca i objętości wyrzutowej (ang. stroke volume - SV), zmiany w oporze obwodowym (ang. peripheral resistance - PR) w poszczególnych obszarach krążeniowych, wzrost ciśnienia tętniczego krwi (ang. blood pressure - BP), a także wzrost wentylacji minutowej (ang. minute ventilation - MV). Umożliwiają one dostosowanie podstawowych funkcji organizmu do nowej sytuacji, a więc do zwiększonego zapotrzebowania na tlen, nasilenia produkcji szkodliwych produktów przemiany materii i przede wszystkim konieczności zapewnienia odpowiedniej perfuzji tkanek, szczególnie bezpośrednio zaangażowanych w wykonywanie pracy podczas wysiłku. W tym celu odpowiedniej modulacji ulega odruch z baroreceptorów, dochodzi do aktywacji tzw. mechanizmów ośrodkowych (ang. central command - CC) i wysiłkowego odruchu presyjnego (ang. exercise pressor reflex - EPR), a także odruchu z chemoreceptorów obwodowych [1–3].

Mechanizmy ośrodkowe

Mechanizmy ośrodkowe reakcji odruchowej na wysiłek fizyczny stanowią wysublimowany przykład tzw. sprzężenia wyprzedzającego, tzn. efekty krążeniowe pojawiają się jeszcze zanim podjęta zostanie właściwa aktywność fizyczna [4–6]. Bodźcem jest już sama chęć podjęcia wysiłku, a także myśl o wykonywanej czynności. Impulsacja eferentna z ośrodków mózgowia zmierza zarówno do efektorów układu sercowo-naczyniowego jak i oddechowego wywołując reakcje hemodynamiczne w postaci wzrostu HR czy SV, a także reakcje oddechowe – tj. wzrost MV [4–6]. Aktywność CC jest istotnym czynnikiem zaburzającym w badaniach nad EPR, gdyż w sposób znaczący zmienia nasilenie reakcji autonomicznego układu nerwowego na podjęty wysiłek fizyczny [4–6]. Stąd w wielu badaniach skupiających się na obwodowych mechanizmach reakcji na wysiłek autorzy różnymi metodami starają się wyeliminować udział tej komponenty. Dostępne sposoby to m. in. (i) generowanie mimowolnych skurczów mięśnia (ang. involuntary muscle contractions) za pomocą elektrostymulacji [7]; (ii) wykonywanie biernych ruchów kończyn badanego przez osoby trzecie [8]; (iii) ćwiczenia bierne na cykloergometrze tandemowym [9]; (iv) rozciąganie mięśni za pomocą specjalnie zaprojektowanych do tego celu urządzeń [10]; (v) bierne ruchy kończyn na specjalnie przygotowanych cykloergometrach jedno-, dwu-, a także czterokończynowych [11,12].

Każda z powyższych metod charakteryzuje się pewnymi ograniczeniami, np. w przypadku rozciągania mięśnia aktywowane są inne włókna niż przy jego skurczu [13], elektrostymulacja mięśnia wywołuje więcej zaburzeń metabolicznych niż skurcz zamierzony z tym samym obciążeniem [14], a osoby trzecie nie są w stanie wykonywać przez dłuższy czas powtarzalnego ruchu, podobnie jak osoba pedałująca na cykloergometrze tandemowym. Najbardziej optymalną z powyższych, obciążoną najmniejszą liczbą ograniczeń jest metoda z użyciem cykloergometrów do ćwiczeń biernych, przy czym możliwość eliminacji zamierzonego napięcia mięśni przy ruchach kończyn górnych jest niewielka, wobec czego do badań w pierwszej kolejności należy użyć urządzeń zaprojektowanych do poruszania kończynami dolnymi.

Wysiłkowy odruch presyjny

Spośród wymienionych wcześniej mechanizmów odruchowych pojawiających się w odpowiedzi na wysiłek fizyczny jedynie EPR związany jest bezpośrednio z aktywnością mięśni poprzecznie prążkowanych. Dzieli się on na dwa odruchy, mające swój początek w dwóch rodzajach receptorów: odruch z mechanoreceptorów i odruch z metaboreceptorów [1,3,4]. Postuluje się, że mechanoreceptory to gołe zakończenia nerwowe i ciałka Paciniego kończące się w tkance łącznej ścięgien mięśni i endoneurium nerwów, zlokalizowane na zmielinizowanych włóknach typu III (Aδ), podczas gdy metaboreceptory stanowią gołe zakończenia nerwowe niezmielinizowanych włókien typu IV (C) kończące się w ścianach włośniczek, żyłek i naczyń chłonnych mięśni szkieletowych [13]. Zagadnienie komplikuje fakt, iż część włókien III i IV typu (opisywanych jako polimodalne) może mieć aktywność zarówno mechanoreceptywną jak i metaboreceptywną [3,13,15]. Dodatkowo wykazano, że pobudliwość mechanoreceptorów może być zwiększona poprzez krążące metabolity wysiłkowe, będące agonistami metaboreceptorów, tj. bradykinina, potas czy produkty metabolizmu kwasu arachidonowego i mlekowego [16,17]. Niemniej jednak dostępne dane wskazują, że to odruch z mechanoreceptorów odpowiada za inicjację i pierwszy etap EPR (włókna typu III jako zmielinizowane cechują się szybszą transmisją sygnału), podczas gdy odruch z metaboreceptorów (dłuższa transmisja sygnału przez włókna typu IV) zaczyna nabierać znaczenia w dalszym etapie wysiłku fizycznego, gdy dochodzi do akumulacji metabolitów – wymienionych już wcześniej potasu, bradykininy, produktów metabolizmu kwasu arachidonowego i mlekowego, a także adenozyny, ATP czy uwodornionych fosforanów [4]. Szczegółowy przebieg łuku odruchowego dla EPR pozostaje nieznany. Nie wiadomo wciąż

w których obszarach mięśni zgrupowane są mechanoreceptory (zakończenia włókien typu III). Nie jest też znany konkretny typ receptora [13]. Wiadomo jednak, że obydwa typy włókien (III i IV) biegną w rogach tylnych rdzenia kręgowego (blaszki Rexeda I, II, V, X) zmierzając do pnia mózgu przez bruzdę grzbietowo-boczną oraz brzuszną część rdzenia kręgowego [13]. Pierwszorzędowy ośrodek odruchu stanowi najprawdopodobniej jądro pasma samotnego (łac. nucleus tractus solitarii, NTS), z którego sygnał przekazywany jest do ośrodków drugorzędowych zlokalizowanych w rdzeniu przedłużonym [3,4,13]. Neuroprzekaźnikami w obrębie ośrodkowego układu nerwowego mogą być glutaminian, asparaginian i substancja P [13]. Drogami odśrodkowymi odruchu są włókna współczulne unerwiające ściany naczyń krwionośnych oraz mięśnia sercowego, a także włókna modulujące aktywność neuronów przywspółczulnych [13]. Obydwie składowe EPR działają w przeważającej mierze synergistycznie, prowadząc do wzrostu napięcia układu współczulnego i spadku aktywności układu przywspółczulnego, co wyraża się głównie wzrostem BP i HR [3]. Czynnikami osłabiającymi aktywność EPR są (i) wzrost produkcji tlenku azotu w NTS, (ii) aktywacja receptorów serotoninowych 5-HT1A oraz (iii) pobudzenie receptorów opioidowych, obecnych zarówno na włóknach III jak i IV typu [3]. Ten ostatni został wykorzystany w badaniach eksperymentalnych nad EPR, w których w celu eliminacji impulsacji dośrodkowej tego odruchu podawano badanym opioid (fentanyl) dooponowo [1,14]. Chcąc wyizolować odruch z mechanoreceptorów od drugiej składowej EPR należy w eksperymencie zastosować łagodny wysiłek dynamiczny, w którym nie będzie dochodziło do istotnego nagromadzenia metabolitów [7]. Aktywność odruchu z metaboreceptorów rzeczywiście nasila się wraz ze wzrostem intensywności ćwiczeń fizycznych, jednak ograniczenie stanowi fakt, że podstawowa aktywność metaboreceptorów obserwowana jest również bez obciążenia wysiłkiem, tzn. nawet wtedy, gdy nie mamy do czynienia z powstawaniem metabolitów przemian beztlenowych w większej ilości [4]. Wykazano, że wysiłek dynamiczny prowadzi do wzrostu stężenia krążących metabolitów [13], choć naturalnie wywołuje on słabszą odpowiedź z metaboreceptorów [4]. Powyższe powiązania bardzo istotnie ograniczają możliwość izolacji odruchu z mechano- i odruchu z metaboreceptorów, choć nie uniemożliwiają badań nad poszczególnymi składowymi. Aby skupić się na odruchu z mechanoreceptorów należy więc zastosować bierne dynamiczne ruchy o umiarkowanej intensywności. O ile odruch z metaboreceptorów doczekał się w literaturze wielu publikacji, o tyle druga składowa EPR wciąż nie została dostatecznie poznana. Dla przykładu – baza danych Scopus gromadzi 34

artykuły zawierające w tytule „mechanoreflex”, podczas gdy publikacje ze sformułowaniem „metaboreflex” występują w niej w liczbie 187. Jeszcze mniej eksperymentalnych danych dostępnych jest z zakresu wiedzy dotyczącej interakcji obydwu składowych EPR. Są to zaledwie pojedyncze badania przeprowadzone na zwierzętach albo na ludziach z wykorzystaniem biernego rozciągania mięśni, a więc modelu nieodpowiadającemu fizjologicznemu wysiłkowi [16–21].

Odpowiedź z mechanoreceptorów

Charakterystyka odruchu z mechanoreceptorów opisywana w różnych badaniach eksperymentalnych nie jest spójna. Dość wspomnieć, że w wielu badaniach wykonanych jeszcze w ubiegłym wieku nie wykazano zmian HR w odpowiedzi na pobudzenie mechanoreceptorów, a próbowano to zrobić poprzez stosowanie bezpośredniego ucisku na mięśnie, rozciąganie mięśni, czy wymuszenie rytmicznych ruchów biernych [15]. Z kolei Al Ani i wsp. [22] w swoim badaniu eksperymentalnym obserwowali gwałtowny wzrost HR w odpowiedzi na elektrycznie stymulowane skurcze mięśni, co w pierwszej kolejności należy wiązać właśnie z odruchem z mechanoreceptorów. Krzemiński i wsp. [23] w badaniach przeprowadzonych na cykloergometrze biernym w 2000 roku zaobserwowali, że zarówno podczas ćwiczeń zamierzonych jak i biernych pojemność minutowa serca wzrasta, ale w przypadku tych pierwszych na skutek wzrostu HR, a w przypadku ćwiczeń pasywnych dzięki zwiększeniu SV. Sugerowało to, że odruch z mechanoreceptorów per se nie wywołuje efektu chronotropowego, działając jedynie inotropowo dodatnio. Dodatkowo, nie można było wykluczyć, że wzrost kurczliwości wynika jedynie ze zwiększonego powrotu żylnego. Należy także dodać, że wysiłek zamierzony związany był z istotniejszym wzrostem CO. Takie wyniki sugerują, że udział odruchu z mechanoreceptorów w zmianie PR jest niewielki. Warto jednak zauważyć, że w przypadku aktywności biernej odczucie zmęczenia było niższe niż przy wysiłku zamierzonym. Można zatem wnioskować, że użyto zbyt niskiej częstotliwości obrotów na cykloergometrze biernym. Co ciekawe, w powyższym eksperymencie zaobserwowano także, iż jedynie ruch pasywny prowokował wzrost średniego ciśnienia tętniczego krwi, co wiązało się z faktem, że wyłącznie podczas ćwiczeń biernych nie dochodziło do spadku oporu obwodowego. Należy jednak pamiętać, że w przypadku ruchów celowych zarówno odczucie intensywności wykonywanego wysiłku jak i stężenie mleczanów we krwi było większe niż w przypadku ćwiczeń biernych. To ostatnie może sugerować, że na wyniki miał również wpływ

odruch z metaboreceptorów. Podobnie, rok później Middlekauf i wsp. [7] stymulując elektrycznie mięsień dwugłowy ramienia, zarówno u osób zdrowych jak i pacjentów z niewydolnością serca, nie obserwowali zmian w HR, natomiast odnotowali wzrost średniego BP. Zgoła odwrotne wyniki uzyskali w kolejnym roku Gladwell i Coote [15] badając reakcję krążeniową na rozciąganie mięśnia trójgłowego łydki, które uznali za najlepszy sposób pobudzenia mechanoreceptorów. Skutkowało ono wzrostem HR bez wpływu na skurczowe BP co sugeruje, że mechanoreceptory – aktywowane podczas rozciągania włókien mięśniowych – biorą udział w reakcji chronotropowej. Doświadczenie to pokazuje, że zmiana BP w odpowiedzi na rozciąganie mięśni nie zależy w istocie od EPR, a raczej stanowi wypadkową wpływu CC, zmian PR i zwiększonego powrotu żylnego na skutek ruchów mięśni. Sugeruje to, że inny mechanizm odpowiada za zmianę HR, a inny za zmianę w BP w odpowiedzi na aktywność fizyczną. Należy jednak pamiętać, że postuluje się, iż inne włókna mechanoreceptywne pobudzane są przy skurczu, a inne przy rozciąganiu mięśni [13]. Co ciekawe, we wspomnianym badaniu [15] efekt chronotropowy pojawiał się tylko w reakcji na stałe rozciąganie, a nie na rytmiczne rozciąganie z częstotliwością 0,5Hz, czym wykluczono udział w reakcji sercowo-naczyniowej proprioreceptorów czy odruchu na rozciąganie z aparatów Golgiego (mechanoreceptory adaptują się wolno, a proprioreceptory szybko). Zwrócono też uwagę na to, iż podczas powysiłkowego niedokrwienia (ang. post-exercise ischemia lub post-exercise circulatory occlusion - PECO) utrzymuje się właśnie wzrost ciśnienia, podczas gdy HR spada. Wskazywałoby to na swoisty dualizm EPR – komponenta mechaniczna wpływająca na HR i metaboliczna modulująca ciśnienie tętnicze poprzez wpływ na tonus mięśniówki naczyń krwionośnych. Tą drugą potwierdzono w wielu badaniach [4]. Niewątpliwie pobudzenie metaboreceptorów wywiera na BP wpływ niezależny od CC, co zostało dobitnie pokazane w eksperymencie, w którym badanym podano dooponowo fentanyl, mający zablokować impulsację aferentną EPR. Pomimo aktywności CC wzrost BP był mniejszy niż w sytuacji gdy fentanylu nie podano [1]. Jak widać z powyższych badań odruch z mechanoreceptorów nie został dostatecznie poznany, a dane co do samych efektów pobudzenia mechanoreceptorów nie są komplementarne.

Odpowiedź z metaboreceptorów

Dane dotyczące odruchu z metaboreceptorów są bardziej spójne niż w przypadku mechanoreceptorów – typowym efektem pobudzenia komponenty metabolicznej EPR jest wzrost BP na skutek wzmożenia napięcia układu współczulnego skutkującego wzrostem całkowitego PR [4,25]. Pobudzenie to uzyskuje się w badaniach najczęściej poprzez zastosowanie wysiłku statycznego oraz PECO [26]. Postuluje się, że odruch z metaboreceptorów nie wywiera istotnego wpływu na HR, natomiast nie jest jasne czy wpływa on na SV [4]. Należy zaznaczyć, że potencjalny wzrost SV w odpowiedzi na pobudzenie metaboreceptorów obserwowany jest głównie w przypadku wysiłku dynamicznego (nietypowego dla aktywacji tego odruchu) i po zaprzestaniu wysiłku - podczas niedokrwienia powysiłkowego, kiedy to spadkowi ulega HR. Sugeruje się, że wzrost SV może wystąpić na zasadzie kompensacji [4] lub/i wynikać z przesunięcia płynów z obszaru trzewnego do serca na skutek wazokonstrykcji trzewnej (prawo Franka-Starlinga).

Wysiłkowy odruch presyjny w stanach patologii

Dowiedzione zostało, że w chorobach układu krążenia, takich jak nadciśnienie tętnicze czy niewydolność serca, podczas aktywności fizycznej dochodzi do wzmożonej aktywacji układu współczulnego i spadku napięcia układu przywspółczulnego, co wyraża się nadmiernym wzrostem HR, BP i PR [1,13,27]. Wykazano, że istotny wkład w tą szkodliwą modulację ma EPR [7, 12-13]. W grupie pacjentów z niewydolnością serca dochodzi do wzmożonej aktywności, czy też zwiększenia pobudliwości mechanoreceptorów. Spekuluje się, że u tych pacjentów pobudliwość mechanoreceptorów zwiększona jest na skutek częstej ekspozycji na zwiększone stężenia metabolitów niedokrwienia [7]. Nie ma zgodności w wynikach badań co do aktywności metaboreceptorów w niewydolności serca [3,13].

Jako że nadmierny wzrost BP w odpowiedzi na wysiłek fizyczny jest silnym predyktorem zgonu z przyczyn sercowo-naczyniowych [1], poszukiwanie sposobów na normalizację patologicznie zwiększonej aktywności EPR u chorych na choroby układu krążenia wydaje się mieć niebagatelne znaczenie kliniczne. W literaturze dostępnych jest niewiele danych na ten temat. W jednym z badań u chorych z niewydolnością serca, stosując 6-tygodniowy trening mięśni przedramienia uzyskano spadek aktywności odruchu z metaboreceptorów – istotniejszy niż w przypadku grupy kontrolnej zdrowych badanych [28]. Podobne wyniki

otrzymano w badaniu na szczurach z niewydolnością serca, u których 7-tygodniowy trening na bieżni istotnie obniżył reakcję autonomiczną na wysiłek fizyczny (wyrażoną jako wzrost HR i BP) do poziomu porównywalnego z tym u zdrowych, niewytrenowanych szczurów [29]. Raz jeszcze podkreślić należy kluczowe znaczenie możliwości interwencyjnej normalizacji aktywności EPR u pacjentów z chorobami sercowo-naczyniowymi, w tym szczególnie z niewydolnością serca, ponieważ wysiłek fizyczny – z jednej strony generujący niekorzystną nadmierną odpowiedź autonomiczną – jest wciąż jednym ze sposobów prewencji wtórnej tych chorób.

Interakcje wysiłkowego odruchu presyjnego

Należy pamiętać, że w warunkach rzeczywistych, podczas wysiłku fizycznego dochodzi do aktywacji zarówno komponenty mechanicznej jak i metabolicznej wysiłkowego odruchu presyjnego. Biorąc pod uwagę fakt, że metabolity mogą uwrażliwiać mechanoreceptory, wynik współdziałania odpowiedzi z mechano- i metaboreceptorów nie musi stanowić prostej sumy ich izolowanych efektów. Z tego powodu, badanie interakcji pomiędzy odpowiedzią z mechano- i metaboreceptorów jest niezwykle istotne dla pełniejszego poznania reakcji organizmu na wysiłek fizyczny, także biorąc pod uwagę kliniczną doniosłość tych mechanizmów. Niestety, niewiele jest danych dotyczących takiej zależności. Dostępne dotychczas badania wykorzystywały zawsze podobną metodę eksperymentalną, tj. poddanie badanego wysiłkowi fizycznemu, następnie zastosowanie PECO i wreszcie dodanie rozciągania mięśni podczas PECO [16, 19-21]. Zastosowanie tej niefizjologicznej kolejności pobudzania poszczególnych składowych EPR wzbudza wątpliwości metodologiczne. Pomimo stosowania tej samej metody wyniki badań nie były spójne, a wręcz okazywały się zupełnie różne. W odpowiedzi na jednoczesną stymulację mechano- i metaboreceptorów mięśni podudzia, w jednym eksperymencie badacze obserwowali wzrost SV i HR bez zmiany BP [19], innym razem raportowali wzrost BP bez zmian w innych parametrach [21]. Taka rozbieżność w wynikach sygnalizuje niedoskonałość stosowanych narzędzi i skłania do poszukiwania nowych, lepszych metod badawczych. W niniejszej pracy zaprezentowano wyniki badania efektów sercowo-naczyniowych i wentylacyjnych interakcji pomiędzy odpowiedzią z mechano- i metaboreceptorów przy użyciu nowatorskiej metody biernego pedałowania na cykloergometrze automatycznym z następczym obustronnym miejscowym zatrzymaniem krążenia w kończynach dolnych. Taka technika pozwoliła na zachowanie fizjologicznej

kolejności pobudzenia poszczególnych składowych EPR dając rzetelny model odpowiedzi odruchowej z mięśni szkieletowych na wysiłek fizyczny.

Czynniki zakłócające i możliwości ich eliminacji

Aby wyeliminować wpływ CC w badaniach nad EPR należy w eksperymencie zastosować ćwiczenia bierne. Biorąc pod uwagę wspomniany wcześniej fakt, że metabolity wysiłku beztlenowego mogą powstawać także przy niezamierzonej aktywności fizycznej, chcąc wyizolować odpowiedź z mechanoreceptorów konieczne jest unikanie intensywnych ćwiczeń. Zapobiega to dodatkowej aktywacji metaboreceptorów na tym etapie. Wiąże się to z drugiej strony z niewielkimi zmianami w parametrach krążeniowych, przez co czyni badania bardziej wymagającymi i podatnymi na błąd. Konieczna jest wówczas staranna eliminacja czynników potencjalnie zakłócających, takich jak wpływ kofeiny, nikotyny, stanu emocjonalnego, zmienionego nastroju czy choćby niewyspania w dniu badania. Dodatkowym problemem mogącym wpływać na wynik badania są także mimowolne skurcze poszczególnych włókien mięśniowych konieczne do utrzymania odpowiedniej postawy ciała czy korekty toru ruchu biernie poruszanej kończyny. Względną eliminację powyższych czynników uzyskuje się poprzez staranne umocowanie poruszanych kończyn do cykloergometru, a także stabilizację ciała badanego przy pomocy narzędzi zewnętrznych (takich jak np. pasy). Konieczne jest także dokładne i wyczerpujące poinformowanie badanego o charakterze prowadzonego doświadczenia i konieczności powstrzymania się od jakichkolwiek ruchów, czy choćby napinania mięśni. Należy również pamiętać, że natężenie sygnału dośrodkowego z mechanoreceptorów zależy od rodzaju włókien mięśniowych, grupy mięśni, ich masy, a także poziomu wytrenowania [30].

5. CELE PRACY

Przedmiotem niniejszej pracy jest (i) ocena interakcji pomiędzy odpowiedzią z mechanoreceptorów i metaboreceptorów mięśni szkieletowych z wykorzystaniem modelu ćwiczeń biernych na cykloergometrze przy użyciu autorskiego protokołu badania – publikacja *„Passive bilateral leg cycling with concomitant regional circulatory occlusion for testing mechanoreflex-metaboreflex interactions in humans”*; (ii) podsumowanie stanu wiedzy oraz zaproponowanie nowych koncepcji i potencjalnych przyszłych ścieżek badawczych odnoszących się do interakcji EPR na podstawie przeglądu literatury, z uwzględnieniem udziału odpowiedzi z mechano- i metaboreceptorów w patogenezie chorób sercowo-naczyniowych - publikacja *„Understanding mechanoreflex and metaboreflex interactions – a great challenge”*.

6. PUBLIKACJE

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RESEARCH ARTICLE

Passive bilateral leg cycling with concomitant regional circulatory occlusion for testing mechanoreflex–metaboreflex interactions in humans

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Abstract

Purpose The exercise pressor reflex (EPR) plays a fundamental role in physiological reactions to exercise in humans and in the pathophysiology of cardiovascular disorders. There is no "gold standard" method for EPR assessment; therefore, we propose a new protocol for testing interactions between the muscle mechanoreflex and metaboreflex (major components of EPR).

Methods Thirty-four healthy subjects (mean age [± standard deviation] 24 ± 4 years, 22 men) were enrolled in the study. During the study, the hemodynamic and ventilatory parameters of these subjects were continuously monitored using our proposed assessment method. This assessment method consists of an initial 5-min rest period (baseline) followed by 5 min of passive cycling (PC) on an automated cycle ergometer (mechanoreceptor stimulation), after which tourniquet cuffs located bilaterally on the upper thighs are inflated for 3 min to evoke venous and arterial regional circulatory occlusion (CO) during PC (metaboreceptor stimulation). Deflation of the tourniquet cuffs is followed by a second 5 min of PC and finally by a 5-min recovery time. The control test comprises a 5-min rest period, followed by 3 min of CO only and a final 5-min recovery.

Results Mean arterial pressure (MAP) and minute ventilation (MV) increased significantly during PC (MAP: from 90 ± 9.3 to 95 ± 9.7 mmHg; MV: from 11.5 ± 2.5 to 13.5 ± 2.9 L/min; both $p < 0.05$) and again when CO was applied (MAP: from 95 ± 9.7 to 101 ± 11.0 mmHg; MV: from 13.5 ± 2.9 to 14.8 ± 3.8 L/min; both $p < 0.05$). In the control test there was a slight increase in MAP during CO (from 92 ± 10.5 to 94 ± 10.0 mmHg; $p < 0.05$) and no changes in the ventilatory parameters.

Conclusion Bilateral leg passive cycling with concomitant circulatory occlusion is a new, simple and effective method for testing interactions between the mechanoreflex and metaboreflex in humans.

Keywords Exercise pressor reflex · Mechanoreceptors · Metaboreceptors · Passive cycling · Circulatory occlusion

Introduction

The exercise pressor reflex plays a fundamental role in physiological responses to exercise in humans [1–4]. It is triggered by the stimulation of muscle metaboreceptors, specifically by the metabolites produced when muscles contract, and by muscle mechanoreceptors, through the mechanical distortion of contracting muscles [1–3], and leads to sympathetic activation and vagal withdrawal that typically manifests as increases in cardiac output and blood pressure [1–3, 5]. These changes enable the human body to maintain perfusion pressure, thereby improving the blood supply to working muscles during exercise [6]. These effects, observed even in passive exercise, are reinforced during voluntary movements by the central mechanism, commonly known as "central command," which is a complex feedforward mechanism originating in the brain [7]. The contribution of central

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command is a confounding factor and therefore should be excluded in experiments investigating the isolated role of muscle mechano- and metaboreflexes. Overactivity of the exercise pressor reflex has been associated with certain cardiovascular disorders, such as arterial hypertension and heart failure, and linked to exaggerated sympathetic outflow and hyperventilation, which are characteristics of these diseases [1, 2, 8–11].

Isolated responses from metaboreceptors can be measured with static exercise testing (e.g. handgrip test) and postexercise regional circulatory occlusion [8, 9], whereas the evaluation of muscle mechanoreflex sensitivity in humans remains a challenge. Several methods have been proposed, such as measuring passive movements [8, 14, 15], electrical stimulation [9, 16] and muscle stretching [17–20], but none of these are considered to be the "gold standard" due to inherent limitations. For example, the reproducibility of measurements of passive movements is a concern due to the measurements being performed by (different sets of) investigators or with custom-built equipment; electrostimulation evokes larger muscular metabolic perturbations than do voluntary movements [21–23]; and stretching muscles stimulate other types of mechanoreceptors than contracting muscles [1]. Even less is known about the interactions between the mechanoreflex and metaboreflex as very few studies have been performed [17–19, 24], all of which used the same muscle stretching protocol, and the results are highly discordant.

Here we propose a new method for testing the mechanoreflex–metaboreflex interactions in humans. The novelty of our method is that (1) it directly compares physiological responses to mechanoreceptor-only and mechanoreceptor–metaboreceptor activation; (2) it uses an exercise model resembling real-life activities (cycling); (3) it utilizes the "physiological" order of mechano- and metaboreflex stimulation (mechanoreceptors are stimulated first); and (4) it uses a commercially available, automated device for passive exercise (instead of custom-built devices or passive movements performed manually by a researcher). Although some of the aforementioned approaches considered separately are not novel (e.g. passive cycling [PC] has been used in an earlier study [14]), we are the first to address all of these factors simultaneously in a single experiment. The aim of this new strategy is to first induce isolated activation of the muscle mechanoreflex (using PC) and then to add metaboreflex stimulation (using circulatory occlusion [CO]) without stopping the PC so that both the mechano- and metaboreflexes are activated simultaneously. We hypothesized that PC alone would increase blood pressure and ventilation, that the subsequent addition of CO to PC would induce additional increases in these variables and that the values of these measures would return to the levels observed before PC and CO following cessation of these interventions.

Methods

Subjects

Thirty-four healthy volunteers participated in the study, of whom 22 were men. Mean age (± standard deviation [SD]), height, weight and body mass index (BMI) of the subjects was 24 ± 4 years, 178 ± 11 cm, 75 ± 15 kg and 23.7 ± 3.2 kg/m^2, respectively. No previous histories of chronic disease were reported. The volunteers were asked to avoid intense exercise and drinking coffee for 24 h before the tests and eating food or smoking cigarettes for 2 h before the tests.

All subjects received detailed information about the study and gave written informed consent prior to participation. The protocol was approved by the local ethics committee. All procedures were performed according to the Declaration of Helsinki of 1964 and its later amendments.

Experimental protocol and equipment

The protocol consists of two tests: the main test and the control test (Fig. 1). During each test, hemodynamic and ventilatory parameters are continuously and noninvasively monitored and recorded. Heart rate (HR, in bpm) is calculated from lead II of the electrocardiogram (BioAmp; ADInstruments, Dunedin, New Zealand). Mean mean arterial pressure (MAP, mmHg), systolic blood pressure (SBP, mmHg) and diastolic blood pressure (DBP, mmHg) are recorded at a sampling frequency of 250 Hz using the Nexfin device (BMEYE B.V., Amsterdam, The Netherlands) and

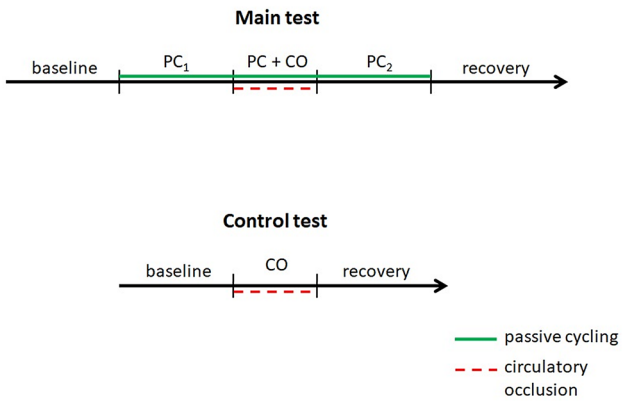

Fig. 1 The protocol consists of two tests (main test and control test) performed in a random order. The main test consists of five consecutive phases: a 5-min resting period; 5 min of passive cycling (PC_1); 3 min of circulatory occlusion during passive cycling ($PC + CO$); a second 5 min of PC after cessation of CO (PC_2); and a 5-min recovery period. The control test comprises three consecutive phases: a 5-min resting period, followed by 3 min of CO and rounded off with a 5-min recovery period

the volume-clamp method [25]. Stroke volume (SV, mL) and total peripheral resistance (TPR, dyn·s·cm^{-5}) are calculated from the recorded pressures using a pulse contour method; higher TPR units reflect stronger peripheral vasoconstriction. Minute ventilation (MV, L/min) is calculated from instantaneous values of the breathing rate (breaths/min) and tidal volume (L), measured using a differential pressure transducer (FE141 Spirometer; ADInstruments) and a breathing circuit consisting of an oronasal face mask (Hans Rudolph, Inc., Shawnee, KS, USA) and a two-way nonrebreathing T-shape valve (Hans Rudolph, Inc.) connected to a flowhead (MLT3000 L; ADInstruments) positioned on the expiratory arm of the breathing circuit. All data are recorded with an acquisition system (PowerLab; ADInstruments) at a sampling frequency of 1 kHz. To ensure that the central command was not engaged, we used a commercially available automated cycle ergometer (Medbike, BTL, UK) that is certified for use in rehabilitation of individuals with neural disorders.

The participants sit on the cycle ergometer with their knees flexed, their feet firmly attached to the pedals and their calves stabilized with rails connected to the pedals to prevent additional voluntary movements (Fig. 2). The distance between the seat and the ergometer is easily adjusted to ensure that there is a slight flexion in the knee when the foot is at its farthest point. The subjects are equipped with tourniquet cuffs attached bilaterally to their upper thighs during the entire protocol (Fig. 3). During the CO period of PC, the tourniquets are inflated (200 mmHg) to trap metabolites in the lower limbs. The pressure level selected is based on similar previously reported experiments [19, 26], taking into account gravitational factors [27] and allowing for the occlusion of venous and arterial circulation without evoking pain.

The main test comprises five consecutive phases: (1) a 5-min resting period; (2) 5 min of PC on the ergometer, with the pedaling rate set electronically at 60 rpm (mechanoreflex activation); (3) 3 min of bilateral upper thigh tourniquet cuff inflation to evoke venous and arterial regional CO during PC (activation of mechanoreflex and metaboreflex); (4) deflation of tourniquets and an additional 5 min of PC (mechanoreflex activation); and finally (5) a 5-min recovery period after cessation of PC. Each subject is instructed to relax and not to use any muscles during the course of study in order to minimize central command contribution. The participants are observed throughout the protocol to ensure they do not contract their muscles voluntarily.

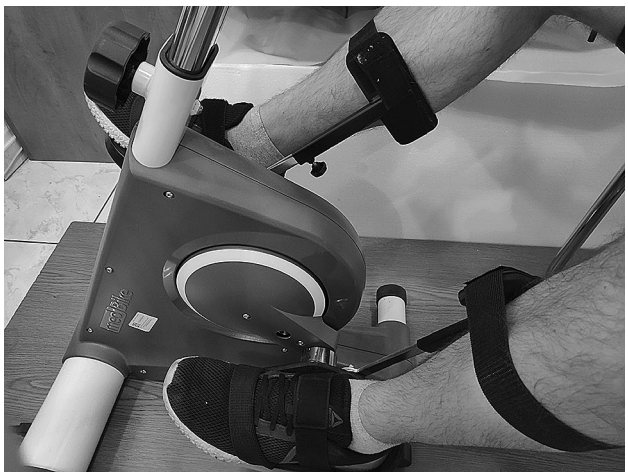

Fig. 2 Rails stabilizing a subject's feet

Fig. 3 Laboratory set-up

The control test is performed to ensure that CO does not evoke hemodynamic or respiratory changes due to, for example, psychological factors or compression-induced activation of the muscle mechanoreflex. It comprises three consecutive phases: (1) a 5-min resting period; (2) 3 min of bilateral upper thigh tourniquet cuff inflation; and (3) a 5-min recovery period.

The tests are performed in a random order during the same visit in our laboratory. All participants rest for 15 min before the procedures. After the experiment, the subjects are asked to assess the pain in their legs during cuff occlusion (0–10 scale) and perceived exertion during PC using a Borg scale (6–20 points) [28].

Statistical analysis

Data are presented as the mean ± SD. All percentage changes were calculated as the difference between the values from the two periods divided by the value from the first period. Hemodynamic and ventilatory parameters from each part of the two tests were analyzed with repeated-measures analysis of variance (ANOVA) and Duncan's post hoc test. The two-way repeated-measures ANOVA was used to compare the differences between

the main and control tests. *t* tests were used for group comparisons. A p value < 0.05 was considered to be significant.

Results

All hemodynamic and ventilatory parameters collected during the main and control tests are summarized in Tables 1 and 2, respectively. Plots for the main test are

Table 1 Hemodynamic and ventilatory parameters recorded in the five consecutive phases of the main test

Hemodynamic and ventilatory parameters[a]	Period of main test[b]					*p* value*			
	Baseline (5-min resting period)	PC_1	PC + CO	PC_2	Recovery	Baseline vs. PC_1	PC_1 vs. PC + CO	PC + CO vs. PC_2	PC_2 vs. recovery
MAP (mmHg)	90 ± 9.3	95 ± 9.7	101 ± 11.0	96 ± 9.8	93 ± 9.8	< 0.001	< 0.001	< 0.001	< 0.001
SBP (mmHg)	120 ± 14.1	130 ± 14.4	135 ± 15.7	131 ± 14.6	125 ± 13.3	< 0.001	< 0.001	0.002	< 0.001
DBP (mmHg)	72 ± 7.0	75 ± 7.4	80 ± 8.5	75 ± 7.4	74 ± 7.5	< 0.001	< 0.001	< 0.001	0.02
TPR ($dyn \cdot s \cdot cm^{-5}$)	1030 ± 225	952 ± 194	1003 ± 219	953 ± 197	1032 ± 231	< 0.001	< 0.001	< 0.001	< 0.001
SV (mL)	96 ± 16.1	109 ± 19.1	104 ± 19.7	109 ± 19.6	100 ± 15.6	< 0.001	< 0.001	< 0.001	< 0.001
HR (bpm)	76 ± 11.2	77 ± 11.8	81 ± 13.6	77 ± 11.6	75 ± 10.8	0.43	< 0.001	< 0.001	< 0.001
TV (L)	0.80 ± 0.3	0.84 ± 0.4	0.93 ± 0.5	0.87 ± 0.3	0.80 ± 0.3	0.49	0.07	0.17	0.22
BR (bpm)	15.3 ± 3.6	17.7 ± 4.0	17.3 ± 3.8	17.5 ± 3.9	15.4 ± 3.5	< 0.001	0.43	0.60	< 0.001
MV (L/min)	11.5 ± 2.5	13.5 ± 2.9	14.8 ± 3.8	14.1 ± 2.7	11.4 ± 2.6	0.02	< 0.001	0.16	< 0.001

Hemodynamic and ventilatory parameters in table are presented as the mean value ± standard deviation (SD) for each consecutive phase of the mean test

*Changes in each parameter are statistically significant according to repeated measures analysis of variance (ANOVA), when all phases are considered together. Note: for TV only, baseline vs. PC + CO and PC + CO vs. recovery are statistically significant according to Duncan's post hoc test ($p = 0.017$ and $p = 0.014$, respectively)

[a]*MAP* Mean arterial pressure, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TRP* total peripheral resistance, *SV* stroke volume, *HR* heart rate, *TV* tidal volume, *BR* breathing rate, *MV* minute ventilation

[b]PC_1 is the first passive cycling (PC) period; it follows baseline (the initial 5-min resting period) and is followed by passive cycling with circulatory occlusion (PC + CO). Once CO ceases, PC continues (PC_2). The last period is the recovery period. For full description, see section Experimental protocol and equipment

Table 2 Hemodynamic and ventilatory parameters recorded in the three consecutive phases of the control test

Hemodynamic and ventilatory parameters	Period of control test[a]			*p* value*	
	Baseline	CO	Recovery	Baseline vs. CO	CO vs Recovery
MAP, mmHg	92 ± 10.5	94 ± 10.0	92 ± 8.9	0.001	0.001
SBP, mmHg	123 ± 14.7	125 ± 13.7	123 ± 11.8	0.06	0.65
DBP, mmHg	73 ± 8.1	75 ± 7.8	73 ± 6.9	< 0.001	0.52
TPR, $dyn \cdot s \cdot cm^{-5}$	1024 ± 216	1061 ± 218	1035 ± 220	< 0.001	0.26
SV, mL	100 ± 14.9	99 ± 15.1	98 ± 14.3	0.45	0.70
HR, bpm	76 ± 10.1	76 ± 11.7	75 ± 11.2	0.79	0.63
TV, L	0.78 ± 0.3	0.86 ± 0.4	0.82 ± 0.3	0.10	0.46
BR, bpm	15.4 ± 3.6	15.6 ± 3.5	15.6 ± 3.6	0.67	0.71
MV, L/min	11.2 ± 2.3	12.4 ± 3.6	11.9 ± 2.8	0.06	0.33

Hemodynamic and ventilatory parameters in table are presented as the mean value ± SD for each consecutive phase of the control test

*Changes in the SBP, SV, HR, TV, BR and MV are not significant statistically according to repeated measures ANOVA when all periods are considered together

[a]Baseline period (5-min resting period) is followed by CO, which is turn is followed by the recovery period. For full description, see section Experimental protocol and equipment

depicted in Fig. 4. During the main test, all parameters exhibited significant changes from baseline when all periods were considered together (all ANOVA $p < 0.001$). The changes in blood pressure and ventilation presented consistent patterns, including an initial increase in response to PC that increased further with CO. A different response was observed in SV, which increased during PC and then decreased slightly with CO. TPR followed the opposite pattern, decreasing with PC and slightly increasing during CO. HR was not affected by PC, but increased during CO. After PC and CO were stopped, the parameters tended to return to the values observed before the respective interventions (see also Electronic Supplementary Material). A slight increase in MAP, DBP, TPR, but no significant changes in the other parameters measured were observed during the control test. The gain in MAP and DBP in the control test was smaller than that in the main test (both $p < 0.01$), while the increase in the TPR was similar between the two tests ($p = 0.19$). There was no difference in self-reported leg pain between the main and control tests (3.5 ± 1.9 vs. 3.6 ± 1.8 on a scale of 10; $p = 0.72$). The rating of perceived exertion in the main test during PC was 6.3 ± 1.1 (range 6–20 points).

Discussion

The aim of this study was to develop a new, safe, simple and automated method for testing mechanoreflex–metaboreflex interactions in humans. We hypothesized that (1) PC alone affects hemodynamic and ventilatory parameters and, in particular, increases blood pressure, SV and MV (mechanoreflex activation); (2) adding CO to PC leads to additional changes, such as additional increases in blood pressure and MV (metaboreflex activation); and (3) once PC and CO cease, these parameters tend to return to the values observed before the aforementioned interventions. The results of this study support our hypotheses. Therefore, for the first time, we present a novel protocol that is effective in stimulating mechano- and metaboreceptors simultaneously and physiologically in a single experiment, using commercially available equipment.

The first step of this study was to choose the optimal technique to stimulate the mechanoreflex. Various methods have been used in earlier studies, such as involuntary muscle contractions with the use of electrostimulation [9, 16]; muscle stretching performed by investigators [17, 19] or by applying custom-built devices [18, 20]; passive movements on tandem bicycle [15] or on custom-built equipment and

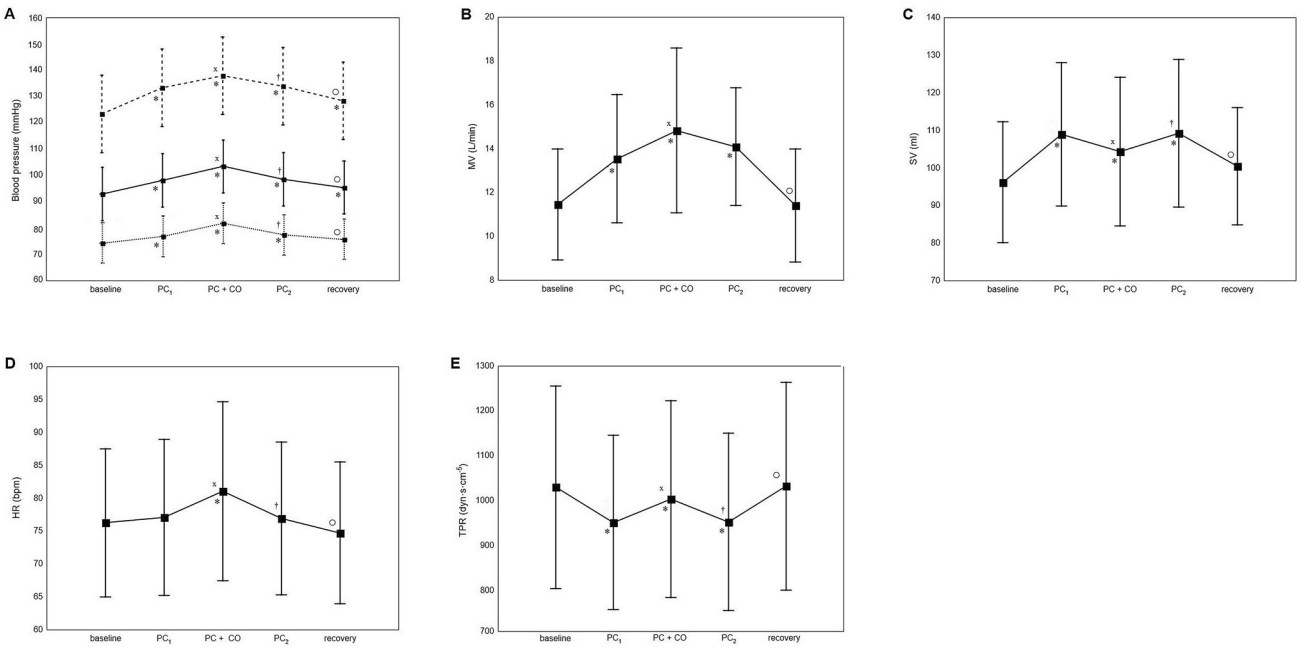

Fig. 4 Plots showing the mean values and standard deviations of the mean arterial pressure (*MAP*; **a**, solid line), systolic blood pressure (*SBP*; **a**, dashed line), diastolic blood pressure (*DBP*; **a**, dotted line), minute ventilation (*MV*; **b**), stroke volume (*SV*; **c**), heart rate (*HR*; **d**) and total peripheral resistance (*TPR*; **e**) in consecutive test periods of the main test. See caption to Fig. 1 for description of the phases of the main test: baseline, PC_1, PC + CO, PC_2, recovery period. Changes in each parameter are statistically significant according to repeated measures analysis of variance when all test periods are considered together. $^{*}p < 0.05$ between baseline and given period, $^{X}p < 0.05$ between PC_1 and PC + CO, $^{\dagger}p < 0.05$ between PC + CO and PC_2, $^{\circ}p < 0.05$ between PC_2 and PC + CO

cycle ergometers [8, 14]. All these methods were designed to reduce the possibility of metabolite accumulation, which can stimulate metaboreceptors, and to eliminate voluntary movements that engage central command. However, electrostimulation and muscle stretching appear to be less reliable than passive movement. The major concern with using electrostimulation is the potentially confounding effect of concomitant activation of muscle metaboreceptors, as it has been shown that electrostimulation induces metabolite production [21–23]. This effect may explain the highly discrepant observations across studies targeting small muscles (slight increase in MAP, no effect on HR) [9] and large muscles (large increase in MAP and HR) [16]. The effects of muscle stretching are also difficult to interpret, given that stretching and contracting muscles stimulate different types of mechanoreceptors [1]. Moreover, stretching does not mimic the physiological model of dynamic exercise.

The results of the few studies that have used stretching to stimulate mechanoreceptors are highly variable. Depending on the type of a muscle, stretching induced an increase in MAP without affecting HR (in agreement with our findings) [20] or a decrease in MAP with an increase in HR [17]. The latter result is inconsistent with those of other studies reporting that mechanoreceptor stimulation induces an increase in MAP [9, 14–16, 20, 29]. Taking these concerns into account, we decided to choose PC to induce the mechanoreflex. This technique was first used by Nobrega et al. [29] and caused elevations in MAP and SV. Similar results were observed in all subsequent experiments involving PC, regardless of whether a tandem bicycle [15] or ergometer was adapted [14]. The technique has also been shown to be applicable for patients with heart failure, in whom it evoked MV increases [26].

Our results confirm that PC stimulates mechanoreceptors, which—most notably—increased SBP (8%; from 120 ± 14 mmHg at baseline to 130 ± 14 mmHg at PC), SV (13%; from 96 ± 16 mL at baseline to 109 ± 19 mL at PC) and MV (17%; from 11 ± 2 L/min at baseline to 13 ± 3 L/min at PC). All parameters decreased after PC was stopped, which suggests that hemodynamic and ventilatory changes persist as long as the mechanoreceptors are stimulated. We used a fully automated and commercially available, adjustable cycle ergometer, originally designed for rehabilitation for paresis and paralysis in lower extremities; it may become the standard device for testing the mechanoreflex.

The second step of this study was to create a valuable method for testing mechanoreflex–metaboreflex interactions in humans. Virtually all protocols used in previous studies to test interactions between mechanoreceptors and metaboreceptors involved muscle stretching [17–19, 24] in the following order of tasks: (1) exercise was performed, (2) post-exercise CO was applied and (3) the muscle was stretched. Aside from the issues with muscle stretching mentioned before, this approach also does not engage both reflexes in a physiological and simultaneous manner. Rather, it creates an interim metabolic background that overlaps with stretching. Our protocol implements a completely different paradigm. First, we used PC, which is effective in stimulating isolated mechanoreceptors and evokes consistent cardiovascular and ventilatory effects; second, we introduced a different order of interventions, wherein CO is applied on the limbs that are being moved passively. This method imitates the physiological stimulation of particular receptors during physical activity. In general, the first response comes from mechanoreceptors, and then, when metabolites accumulate, the metaboreflex starts to induce hemodynamic changes [1, 7].

Previous studies on mechanoreflex–metaboreflex interactions yielded inconsistent results, even when the same methods and muscles were used. Stretching of the calf muscle during CO in one study resulted in an increase in SV and HR without any change in MAP [18], whereas in another study it induced only a small increase in DBP [19]. In yet another study, isolated wrist stretching did not result in any changes in hemodynamic parameters, with only a small increase in MAP occurring when CO was added to stretching [24]. Using our protocol, we observed that almost all of the tested parameters showed regular, characteristic patterns in response to PC and CO. Additional and significant increases in blood pressure and MV were induced by CO during PC, indicating that the stimulation of metaboreceptors resulted in an additional response. These observations suggest our new protocol is a reliable tool for testing mechanoreflex–metaboreflex interactions in humans, with greater validity than protocols based on muscle stretching.

Interestingly, we observed a pattern of changes in HR that suggests hyperadditive interactions between the metabo- and mechanoreflex. Specifically, HR was not affected by PC or CO separately, but it increased when CO was added to PC. A lack of HR response to PC has been shown previously [14, 29]. Similarly, the isolated stimulation of metaboreceptors does not produce essential increases in HR [7]. The potential influence of the metaboreflex on HR is masked, even during CO, by parasympathetic reactivation, mainly due to a loss of central command [30–32]. Barbosa et al. [33] showed that blockade of the exercise pressor reflex attenuates the HR response to active cycling, which indicates that the increase in HR is also not caused solely by central command. Considering these facts and the results of our study, we can conclude that the aforementioned increase in HR is probably a unique example of cooperation between the mechanoreflex and metaboreflex. Thus, to evoke a substantial increase in HR, both mechanoreceptors and metaboreceptors must be stimulated. The aggregate feedback from both types of receptors is essential to provide a sufficient stimulus that meets the threshold for a change in HR.

Finally, the exaggerated exercise pressor reflex in heart failure and hypertension is presumed to be a relevant component of autonomic dysfunction, which is characteristic of these disorders [1, 2, 8–11]. Regarding the global character of these conditions, it is extremely important to comprehensively understand the precise mechanisms of deterioration in the metabo- and mechanoreflex. This knowledge may enable development of targeted therapies for cardiovascular diseases, based on selective blockade of the components of the exercise pressor reflex [34] and specific exercise training [1]. Thus, introducing a new reliable method for testing the metabo- and mechanoreflex is essential for clinical purposes as well.

Limitations

It is difficult to eliminate voluntary muscle contractions when an individual's legs are being moved by an ergometer. To prevent this disturbance and stabilize subjects' calves, we use rails connected to the ergometer pedals (Fig. 2). The rails are standard parts of the ergometer. The subjects are also asked to relax, not to perform any movements and not to think about exercise. We did not notice any voluntary movements in the subjects throughout the protocol, and the mean physical effort rating on the Borg scale was very low. However, electromyography signals from the leg muscles were not recorded and thus central command contribution cannot be entirely excluded. We attributed the slight increase in MAP, DBP, and TPR in the control test to the modest accumulation of metabolites at rest and stimulation of metaboreceptors, although other factors cannot be excluded. It is unlikely that these changes were caused by pain, since we found no difference between the severity of pain in the limb caused by CO between the main and control tests.

Conclusions

Our protocol has, for the first time, introduced the application of CO during PC, which allows us to mimic a physiological model of dynamic exercise. With the use of this scheme, we confirmed our hypothesis that PC evokes increases in blood pressure, SV and MV (mechanoreflex activation); adding CO to PC induces additional increases in blood pressure and MV (metaboreflex activation); and these parameters return to the values observed before PC and CO after these interventions are stopped. Our model has several advantages since it involves a safe, simple and automated method of stimulating mechanoreceptors in a physiological way and, additionally, stimulating metaboreceptors without terminating mechanoreceptor activation. We believe that this method will provide new opportunities to study interactions between these two components of the exercise pressor reflex, which is an intriguing area of scientific research but remains to be fully elucidated.

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Author contributions AL, BP, WŁ, MFP and BP conceived and designed the study; AL and WŁ collected the data; AL wrote the first draft the manuscript; AL, BP, WŁ, MFP and BP checked and corrected manuscript. All authors read and approved the final draft of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Review Article

Understanding mechanoreflex and metaboreflex interactions – a great challenge

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ABSTRACT

The exercise pressor reflex (EPR) plays an essential role in cardiovascular and ventilatory responses to physical activity. Despite immense meaning and increasing validation of the EPR, there is no agreement on the character of interactions between its components and other reflexes in health and disease. The data addressing this issue remain incomplete and incoherent, partially due to various challenges in testing these pathways. The mounting evidence of EPR malfunction contribution to sympathetic over-activation in heart failure and other cardiovascular diseases shows clinical importance of comprehensive understanding of these mechanisms. In this review, we briefly summarize experiments focused on the issue of interactions between mechano-, metabo, chemo-, and baroreflex during exercise. We also address potential reasons of discrepancies in the results, identify gaps in this particular scientific area and propose notional pathways for future research. This article highlights the clinical importance of the EPR deterioration in heart failure pathophysiology and discusses potential therapies focused on restoring the reflex pathways. In addition, consideration is given to the latest sophisticated experiments in this area, underlining the need of changing the paradigm in EPR interactions studying – from teleological to mechanistic approach.

Keywords: Exercise pressor reflex, Mechanoreflex, Metaboreflex, Interactions, Heart failure

INTRODUCTION

One of the most essential parts of the reflex response to physical effort in human is the exercise pressor reflex (EPR) which consists of mechanoreflex and metaboreflex.[1-3] Deactivation of EPR in healthy human results in immediate deterioration of cardiovascular and ventilatory reaction to exercise, expressed by drop in heart rate (HR) (10%), blood pressure (8%), pulmonary ventilation (10%), hemoglobin saturation (3%), and also shortening of time to exhaustion (22%) as well as increase in peripheral muscle fatigue development (67%).[4] Despite their ultimate significance in exercise physiology, there is still no agreement on precise effects and interactions between mechano- and metaboreflex. Data from human studies are conflicting, showing that EPR testing is a remarkable challenge. Comprehensive understanding of metabo and mechanoreceptors stimulation effects is of great importance not only for the physiological basis but also for clinical purposes. Since EPR dysfunction has been associated with arterial hypertension and heart failure,[1,2,5-8] precise knowledge about its interactions is vital also for developing new targeted therapies in these conditions.[1,9] In this review, we present experiments addressing the issue of interactions between mechano- and metaboreceptors, as well as between EPR and other reflexes involved in cardiovascular control during exercise. We discuss potential reasons of discrepancy in

the results of the studies and attempt to synthesize available data into the coherent message. We also depict clinical importance of EPR and identify possible pathways for future research in this intriguing field.

METHODOLOGY

Scopus, PubMed, and Google Scholar databases have been searched using following keywords (inclusion criteria): Metaboreceptors, mechanoreceptors, chemoreceptors, baroreceptors, mechanoreflex, metaboreflex, chemoreflex, baroreflex, EPR, effects, and interactions. More than 300 papers have been initially considered to include into the review. In the first step, manual screening of abstracts was performed. The exclusion criteria comprised: Misguided methodology (i.e., inappropriate statistical tests), irrelevant results and conclusions, language other than English and journal not included in the "InCites Journal Citation Reports" list. Subsequently, the full texts were comprehensively read and assessed in terms of methodology (subjects, methods, and statistical tests) and the results-conclusions relationship. Papers that did not meet the quality criterion in these fields were excluded at this stage. Eventually, after final selection 76 original research articles, 13 review articles, three letters to the editor, two editorials, two symposium reports, and one exchange of views were analyzed to prepare this review.

EFFECTS OF MECHANO- AND METABOREFLEX – LESSONS FROM THE PAST

EPR is often considered as one reflex, which is misleading. It is highly important to distinct two components of this mechanism, since they exert different effects. Faultiness of the generalization approach was clearly shown in case of carotid bodies. For decades peripheral chemoreflex was considered simple pathway, it was believed that hypoxia and hypercapnia stimulate chemoreceptors in carotid bodies, which results in hyperventilation, vasoconstriction and general sympathoexcitation. Thanks to titanic scientific work and thoughtful research of many investigators with Prof. Paton on the front line – it turned out glomus cells are divided into sub-populations responsive only to hypoxia or hypercapnia exclusively and that the effect of stimulation (hyperventilation, vasoconstriction, or sympathoexcitation) depends on the kind of particular stimulus.[10,11] Therefore, when studying the EPR interactions, it is vital to first distinguish effects of individual components (mechano- and metaboreflex). One can speculate, that there are even more than two separate pathways in EPR, that is, different cells responsive for various metabolites or for different kinds of mechanical stimulation, which will be discussed in subsequent paragraphs. Although there is general agreement that both metabo- and mechanoreflex lead to vagal withdrawal and sympathoexcitation, assignment of precise cardiovascular effects to a particular component is not consistent among the studies.[1-3,12] The first reason of the discrepancy is that researchers use different methods of stimulating mechanoreceptors. In the past, this was achieved by passive cycling,[5,13-15] electrical stimulation,[6,16] or passive stretching.[17-20] Furthermore, different kind of muscles were stimulated in previous studies – thigh,[5,13-17] calf,[19,20] arm,[6] and forearm[21] muscles. Immensity of the methods proposed to evoke mechanoreceptors response shows that testing the mechanoreflex is a challenging task. Almost all of available data confirm that the main result of mechanoreceptors activation is increase in mean arterial pressure.[6,13-16,18,22,23] However, there is lack of concordance between particular studies in case of impact of mechanoreflex on other parameters, such as HR and stroke volume (SV). Fortunately, there is more consistency about cardiovascular effects of metaboreflex – the typical effect of metaboreceptors stimulation is gain in blood pressure resulting from increase in total peripheral resistance, which is generally evoked by static exercise, followed by circulatory occlusion (CO).[24,25]

THE CLINICAL IMPORTANCE OF MECHANO- AND METABOREFLEX INTERACTIONS

Although mechanoreflex and metaboreflex exert individual effects on cardiovascular system, the combined outcome of simultaneous stimulation of both types' receptors is not always a simple sum of them.[15,19,21,26] This fact is essential in clinical setting. Exercise training is well known for its beneficial health effects, particularly in cardiovascular diseases, such as hypertension, coronary artery disease, or heart failure.[27,28] On the other hand, EPR is impaired in these conditions which probably raises cardiovascular risk, decreases exercise capacity, and contributes to progression of muscle fatigue and dyspnea.[2,7,8,29-34] The deterioration of EPR is characterized partially by hyperactivity of mechanoreflex[1,2,7-9,23,31,35-44] and partially by alteration in metaboreflex activity. The character of the latter in heart failure is controversial – some experiments show abnormally high response of metaboreflex,[7,8,23,31,37-41,45,46] whereas other studies report diminished activation.[1,2,9,42-44] There are many factors that contribute to this discrepancy among the experiments, such as heterogeneous groups of patients, different exercise protocols, difficulties in isolating the metaboreflex, and different indicators of metaboreflex activation – muscle sympathetic nerve activity (MSNA), minute ventilation, blood pressure, or vascular resistance. Apart from the ambiguities, the most important aspect is to comprehend how do the metabo- and mechanoreflex act together, since in real-life conditions there is always general stimulation of EPR. However, the proportion of mechanoreflex activation to metaboreflex activation is different for various kinds of physical activity (i.e., static,

dynamic, and stretching).[1,24] Therefore, understanding of interactions between particular components of EPR and mechanisms of its impairment in particular disease is vital for clinical purposes: (i) to develop specific interventions for restoring normal response to physical activity and reducing the risk of exercising and (ii) to establish if given reflex pathway should be blocked or stimulated.

Several studies (both in animals and humans) proved that exercise training can revert deterioration of EPR in heart failure.[7,31,42,47-50] This reversion seems to have a tremendous significance to exercise capacity in patients. According to "muscle hypothesis" of heart failure and its neurohormonal component – contribution of EPR to exercise intolerance in heart failure patients is probably greater than contribution of hemodynamic alterations, such as decline in left ventricular ejection fraction and cardiac output.[31,32,51] This hypothesis explains startling observation that despite normalization of cardiovascular parameters in heart transplant recipients, exercise tolerance remains impaired.[52,53] Training programs applied in previous experiments included 6-week of forearm exercise,[7,50] 7-week treadmill training,[47] 4-week inspiratory muscle training,[48] 6-month exercise-based cardiac rehabilitation[49] resulted mainly in reduction in blood pressure, minute ventilation, vascular resistance, and MSNA in response to acute physical activity. Data from available studies do not allow to make conclusions on the mechanisms of these advantageous effects. Unfortunately, lack of mechanistic studies is a general issue with EPR testing.[54] Lately, it was suggested that recruitment of more muscle mass in exercise programs may be beneficial in restoring normal EPR functioning in patients with heart failure.[32] However, further studies are warranted to determine the optimal training regimen.

Very little is known about the potential pharmacological agents that could modulate EPR in pathological condition. Intra-arterial gadolinium injections were used to attenuate response from mechanoreceptors in cats, mice, and rats,[54-57] although their usefulness was never confirmed in human studies. Experiments using intra-arterial injection of another agent indomethacin – showed encouraging results. This inhibitor of prostaglandin synthesis exhibited potential of reducing mechanoreflex activity in both cats[58] and humans.[59] Unfortunately, there were no further studies encompassing patients with heart failure or even healthy humans but using different route of administration. Naturally, intra-arterial injections could not be considered as a long-term treatment method in a real-life clinical setting. Chaiyakul *et al*.[60] displayed that stimulation of serotonin receptors (5-HT_{1A}) within rostral ventrolateral medulla attenuates EPR response to static exercise in rats. Considering that agonists of 5-HT_{1A} receptors are widely used in psychiatry (buspirone, tandospirone, vilazodone, and vortioxetine) it would be very interesting to assess their effects on EPR in patients with concomitant heart failure or other cardiovascular comorbidities. Very interesting contributions have been done using analgesic balm with capsaicin – an active compound of chili peppers.[61-63] First, the balm was used in decerebrated cats on the skin surface over muscles and significantly decreased blood pressure reflex responses to electrically-evoked static contractions.[62,63] Then, the approach was translated on healthy humans and confirmed that topically applied capsaicin attenuated blood pressure and MSNA during metaboreflex activation.[61] Further studies in heart failure patients is highly warranted. Lately, Li and Garry opened new opportunities in EPR interactions testing in health and variety of diseases.[54] They introduced a novel murine mode, which allows for more comprehensive investigation of mechano- and metaboreflex, due to unfettered genetic modification possibilities and exploration of the molecular mechanisms of EPR. We do hope the murine model will contribute to discovering and development of new pharmacological agents targeted at EPR.

PROTOCOLS FOR TESTING INTERACTIONS

The available data on the interactions between mechano- and metaboreflex are very limited. Most of experiments use similar method: First exercise, then CO and at last muscle stretching during CO.[17,19-21] In recent paper from our laboratory, we proposed a different, novel method for testing mechanoreflex-metaboreflex interactions.[15] In this study, participants were subjected to bilateral passive cycling, during which bilateral leg CO was added. The alternative method of mechanoreceptors stimulation and different order of interventions were performed to mimic physiological model of dynamic exercise. To activate metaboreflex all of the available studies report inflation of tourniquets to 200[15,19,20] or 250 mmHg[17,21,64] which ensures that both arterial and venous circulation are occluded.

THE EFFECTS OF SIMULTANOEUS MECHANO- AND METABORECEPTORS ACTIVATION

Animal research suggests metabolites sensitize mechanoreceptors.[65-68] Unfortunately, there is some inconsistency in results of particular human studies. While metaboreceptors activation were always achieved by CO, to obtain mechanoreflex response – thigh,[15,17,64] calf,[19,20] or forearm[21] muscles were subjected to static stretching,[17,19-21] dynamic stretching,[17] passive movement performed manually by a researcher[64] or passive cycling.[15] This diversity resulted in different observations. All analyzed studies are presented comprehensively in [Table 1]. One study reported hyperadditive interaction between mechano- and metaboreflex in case of muscle sympathetic nerve activity (MSNA) and mean arterial pressure.[21] One experiment revealed hyperadditive reaction in case of heart rate and

Table 1: Studies focused on metaboreflex-mechanoreflex interactions.

Authors Title	Subjects	Mechanoreflex stimulation method	Metaboreflex stimulation method	Mechanoreflex stimulation effect	Metaboreflex stimulation effect	Simultaneous stimulation effect
Venturelli *et al.* Central and peripheral responses (…)	10 healthy volunteers (all males) Age: 25±1 years Height: 181±2 cm Weight: 77±2 kg	Unilateral passive knee stretching (static and dynamic)	Unilateral CO (250 mmHg)	Static stretch: (+) HR, CO (slight) (−) MAP (slight) Dynamic stretch: (+) HR, CO (−) MAP (slight)	n/a (no metaboreflex stimulation alone)	With static stretch: (+) MAP (slight) With dynamic stretch: no changes
White *et al.* The pulmonary vascular response (…)	9 healthy volunteers (4 males) Age: 27±4 years Height: n/a Weight: n/a	Unilateral passive static calf stretching	Unilateral post-exercise CO (250 mmHg)	No changes	(+) SPAP, MAP, SBP, DBP, (maintained elevation)	(+) SPAP, MAP, SBP, DBP (maintained elevation, similar to metaboreflex stimulation alone), **CO, HR, SV**
Fisher *et al.* Cardiovascular responses to human calf (…)	8 volunteers (7 males) Age: 22±1 years Height: 180±2 cm Weight: 76±3 kg	Unilateral passive static calf stretching	Unilateral post-exercise CO (200 mmHg) preceded by 3 different initial workloads	(+) DBP	(+) DBP (maintained elevation)	(+) DBP (irrespectible of initial workload)
Cui *et al.* Effects of muscle metabolites on responses (…)	12 healthy volunteers (8 males) Age: 26±1 years Height: 178±3 cm Weight: 76±2 kg	Unilateral passive wrist stretching (static and dynamic)	Unilateral post-exercise CO (250 mmHg)	Static stretch: no changes Dynamic stretch: (+) MSNA (transient)	(+) MSNA, MAP, (maintained elevation)	With static stretch: **(+) MSNA, MAP** (greater than during metaboreflex stimulation alone) With dynamic stretch: Not available
McDaniel *et al.* Central and peripheral contributors (…)	9 healthy volunteers (all males) Age: 33±9 years Height: 180±8 cm Weight: 85±17 kg	Unilateral passive movement of the knee performed manually by a researcher	Unilateral CO (250 mmHg)	(+) SV, HR, CO (transient) (−) MAP (transient)	(+) MAP (transient)	(+) MAP; SV, HR, CO (transient, slightly smaller than during mechanoreflex stimulation alone)
Lis *et al.* Passive bilateral leg cycling (…)	34 healthy volunteers (22 males) Age: 24±4 years Height: 178±11 cm Weight: 75±15 kg	Bilateral passive cycling	Bilateral CO (200 mmHg)	(+) MAP, SBP, DBP, SV, MV (−) TPR	(+) MAP, DBP, TPR (slight)	(+) MAP, SBP, DBP, MV, **HR**

The table shows particular studies and data on their authors, subjects, methods, and effects of particular interventions. Age, height, and weight are shown as mean values ± standard deviations. Analyzed parameters comprise; MAP: Mean arterial pressure, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, TPR: Total peripheral resistance, SV: Stroke volume, HR: Heart rate, MV: Minute ventilation and MSNA: Muscle sympathetic nerve activity, CO: Circulatory occlusion. Parameters in bold presented hyperadditive pattern of response. n/a: Not available

additive when it came to mean arterial pressure. [15] In one study there was hyperadditivity in case of cardiac output, heart rate and stroke volume.[19] One experiment showed simple additivity in case of diastolic blood pressure[20] and two postulated marginal interactions between these reflexes[17,66] (experiment of McDaniel *et al.*[66] was conducted to assess the role of hyperemia during passive movement, although results can be also addressed to the metaboreflex-mechanoreflex

interactions). One can say that the discrepancies come from different kind of methods used in particular studies. However, even when the same method was applied (static calf stretching with CO) the results were different. Fisher *et al*.[20] showed that both metaboreflex and mechanoreflex increase diastolic blood pressure, but there is no additional gain when both reflexes act together. They also reported that not metabo- nor mechanoreflex or simultaneous stimulation had any effect on HR. Inversely, White *et al*.[19] displayed that static calf stretching alone did not result in any alteration, but when performed during CO – evoked increase of HR and SV. This is partially consistent with results of study from our laboratory[15] in which not passive cycling nor CO affected HR, but passive cycling during CO resulted in increase of this parameter. This can be certainly interpreted as an example of hyperadditivity between these two reflexes.

It should be underlined that the character of interaction is not always positive or neutral. It might be also negative, although it does not mean that it is not beneficial. It has been perfectly shown on pulmonary arteries.[19] While stimulation of metaboreceptors with CO evoked increase in pulmonary vascular resistance, adding mechanoreflex activation with calf stretching attenuated this reaction, thus facilitating blood flow through the pulmonary vascular bed during exercise.

ISSUES WITH TESTING EPR INTERACTIONS

The main issue that we identified is the choice of method for stimulating mechanoreceptors. The majority of experiments use muscle stretching to activate mechanoreflex. This approach, based on an assumption that stretch stimulates the same Group III afferents as does contraction, is unfortunately erroneus. Hayes, Kindig and Kaufman showed in their excellent animal study, that out of 30 Group III mechanosensitive muscle afferents, 18 responded to contraction, and 14 to stretch, although only seven responded to both stimuli.[69] Furthermore, conduction velocities of the afferents differed depending on the kind of stimulus.[69] The evidence of this diversity was provided also in humans by Gladwell *et al*., who studied cardiovascular reactions to passive stretching during alterations in vagal tone.[70] They proposed to distinct so called "tentonoreceptors," which would be a special subgroup of mechanoreceptors mediating increase in HR but not blood pressure, particularly in response to stretching.[70,71] Static stretching does not seem to be an optimal technique of mechanoreceptors stimulation, also for another reason – in some experiments it did not evoke any reactions when performed alone, regardless of the type of the muscle.[19,21] The situation was slightly different when dynamic stretching or dynamic passive movement was performed – this resulted in only transient alterations in cardiovascular parameters and MSNA.[21,64] Apparently, mechanoreceptors are very heterogenous in their nature and reflex effect depends on the location of the receptor (thigh, calf, arm, etc.) and kind of stimulus (stretching, contracting). Researchers need to be very careful when choosing the method in their experiment and extrapolating the results on general mechanoreflex functioning. Surely, we identify different kinds of stretching of various muscles as a main reason of the discrepancy in results of available studies. In our opinion, all of the aforementioned facts should force researchers to seek one, unified protocol for testing mechanoreflex-metaboreflex interactions. That is why we proposed passive bilateral cycling with concomitant CO.[15]

The use of CO to activate the metaboreflex is not so controversial, although some authors indicate, that the sympathoexcitation after CO might result from unloading of cardiopulmonary receptors.[72,73] That is why it is essential to occlude both arterial and venous circulation. This approach does not reduce the relative venous return and therefore enables to link the observed cardiovascular effects to metaboreceptors stimulation.[74] There is, however, another issue with CO - most of the studies use post-exercise CO, which precludes quantitative assessment of interaction (the onset of stimulation of metaboreceptors appears right after the end of mechanoreceptors activation).

The other reasons for difficulties in the assessment of mechano- and metaboreflex interactions are listed below:

- Some of the Type III and IV afferents may be polymodal – susceptible both to mechanical distortion and metabolite accumulation (data from animal studies)[65,67]
- Difficulty in mimicking physiological conditions that apply only to one component of the EPR (only mechanical distortion or only metabolite accumulation)
- Need for exclusion of central command
- Interactions with other reflexes (baroreflex and chemoreflex)[16,26,75,76]
- Lack of control group in some studies (should be mechanoreflex alone, metaboreflex alone, and mechanoreflex + metaboreflex)[17,64]
- Lack of complete information about changes of each parameters (e.g., only diastolic blood pressure and HR showed in results).[20]

WHAT ARE THE MECHANOREFLEX-METABOREFLEX INTERACTIONS?

Most of authors agree that there is at least additive interaction between mechano- and metaboreflex in case of blood pressure – according to some investigators even hyperadditive [Table 1]. Available data suggest that it is similar with HR. These interactions seem reasonable, since they help to provide blood supply to muscles engaged in exercise. However, some methods might not allow to display these reactions. It is worth to notice that in majority of studies the number of participants varied between 8 and 12[17,19-21,64]

and only in one it was 34.[15] This raises assumptions that some interactions could not be revealed due to the small group size effect. Nevertheless, based on the available studies, we can also identify negative interaction between these two reflexes in case of the pulmonary vascular resistance and positive in case of cardiac output.

INTERACTIONS OF EPR WITH OTHER REFLEXES

Mechano- and metaboreflex, as part of a greater mechanism that respond to physical activity, also do interact with other reflexes, namely, chemoreflex[26,75,77] and carotid baroreflex.[16,76] In their elegant study Silva *et al*.[26] exposed healthy subjects to inhalation of 12% O_2 during isocapnia to stimulate the peripheral chemoreflex with and without concomitant passive knee movement (mechanoreceptors activation). They reported hyperadditive interactions between both reflexes in case of minute ventilation. Interestingly, it was achieved probably due to different pathways operating in both reflexes, since mechanoreceptors stimulation resulted in an increase of breathing frequency, whereas chemoreflex activation produced gain in tidal volume. Surely, this cooperation enables potentiation of ventilation during physical activity to provide more oxygen to working muscles. This suggests that the hyperadditive reaction can occur when particular parameter is modified by different reflexes through distinct pathways. Similarly, hyperadditive interaction between EPR and peripheral chemoreflex was reported recently in case of blood pressure and HR.[75] Authors used sophisticated method with intrathecal injection of fentanyl to block EPR afferent fibers in three different breathing protocols (ambient air, normocapnic hypoxia, and normoxic hypercapnia). They displayed also that peripheral chemoreflex and EPR act in a hypoadditive manner in case of responses in leg blood flow and leg vascular conductance. Unfortunately, the method they used did not allow to distinguish which part of EPR (mechanoreflex, metaboreflex, or both) was responsible for observed reactions. Another great contribution was made by Bruce and White,[77] who performed four different protocols of mechano- and metaboreflex activation during normoxic hypercapnia or ambient air breathing. They provided an evidence of hyperadditive interaction between central chemoreflex and isolate mechano- or metaboreflex in case of minute ventilation.[77] Likewise, the blood pressure response was hyperadditive when mechanoreflex and central chemoreflex acted together.[77] There were also other contributions focused on simultaneous activation of EPR and chemoreflex, although use of voluntary exercise without intrathecal fentanyl does not allow to exclude central command and therefore address results to EPR itself.[78-82]

Studies on interactions between EPR and carotid baroreflex also yielded interesting results. Hureau *et al*.[16] used lumbar intrathecal fentanyl to block EPR afferent fibers in humans during electrically evoked and voluntary knee extension. In their cleverly designed experiment they revealed that EPR does not influence carotid baroreflex sensitivity, but resets its operation point for both blood pressure and HR during exercise, thus allowing increase in both parameters when it is crucial. There is also one more enlightening fact that arises from the aforementioned study – fentanyl injection did not change resting mean arterial pressure and HR. This suggests that the input from mechano- and metaboreceptors is not tonic but appears only when exercise is performed. Therefore – in case of future therapeutic goals – simple blockade of the EPR will not be successful in hypertension at rest. Unfortunately, as authors decided to choose electrical stimulation to induce isometric muscle contraction, we cannot attribute these results particularly to mechano- or metaboreflex. This is mainly due to the fact, that electrostimulation evokes even greater metabolic perturbation than voluntary exercise[83-85] and therefore contribution of metaboreflex cannot be excluded. Nevertheless, in another study on animals it was shown that the mechanoreflex activation is responsible for resetting of the baroreflex.[86] A kind of complement to this story may be an excellent study of Kaur *et al*.[76] focused on interactions between metaboreflex and carotid baroreflex in canine. Authors used graded reductions in hindlimb blood flow during dynamic exercise (metaboreflex activation), followed by simultaneous bilateral carotid occlusion (baroreflex activation). The magnitude of an increase in blood pressure denoted simple additive interaction between these two reflexes, although the mechanisms for the response were different. Metaboreflex-induced increase in blood pressure occurred due to gain in cardiac output, hart rate, and ventricular contractility, whereas baroreflex evoked further rise through decrease in vascular conductance. Interestingly, this decrease occurred less in the ischemic hindlimb vasculature than in all remaining vascular beds, thus redirecting blood flow to the ischemic muscle. This unique preferential peripheral vasoconstriction protected active hindlimb muscle against the progression of ischemia. Unfortunately, this observation was never confirmed in human studies.

WHERE THE INTERACTIONS TAKE PLACE?

It is still not known on which level of nervous systems interactions of EPR take place. When it comes to interactions between peripheral chemoreflex and mechanoreflex, as Silva *et al*.[26] suggested, the interaction probably occurs in the central nervous system (the nucleus tractus solitarii or the retrotrapezoid nucleus), since there is no connection between these two pathways before it. For baroreflex-mechanoreflex

interactions site, Gladwell *et al.*[70] proposed cardiac vagal neurons (parts of the nucleus ambiguus and the dorsal motor nucleus of the vagus). The issue is much more complex regarding internal interactions between metabo- and mechanoreflex – their receptors might even have the same afferent fibers.[34,87-89] For separate fibers – the first synapse is located in the spinal cord's dorsal horn (Rexed's laminae I, II, V, and X)[1,90,91] and this can be first potential location to interact. The primary site of EPR is probably the nucleus tractus solitarii,[1,91] which is the next probable interaction's place. This is very likely, since in animal experiments it was found that the nucleus tractus solitarii is a complex site of various convergence patterns for baroreflex, chemoreflex, and Hering-Breuer reflex.[92,93] Other neurons that are engaged in EPR and could be presumptive interaction's sites are nucleus ambiguous, rostral ventral medulla, lateral tegmental field, and caudal ventrolateral medulla.[1,94,95] Nevertheless, all of the possible mechanisms given above are only speculations, that still need to be tested in mechanistic studies. All interactions and their presumable neuroanatomical locations are depicted schematically on [Figure 1].

PERSPECTIVES

Up to date, the issue of EPR interactions did not receive much attention from researchers. Regarding available data, we can state that the effects of mechanoreceptors activation and interactions between mechano- and metaboreceptors are complex and depend on the method of testing. That is presumably because of stimulating different types of mechanoreceptors with various methods, since mechanoreceptors seem to constitute a heterogenous group. Nevertheless, there is most likely hyperadditive interaction in case of blood pressure and HR, as well as hypoadditive interactions in case of pulmonary vascular resistance. In addition, hyperadditive interrelation in case of blood pressure, HR, and minute ventilation was identified between EPR and chemoreflex (both central and peripheral). EPR has been also proved to change baroreflex setpoint during physical activity. Apart from simply additive interaction between metaboreflex and baroreflex, the latter probably helps redirecting blood flow to the ischemic muscle during simultaneous stimulation. Given the gaps in available research, a comprehensive experiment comparing directly different methods of testing mechano- and metaboreflex simultaneously is warranted. The number of subjects should be certainly higher than usual 10, powered to accurately display particular interactions.

Surely, the big gap in the discussed area is ventilatory effects of EPR interactions. The majority of data center on cardiovascular reactions, whereas muscle afferent feedback is responsible for approximately half of the ventilatory response during moderate physical activity![34,96] This issue has also essential clinical meaning – the dyspnea resulted from abnormally augmented EPR in pathological condition awaited an exceptional term "breathless with over-excitement."[34] We believe that progress in research focused on ventilatory effects of interactions between mechano-, metabo-, and chemoreflex will open the way to search for novel therapies, targeted on the components of EPR. We also acknowledge that there is a need for changing a paradigm in pressor reflex testing – from teleological to mechanistic approach [Figure 2]. Fortunately, last year brought studies focused on molecular alterations of EPR in heart failure patients[97] and creating animal model of mechano- and metaboreflex

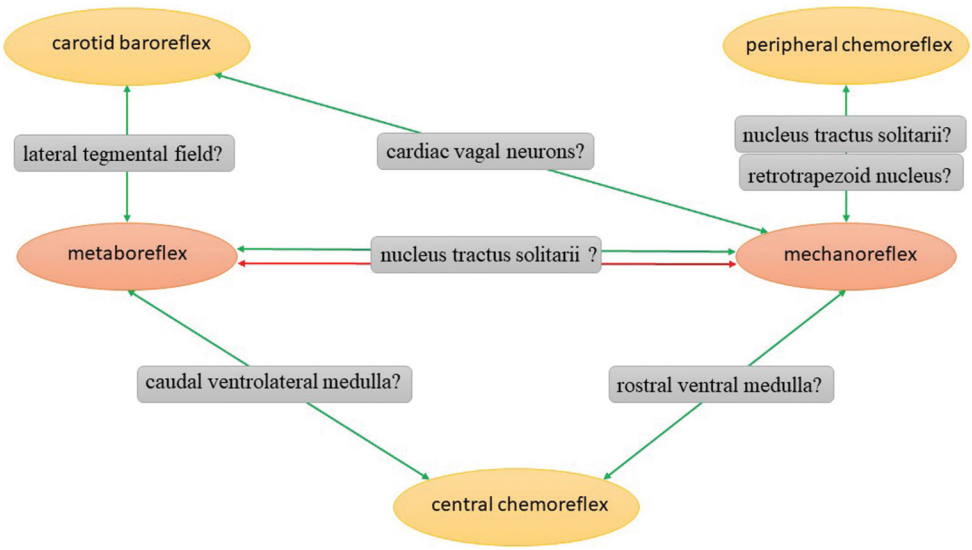

Figure 1: The scheme shows interactions of exercise pressor reflex and their presumable neuroanatomical locations. Green arrows symbolize positive interactions, whereas red arrows reflect negative interactions.

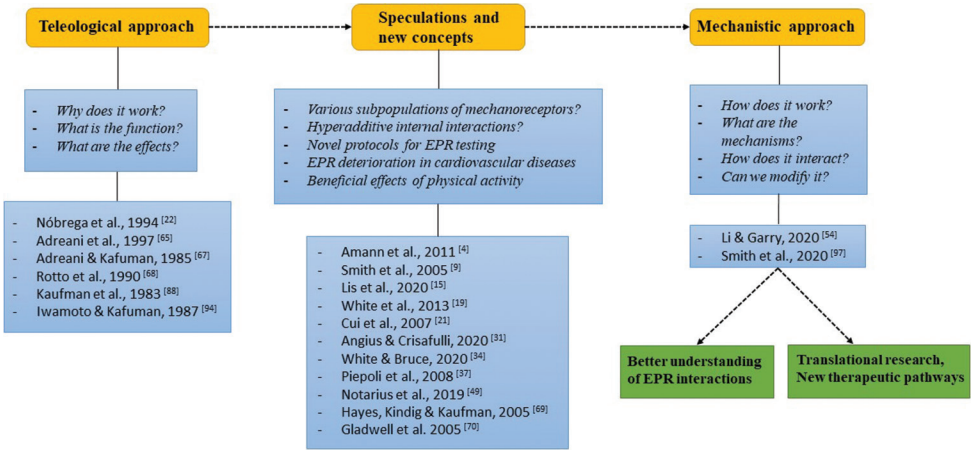

Figure 2: The flow chart diagram depicts the concept of changing paradigm in exercise pressor reflex (EPR) testing. Starting with teleological approach and experiments that revealed functions and effects of EPR, going through speculations and new concepts made on the basis of teleological studies, ending on mechanistic approach, focused on precise mechanisms which enable better understanding of EPR interactions and opening new therapeutic possibilities.

allowing for genetic modifications and more profound exploration of reflex deterioration mechanisms.[54] We do hope that more abundant mechanistic knowledge will allow for discover and develop pharmacological agents, possible to use in patients with defective EPR. However, even having effective pharmacotherapy, we cannot forget about the exercise training. Despite the solid evidence of salutary effects of training programs in patients with impaired EPR, this topic still needs much more exploration, focused on the mechanisms, and optimal regimens of exercise.

Finally, studying comprehensively this intriguing, still not fully elucidated topic, one should always remember to consider not only the isolate reflexes, but interactions between them, as to "not lose sight of the forest for the trees."

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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7. WNIOSKI

1. Bierne obustronne pedałowanie z jednoczesnym miejscowym zatrzymaniem krążenia w kończynach dolnych jest nowoczesną, skuteczną i bezpieczną metodą badania interakcji pomiędzy odpowiedzią z mechanoreceptorów i metaboreceptorów mięśni szkieletowych u osób zdrowych.

2. Pobudzenie mechanoreceptorów mięśni szkieletowych wywołuje wzrost ciśnienia tętniczego krwi, objętości wyrzutowej serca i wentylacji minutowej u osób zdrowych.

3. Dodanie odpowiedzi z metaboreceptorów do trwającej aktywacji mechanoreceptorów mięśni szkieletowych powoduje dalszy wzrost ciśnienia tętniczego krwi i wentylacji minutowej.

4. Odpowiedź z mechanoreceptorów i metaboreceptorów mięśni szkieletowych u osób zdrowych charakteryzuje się hiperaddytywnością w kontekście częstości akcji serca.

5. Konieczne są dalsze badania mechanistyczne nad interakcjami pomiędzy wysiłkowym odruchem presyjnym a pozostałymi odruchami zaangażowanymi w regulację autonomiczną podczas wysiłku fizycznego, co może pozwolić na wprowadzenie nowych metod leczenia ukierunkowanych na modulację receptorów i pozostałych komponent powyższych odruchów.

8. PODSUMOWANIE

Odruch z mechanoreceptorów i metaboreceptorów mięśni szkieletowych, ma niebagatelne znaczenie nie tylko w fizjologii wysiłku fizycznego, ale także w patogenezie chorób sercowo-naczyniowych, takich jak nadciśnienie tętnicze, choroba niedokrwienna serca czy niewydolność serca. Kluczowe dla zrozumienia reakcji organizmu na wysiłek fizyczny jest poznanie interakcji pomiędzy powyższymi odruchami. Pomimo doniosłego znaczenia, zagadnienie to nie doczekało się dotychczas wielu badań, a dostępne dane odznaczają się niejednorodnością i niską powtarzalnością. Dotychczasowe publikacje z zakresu interakcji wysiłkowego odruchu presyjnego zostały syntetycznie omówione w publikacji *„Understanding mechanoreflex and metaboreflex interactions – a great challenge”.* Szczególną uwagę poświęcono metodologii badania poszczególnych łuków odruchowych i dyskrepancji pomiędzy otrzymywanymi przez badaczy wynikami, z heterogennością mechanoreceptorów na czele. Podkreślono także powiązania odpowiedzi z mechano- i metaboreceptorów mięśni szkieletowych z pozostałymi mechanizmami odruchowymi biorącymi udział w regulacji autonomicznej podczas aktywności fizycznej – odruchem z chemoreceptorów (zarówno obwodowych jak i ośrodkowych) oraz odruchem z baroreceptorów. Zwrócono ponadto uwagę na udział wysiłkowego odruchu presyjnego i jego interakcji w rozwoju chorób sercowo-naczyniowych, a w szczególności niewydolności serca. Ukazano potencjalne ścieżki terapeutyczne mogące odwrócić niekorzystne efekty autonomiczne wynikające z uszkodzenia wysiłkowego odruchu presyjnego w tej chorobie. Pośród nich wskazano na szczególną rolę treningu fizycznego.

W publikacji *„Passive bilateral leg cycling with concomitant regional circulatory occlusion for testing mechanoreflex-metaboreflex interactions in humans”* po raz pierwszy wprowadzono skuteczną, nowoczesną, powtarzalną i bezpieczną metodę jednoczesnej stymulacji mechano- i metaboreceptorów naśladującą fizjologiczny wysiłek fizyczny. Dzięki jej zastosowaniu sformułowano hipotezę hiperaddytywnej interakcji pomiędzy obydwoma odruchami w kontekście częstości akcji serca. Użycie komercyjnego cykloergometru (pierwotnie zaprojektowanego do ćwiczeń biernych dla pacjentów z niedowładem kończyn dolnych) z pewnością ułatwi stosowanie zaprezentowanego protokołu przez badaczy na całym świecie. Pozwoli to na dokładniejsze poznanie relacji pomiędzy obiema składowymi wysiłkowego odruchu presyjnego a innymi odruchami zaangażowanymi w reakcję na wysiłek

fizyczny, co w przyszłości może zaowocować wprowadzeniem nowych skutecznych metod leczenia, ukierunkowanych na modulację poszczególnych łuków odruchowych. Należy w tym miejscu podkreślić, że przedstawiony protokół i wyniki badań nie wyczerpują zagadnienia, a stanowią punkt wyjścia dla kolejnych eksperymentów, tym razem skupionych na mechanizmach opisanych interakcji. Koncepcja zmiany paradygmatu w badaniach nad wysiłkowym odruchem presyjnym - od podejścia teleologicznego do mechanistycznego – została zaprezentowana w publikacji *„Understanding mechanoreflex and metaboreflex interactions – a great challenge".* Taka ścieżka z pewnością otworzy nowy etap w badaniach nad odpowiedzią z mechanoreceptorów i metaboreceptorów mięśni szkieletowych i umożliwi przełożenie wiedzy pochodzącej z nauk podstawowych (takich jak fizjologia) na nowoczesne rozwiązania kliniczne, w szczególności w dziedzinie kardiologii. Niniejszy cykl publikacji stanowi istotny wkład w pogłębienie wiedzy i wzbogacenie metodologii dotyczącej badania interakcji pomiędzy odruchami z mechano- i metaboreceptorów, wskazując przy tym na obecne luki w danych naukowych i perspektywy na przyszłość. Udowadnia także, że tematyka regulacji odruchowej w odpowiedzi na wysiłek fizyczny jest wciąż aktualna i atrakcyjna, zarówno z punktu widzenia fizjologii jak i kardiologii.

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10. OŚWIADCZENIA WSPÓŁAUTORÓW

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Oświadczam, że w pracy:

Passive bilateral leg cycling with concomitant regional circulatory occlusion for testing mechanoreflex-metaboreflex interactions in humans; Adrian Lis, **Wojciech Łopusiewicz**, Massimo F. Piepoli, Beata Ponikowska, Bartłomiej Paleczny. Clin. Auton. Res. 30, 549–556 (2020).

mój udział polegał na:

- pomocy w rekrutacji badanych

- pomocy w wykonaniu eksperymentu

Wojciech Łopusiewicz

Podpis

SERVIZIO SANITARIO REGIONALE
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Dipartimento di Emergenza Urgenza
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il direttore

Piacenza, 12th May 2021

STATEMENT

I hereby declare, that in article:

Passive bilateral leg cycling with concomitant regional circulatory occlusion for testing mechanoreflex-metaboreflex interactions in humans; Adrian Lis, Wojciech Łopusiewicz, Massimo F. Piepoli, Beata Ponikowska, Bartłomiej Paleczny. Clin. Auton. Res. 30, 549–556 (2020).

my contribution included:
- assistance in study conception and design
- corrections of the manuscript

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- pomocy w zaprojektowaniu eksperymentu,
- wsparciu merytorycznym w analizie i interpretacji wyników,
- pomocy przy pisaniu i korekcie manuskryptu,

a w pracy:

Understanding mechanoreflex and metaboreflex interactions – a great challenge; Adrian Lis, **Bartłomiej Paleczny**, Beata Ponikowska; Indian J Physiol Pharmacol. (2021).

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