Uniwersytet Jagielloński
Collegium Medicum

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# New non-pharmacological treatment methods in heart failure

*Nowe metody niefarmakologicznego leczenia niewydolności serca*

*Praca doktorska*

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Pracę wykonano w I Klinice Kardiologii i Elektrokardiologii Interwencyjnej oraz Nadciśnienia Tętniczego Uniwersytetu Jagiellońskiego Collegium Medicum w Krakowie

Kierownik jednostki: Prof. dr hab. n. med. Marek Rajzer

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*Składam serdeczne podziękowania*
*Pani Profesor Danucie Czarneckiej,*
*Pani Profesor Kalinie Kaweckiej-Jaszcz,*
*wszystkim Współpracownikom z*
*I Kliniki Kardiologii i Elektrokardiologii*
*Interwencyjnej oraz Nadciśnienia Tętniczego*
*Uniwersytetu Jagiellońskiego Collegium Medicum,*
*a także Panu Profesorowi Gianfranco Paratiemu*
*i Kolegom oraz Koleżankom z Istituto Auxologico Italiano z Mediolanu*
*za pomoc w powstaniu tej pracy.*

*Pracę dedykuję Żonie i Dzieciom*

## SPIS TREŚCI

## 1. Wykaz publikacji stanowiących rozprawę doktorską

Niniejszą rozprawę doktorską pt.: „Nowe metody niefarmakologicznego leczenia niewydolności serca" stanowi monotematyczny cykl trzech artykułów, opublikowanych w międzynarodowych recenzowanych czasopismach naukowych, indeksowanych w bazie PubMed oraz znajdujących się na Liście Filadelfijskiej.

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## 2. Wstęp

Definicje niewydolności serca (NS) w ostatnich kilku dekadach ulegały często modyfikacjom. W aktualnych wytycznych Europejskiego Towarzystwa Kardiologicznego (ESC) eksperci definiują NS jako zespół kliniczny, w którym u chorego występują typowe objawy podmiotowe [1]. Częstość występowania NS w krajach rozwiniętych to 1-2%, zapadalność natomiast wynosi 5-10 na 1000 [2] i zwiększa się w związku ze starzeniem się społeczeństwa i poprawą przeżycia pacjentów z chorobami do niej predysponującymi takimi jak nadciśnienie tętnicze, choroba niedokrwienna serca czy cukrzyca. Ponadto, mimo istotnej poprawy leczenia, umieralność pacjentów z NS uległa w ostatnich latach niewielkiemu zmniejszeniu, a rokowanie dalej pozostaje niekorzystne [3]. Szacuje się, że w przyszłości koszty leczenia NS znacznie wzrosną i będą stanowić znaczne obciążenie dla systemów zdrowotnych [4].

Podstawowym leczeniem przewlekłej niewydolności serca jest farmakoterapia. Według wytycznych ESC do głównych grup leków, których bezpieczeństwo i skuteczność zostało potwierdzone w licznych randomizowanych badaniach, należą inhibitory konwertazy angiotensyny, antagoniści receptora angiotensyny, beta-blokery i antagoniści aldosteronu. Korzystne efekty leczenia wykazano także dla inhibitorów neprilizyny, co znalazło odzwierciedlenie w wytycznych, jednak aktualnie koszt takiej terapii powoduje znaczne ograniczenie jej dostępności [1]. Nie można także zapomnieć o potencjalnych działaniach niepożądanych leków, w tym hipotensji, stąd konieczne jest rozpoczynanie leczenia od małych dawek i powolna jego eskalacja.

Z metod niefarmakologicznych klasę zaleceń I A posiadają jedynie dwie metody: wielodyscyplinarna opieka nad pacjentami i trening wysiłkowy [1]. Inne interwencje niefarmakologiczne, jak ograniczenie spożycia sodu, są dyskusyjne [5]. Dotychczasowe dane skłaniają do ciągłego poszukiwania nowych metod leczenia NS, charakteryzujących się niską uciążliwością dla pacjentów [6]. Istotne znaczenie mogą mieć zwłaszcza nowe metody

niefarmakologiczne, a wśród nich terapie opierające się na wykorzystaniu treningu wolnego oddychania oraz denerwacji tętnic nerkowych.

Zaburzenia oddychania, począwszy od płytkiego oddechu aż po oddech Cheyne'a-Stokesa często występują w przebiegu zaawansowanej NS i wiążą się z gorszym rokowaniem [7]. Zaburzenia oddychania w czasie snu, głównie pod postacią centralnych bezdechów, występują nawet u 76% pacjentów z NS [8] i ich nasilenie wydaje się korelować z jej ciężkością [9]. Wolne oddychanie może mieć korzystny wpływ na pracę układu sercowo-naczyniowego. Wykazano, że zmniejszona częstość oddechów (około 6 oddechów na minutę) w niewydolności serca: zwiększa spoczynkową saturację krwi, poprawia wymianę gazową w płucach, zwiększa tolerancję wysiłku, redukuje uczucie duszności, a także zmniejsza nadmierną aktywację sympatyczną i zwiększa wrażliwość baroreceptorów [10,11].

Utrzymanie pożądanej częstości oddechów może jednak być dla pacjenta trudne. Aby to ułatwić zaprojektowane zostało urządzenie RESPeRATE, które poprzez sygnały wizualne i dźwiękowe wskazuje konieczność zrobienia wdechu i wydechu. Dotychczas było ono stosowane jako niefarmakologiczna metoda wspomagająca leczenie nadciśnienia tętniczego, które jest częstą przyczyną rozwoju NS. Zalecenia dotyczące stosowania tego urządzenia zostały ujęte przez American Heart Association (AHA) w stanowisku z 2013 roku dotyczącym niefarmakologicznych metod obniżania ciśnienia tętniczego [12]. Urządzenie to zostało zaakceptowana przez US Food and Drug Administration (FDA) w redukcji ciśnienia tętniczego oraz w leczeniu stresu.

Około 20 lat temu do leczenia niewydolności serca wprowadzono nową metodę stymulacji – terapię resynchronizującą (CRT). Polega ona na skoordynowanej stymulacji zarówno prawej jak i lewej komory serca, co przywraca fizjologiczną chronologię pracy komór i niweluje zjawisko dyssynchronii [13]. Wciąż jednak pozostaje grupa chorych, u których nie przynosi ona spodziewanych rezultatów i nie następuje poprawa kliniczna. Zjawisko to może

dotyczyć około 30% pacjentów jeżeli bierze się pod uwagę objawy kliniczne i aż 40-60% chorych, jeśli ocenie podlegają parametry bardziej obiektywne jak wielkość i frakcja wyrzutowa lewej komory. Przyczyny braku odpowiedzi na terapię resynchronizującą są złożone i nie do końca poznane [14].

Aktywacja współczulnego układu nerwowego odgrywa kluczową rolę w rozwoju i progresji chorób układu sercowo-naczyniowego – m.in. nadciśnienia tętniczego i niewydolności serca [15]. Ostatnio odnotowuje się ponownie zwiększone zainteresowanie obiecującą metodą terapii w opornym nadciśnieniu tętniczym - denerwacją tętnic nerkowych. Istnieją podstawy by przypuszczać, że denerwacja tętnic nerkowych u chorych z opornym nadciśnieniem tętniczym prowadzi do zmniejszenia ogólnoustrojowej aktywności układu współczulnego [16]. Wobec powyższych obserwacji również w niewydolności serca można spodziewać się zmniejszenia systemowej nadmiernej aktywności układu współczulnego po zastosowaniu tej metody.

## 3. Cele pracy:

Celem pracy była ocena bezpieczeństwa i wpływu na wydolność fizyczną, parametry hemodynamiczne oraz jakość życia:

a) treningu wolnego oddychania u objawowych pacjentów z niewydolnością serca z obniżoną frakcją wyrzutową lewej komory

b) denerwacji tętnic nerkowych u objawowych pacjentów z niewydolnością serca z obniżoną frakcją wyrzutową lewej komory pomimo optymalnej farmakoterapii oraz terapii resynchronizującej

**4. Metodyka badania:**

*Trening wolnego oddychania u objawowych pacjentów z niewydolnością serca z obniżoną frakcją wyrzutową lewej komory*

W badaniu chorzy z przewlekłą NS z obniżoną frakcją wyrzutową lewej komory (LVEF), ze standardową terapią farmakologiczną, byli leczeni w sposób randomizowany trwającym 10-12 tygodni treningiem wolnego oddychania (slow breathing training, SBT) naprzemiennie ze standardową terapią NS o tym samym czasie trwania (cross-over open trial). W treningu oddechowym zostały zastosowane urządzenia RESPeRATE (InterCure Ltd., Lod, Israel), które składają się z czujnika monitorującego ruchy oddechowe oraz skomputeryzowanego urządzenia generującego wzorzec muzyczny przekazywany następnie do słuchawek. Podczas SBT pacjenci wykonywali dwukrotnie w ciągu dnia trwający 15 min trening za pomocą aparatu RESPeRATE z częstością 6 oddechów/min. U wszystkich chorych wyjściowo oraz po każdej z dwóch faz badania zbierano dane kliniczne, wykonywano: polisomnografię, badanie czynności układu autonomicznego, badanie echokardiograficzne, test 6-min marszu (6-minute walk test, 6MWT), 24-h monitorowanie EKG metodą Holtera, badanie jakości życia (kwestionariusz Minnesota (MLHFQ)) oraz badania laboratoryjne.

*Denerwacja tętnic nerkowych u objawowych pacjentów z niewydolnością serca z obniżoną frakcją wyrzutową lewej komory nieodpowiadających na terapię resynchronizującą.*

Objawowych pacjentów z niewydolnością serca z obniżoną frakcją wyrzutową lewej komory nieodpowiadających na terapię resynchronizującą przydzielono losowo do grupy interwencji oraz kontrolnej. W grupie interwencyjnej podczas pierwszej hospitalizacji wykonano procedurę ablacji tętnic nerkowych prądem o częstotliwości radiowej cewnikiem Symplicity (Medtronic) z dostępu przez tętnicę udową. W trakcie zabiegu wykonywano do 6 ablacji

punktowych, natomiast w grupie kontrolnej zabieg ten nie był wykonywany. Wyjściowo i po 1, 6, 12 i 24 miesiącach przeprowadzano ocenę obejmującą ocenę czynności układu autonomicznego, ocenę ciśnienia obwodowego, echokardiografię przezklatkową, badanie jakości życia z zastosowaniem kwestionariusza Minnesota, 6MWT, ocenę funkcji nerek i wybrane badania biochemiczne z uwzględnieniem NT-proBNP jako markera nasilenia niewydolności serca.

Do analizy statystycznej wykorzystano pakiet Statistica 10. Za graniczny poziom istotności (p) przyjęto wartość 0.05. Szczegółowy opis wykorzystanych analiz statystycznych znajduje się w każdym z opublikowanych artykułów składających się na dysertację.

Na przeprowadzenie badań uzyskano zgody Komisji Bioetycznej Collegium Medicum Uniwersytetu Jagiellońskiego (KBET/90/B/2007 z dnia 15 listopada 2007 r. oraz KBET/73/B/2012 z dnia 22 marca 2012 r.). Badania były finansowane ze środków Narodowego Centrum Nauki.

## 5. Artykuły stanowiące monotematyczny cykl publikacji

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# Blood pressure changes in patients with chronic heart failure undergoing slow breathing training

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ORIGINAL ARTICLE

# Blood pressure changes in patients with chronic heart failure undergoing slow breathing training

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**ABSTRACT**

*Background.* Slow breathing training (SBT) has been proposed as a new non-pharmacological treatment able to induce favorable effects in patients with chronic heart failure (CHF). However, no information is available regarding its effects on orthostatic blood pressure (BP) changes in these patients, an issue of practical relevance given the reported BP-lowering effect of SBT. The aim of this study is to evaluate the influence of SBT on BP and whether SBT induces orthostatic hypotension (OH) or changes in quality of life (QoL) in CHF patients. *Methods*. The analysis was performed as part of an ongoing crossover open trial aimed at assessing the clinical effectiveness of SBT in treated patients with CHF. The patients underwent 10–12 weeks of SBT with the RESPeRATE device and 10–12 week follow-up under usual care. Patients were randomly divided into two groups: group I began with SBT, followed by usual care; group II began with usual care, followed by SBT. Patients undergoing SBT were asked to perform each day two separate 15 min sessions of device-guided SBT at a breathing frequency of 6 breaths/min. In all patients, before the enrollment and after each study phase, clinical data collection and BP measurements in sitting, supine and standing position were performed. OH was defined as a decrease of $\geq 20$ mmHg in systolic blood pressure (SBP) or $\geq 10$ mmHg in diastolic blood pressure (DBP) within 3 min of standing. QoL was assessed three times at the beginning, and after each phase of the study by the Minnesota Living with Heart Failure (MLHF) questionnaire. *Results*. Forty patients (two equal groups) completed the study, with the following baseline characteristics: 32 males/eight females, age 63.3 ± 13.4 years, 25 with ischemic CHF, 37 in New York Heart Association class II and three in class III, left ventricular ejection fraction 30.8 ± 6.7%, mean BP 138.7 ± 16.5/83.1 ± 11.5 mmHg, 23 with arterial hypertension and four with a history of stroke. There were no significant differences between the groups in clinical characteristics, SBP and DBP at rest, while seated and before and after standing up. OH prevalence was low and did not change during the study (10% vs 10%). No significant difference in average SBP and DBP changes secondary to body position were found when comparing the two study phases. Decrease in MLHF score was observed in group I during SBT ($p = 0.002$), but not in group II. *Conclusions*. Our data indicate that SBT is safe, does not affect the prevalence of OH in CHF patients and shows a non-significant tendency to improve QoL. These results should be confirmed in a larger sample of patients to support the safety of SBT and its possible benefits as a novel component of cardiorespiratory rehabilitation programs in CHF.

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## Introduction

Despite unquestionable advances in treatment causing prolongation of survival, chronic heart failure (CHF) remains an important cause of death among patients with cardiovascular diseases. The prevalence of CHF increases with age and with longer lifetime (paradoxically due to better management of acute events) in patients with hypertension and coronary heart disease, diseases that constitute the most common causes of CHF [1–3]. The Framingham Study showed that more than 90% of participants who developed CHF had antecedent hypertension [4]. In recent years, the mortality of CHF patients has only slightly improved [5]. Moreover, it is estimated that in the future CHF treatment costs will increase considerably [6]. It is worth underlining that symptomatic heart failure negatively influences the quality of life (QoL) in patients by restricting various areas and domains of physical (fatigue, dyspnea, low physical capacity), psychological (emotional distress, depression) and social activities [7].

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A continuing search for treatment modalities able to improve outcomes and QoL, and characterized by low nuisance for CHF patients, is therefore necessary. New non-pharmacological methods, including slow breathing training (SBT), may be of particular interest in this regard [8].

Slow breathing has a beneficial impact on the function of the cardiovascular system in CHF patients [9]. It has been shown that slow respiratory rate in CHF increases blood oxygen saturation at rest, improves respiratory exchange in the lungs, increases exercise tolerance by reducing the sensation of breathlessness and reduces excessive sympathetic activation, with a parallel increase in baroreceptor sensitivity reflecting parasympathetic modulation [10]. It has been demonstrated that slow and deep respiration suppresses steady-state sympathetic nerve activity in patients with high levels of resting sympathetic tone, as in heart failure [11].

To self-maintain a constant and low number of breaths per minute is a difficult task for a patient. Devices that give visual and audible signals to help patients to achieve a desired frequency of breathing may be used. One such device is the RESPeRATE (InterCure, Lod, Israel). So far, the device has been used as a non-pharmacological method for lowering high blood pressure (BP). Recommendations for the use of RESPeRATE have been recognized by the American Heart Association in the statement describing non-pharmacological methods for lowering BP [12].

An intervention potentially able to lower BP could lead to orthostatic hypotension (OH) in CHF patients, who commonly face low BP levels either spontaneously or owing to pharmacological treatment for their condition. Immediately after standing up, a gravitational displacement of blood occurs, with a decrease in venous return to the heart and reduction in left ventricular (LV) filling [13]. The result is a reduction in stroke volume and cardiac output, which could lead to hypotension, but which is commonly counteracted by the resulting reduction in arterial baroreceptor stimulation and by the consequent marked decrease in parasympathetic activity mediated by the vagus nerve, leading to a heart rate increase, and the increase in sympathetic activity, leading to peripheral vasoconstriction and to a greater LV contractility [14]. Patients with CHF demonstrate a dysfunction of this baroreflex-mediated mechanism [15], which may be one of the causes of the occurrence of OH in these individuals.

In healthy elderly people, the incidence of OH is estimated to be around 5–30% [16]. OH itself is associated with an increased risk of cardiovascular disease [17]. There is limited information, however, on the frequency of OH in patients with CHF. This is an important issue, because of the results of the Italian GISSI-HF study: in almost 7000 patients with CHF it was shown that low systolic blood pressure (SBP) increases the risk of early death [18].

The aim of this study was to evaluate the influence of SBT on BP and whether this recently proposed new type of non-pharmacological treatment induces OH and influences QoL in patients with CHF.

## Materials and methods

### *Study design*

The study is an ongoing crossover open trial where patients, in random order, undergo a 10–12 week period of SBT with the RESPeRATE device (InterCure, Lod, Israel) and a 10–12 week follow-up period under usual care without breathing exercises. Patients were randomly divided into two groups: group I started with SBT followed by usual care; group II started with usual care, followed by SBT (Figure 1). Patients randomized to SBT were asked to perform each day two separate 15 min sessions of device-guided SBT at a breathing frequency of 6 breaths/min. In all patients, before the enrollment and after each study phase, clinical data collection, BP measurements in supine and standing positions,

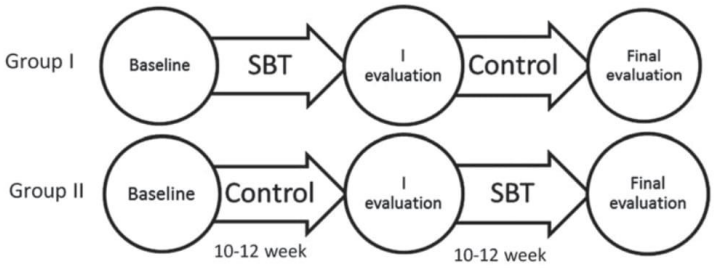


Figure 1. Study design. SBT, slow breathing training.

polysomnography, beat-to-beat BP monitoring, echocardiography, Six-Minute Walk Test, 24 h Holter monitoring, QoL assessment through the Minnesota Living with Heart Failure (MLHF) questionnaire and laboratory tests were performed. Optimized pharmacological treatment was kept constant during the study.

### Study population

Patients aged >18 years with New York Heart Association (NYHA) class II–III CHF, with left ventricular ejection fraction (LVEF)<40% (echocardiography) under stable clinical conditions, with no cardiovascular interventions in the past 3 months and who were stable on pharmacological treatment in the past 4 weeks were enrolled. Sinus rhythm presence was required and checked by 24 h Holter electrocardiogram monitoring. The patients had to be able to perform breathing exercises following instructions received during a previously completed supervised training session. Patients who had undergone heart transplantation, patients who were within 3 months since the end of traditional cardiac rehabilitation, and those with serious chronic obstructive pulmonary disease (forced expiratory volume in 1 second<50%), ventricular arrhythmias or conduction abnormalities (ventricular tachycardia, ventricular fibrillation, atrioventricular block grade II and III) were excluded.

### Blood pressure measurement

BP measurements were performed with a validated oscillometric device (OMRON M6 (OMRON Corporation, Kyoto, Japan)) at the brachial artery, while the patient was sitting, at room temperature, at a fixed time of day (between 08.00 and 11.00 h), having refrained from eating and smoking for at least 30 min, and after 10 min of rest. The measurements were performed twice with an interval of at least 5 min and mean values were calculated.

To diagnose OH, subjects were studied in the morning, in the supine position, in a quiet and dimly lit room after an overnight fast. Non-invasive BP measurements were taken with an arm cuff (OMRON M6) after 10 min rest in the supine position. OH was defined as a decrease of ≥20 mmHg in SBP or ≥10 mmHg in diastolic blood pressure (DBP) within 3 min of standing [13].

### Slow breathing training (RESPeRATE device)

The system includes a belt-type respiration sensor connected to a computerized box that generates musical patterns through earphones. The device guides the user to slow their breathing, with the expiration phase being longer than the inspiration phase. After a "recognition" phase, during which the device learns the user's natural breathing patterns, it starts guiding the user to breathe more slowly in the following way: (i) the sensor monitors continuously breathing movements; (ii) the computerized box detects the breathing patterns and average inhale/exhale duration over the last four respiratory cycles; (iii) it synthesizes musical patterns with "inspiration" and "expiration" guiding tones with related but different durations (longer in expiration); and finally (iv) the user voluntarily and effortlessly synchronizes inhaling and exhaling movements with the guiding tones. As a result, breathing frequency is reduced from the initial spontaneous rate (usually 14–18 breaths/min) to a rate of 6–8 breaths/min, with prolonged exhalation [19].

### Echocardiography

The same experienced operator, blinded to patients' allocation, performed the echocardiographic examinations of all patients (General Electric VIVID7 (GE Healthcare, Little Chalfont, United Kingdom), probe 2.5 MHz). The measurements, i.e. M-mode, 2D and Doppler method, were performed according to the standards required by the American Society of Echocardiography [20]. LVEF was measured with Simpson's technique based on the average from at least three registered cycle heart beats.

### Minnesota Living with Heart Failure Questionnaire

Patients completed the Polish version of the 21-item MLHF questionnaire to assess disease-specific QoL. The questionnaire asks about how much the heart condition has affected the patient's life during the past month. Each item is rated on a Likert scale between 0 (no impairment) and 5 (very much impaired), resulting in a total score between 0 and 105 for total QoL. The MLHF also allows one to compute subscores for the physical (eight items, range 0–40) and emotional (five items, range 0–25) aspects of QoL [21]. Lower MLHF scores indicate better QoL.

### Statistical analysis

All data were analyzed using the Statistica PL software (v. 10.0; StatSoft). Categorical variables are reported as percentages and continuous variables as means and standard deviation (SD). The chi-squared test was applied to all categorical variables. For continuous variables, analysis of variance (ANOVA) was used. A $p$ value of less than 0.05 was considered to indicate statistical significance.

## Results

Forty patients aged 23–88 years completed the study. Clinical characteristics of the enrolled patients are shown in Table I. Secondary forms of cardiomyopathy were the most prevalent causes of CHF: 25 patients (62.5%) had ischemic cardiomyopathy, two patients had a diagnosis of CHF as a result of myocarditis, in one patient heart failure had developed as a result of systemic disease (sarcoidosis) and 12 patients had primary dilated cardiomyopathy of unknown etiology. There were no significant differences in the studied parameters between the groups at baseline (Table I).

Before enrollment all patients had to be under constant pharmacotherapy for at least 4 weeks, according to the current European Society of Cardiology (ESC) guidelines [2], consisting of beta-blockers and angiotensin-converting enzyme inhibitors (ACEIs) (in four patients angiotensin receptor antagonists because of intolerance to ACEIs) at the maximum tolerated dose. The majority of patients used diuretics. In addition, all patients with LVEF below 35% received a mineralocorticoid receptor antagonist; one patient received ivabradine in accordance with the recommendations of the ESC. Three patients in the study required intensification of diuretic treatment owing to heart failure exacerbation (worsening of peripheral edema): two during the control period (groups I and II) and one during SBT.

There was a significant reduction in SBP and DBP between baseline and the final evaluation in group I. In group II the same trend was present, although it did not reach statistical significance (Table II). The prevalence of OH was low (10% at baseline, 12.5% at 12 weeks and 10% at final evaluation) and did not change between the phases of the study (Table III). The average changes in SBP/DBP after changing position were also not significant (Table IV).

A decrease in MLHF questionnaire score was observed in group I during SBT. In group II a similar decrease was present only after completion of the study. There were no differences between the groups in the MLHF score at any time during the study (Figure 2).

## Discussion

A few previous reports have suggested that SBT may be a useful adjunct to standard treatment in patients with CHF. The acute effects of slow breathing in heart failure patients were assessed by Bernardi et al., who reported an improvement in blood oxygenation and exercise performance without significant changes in BP after 4 min of breathing at a rate of 6 breaths/min. In a small subgroup of participants who underwent 1 month of SBT, long-term benefits in terms of blood oxygenation and in objective and subjective indices of exercise

Table I. Baseline characteristics of the study groups.

| Parameter | Group I ($n = 20$) | Group II ($n = 20$) | All ($n = 40$) | $p$ |
|---|---|---|---|---|
| Age (years) | 65.5 ± 11.6 | 61.2 ± 15.0 | 63.3 ± 13.4 | 0.57 |
| Male gender (%) | 15 (75) | 17 (85) | 32 (80) | 0.46 |
| NYHA class II/III ($n$) | 18/2 | 19/1 | 37/3 | 0.50 |
| Ejection fraction (%) | 31.7 ± 6.7 | 29.9 ± 6.9 | 30.8 ± 6.7 | 0.41 |
| SBP sitting (mmHg) | 141.6 ± 14.5 | 135.9 ± 18.2 | 138.7 ± 16.5 | 0.42 |
| DBP sitting (mmHg) | 84.4 ± 11.6 | 81.9 ± 11.6 | 83.1 ± 11.5 | 0.53 |
| SBP supine (mmHg) | 122.0 ± 15.7 | 128.4 ± 19.5 | 125.4 ± 17.9 | 0.27 |
| DBP supine (mmHg) | 70.8 ± 9.5 | 74.5 ± 11.0 | 72.8 ± 10.3 | 0.56 |
| SBP standing (mmHg) | 119.2 ± 19.1 | 126.1 ± 16.0 | 122.8 ± 17.6 | 0.23 |
| DBP standing (mmHg) | 73.3 ± 11.1 | 77.3 ± 14.2 | 75.4 ± 12.8 | 0.34 |
| Minnesota Quality of Life (points) | 49.7 ± 10.0 | 48.7 ± 14.2 | 49.2 ± 12.2 | 0.79 |
| Ischemic heart disease (%) | 15 (75) | 10 (50) | 25 (62.5) | 0.07 |
| Hypertension (%) | 12 (60) | 11 (55) | 23 (57.5) | 1.0 |
| Stroke (%) | 2 (10) | 2 (10) | 4 (10) | 0.50 |
| Diabetes (%) | 5 (25) | 8 (40) | 13 (32.5) | 0.48 |

Data are shown as mean ± SD or $n$ (%).
NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table II. Changes in sitting blood pressure values (mmHg) among different study phases.

| Group | Baseline SBP/DBP | At 12 weeks SBP/DBP | Final evaluation SBP/DBP | $p$ baseline–12 weeks | $p$ 12 weeks–final | $p$ baseline–final |
|---|---|---|---|---|---|---|
| I ($n = 20$) | 147.2/87.3 | 134.7/80.5 | 132/77.7 | 0.06/0.17 | 0.85/0.73 | 0.02/0.04 |
| II ($n = 20$) | 140.2/84.3 | 138.0/84.2 | 134.3/81.4 | 0.79/0.99 | 0.91/0.70 | 0.53/0.69 |
| $p$ I vs II | 0.32/0.53 | 0.65/0.48 | 0.29/0.24 | | | |

SBP, systolic blood pressure; DBP, diastolic blood pressure.

performance were confirmed. Changes in BP after the SBT period were not reported in this study [10]. The information on the beneficial effects of SBT was further extended by a study by Parati et al. on 24 patients with CHF who underwent SBT using the same device as in the present report. These effects included reductions in NYHA class and pulmonary artery pressure, and improvement in ejection fraction, ventilatory variables and QoL [9].

The data on the effects of slow breathing and SBT on BP in patients with CHF are limited and inconsistent. During a slow breathing session, BP was unchanged in the study by Bernardi et al. [10]. Another paper from this group reported, however, a significant decrease in BP during a 4 min slow breathing session in CHF patients (but not in healthy controls) [22]. This discrepancy may be explained by impaired responses of the arterial baroreflex and chemoreflex occurring during slow breathing in CHF and in hypoxic patients [22,23]. Further insight into the possible mechanisms comes from a study by Bilo et al., performed in healthy volunteers exposed to high altitude (a condition in many regards similar to heart failure with hypoxemia). In this setting, a 15 min session of slow breathing induced a decrease in BP level, possibly due to the deactivation of peripheral chemoreceptors by increased blood oxygenation and consequent reduction of sympathetic drive [24].

In our study we found no changes in BP level after a period of SBT. This result is in line with the randomized trial by Ekman et al., in which 30 CHF patients underwent a 4 week period of SBT with the RESPeRATE device, while 35 CHF patients listened to music from a compact disc player (control group) [25]. In the study by Parati et al., only a non-significant reduction in BP was observed, mainly in patients with high baseline values [9].

Table III. Prevalence of orthostatic hypotension by group and study phase.

| Group ($n = 20$) | Baseline | At 12 weeks | Final evaluation |
|---|---|---|---|
| I (SBT/usual care) | 2 (10) | 2 (10) | 1 (5) |
| II (usual care/SBT) | 2 (10) | 3 (15) | 3 (15) |
| *p* | 0.52 | 0.66 | 0.32 |

Data are shown as *n* (%).
SBT, slow breathing training.

To our knowledge, this is the first study to assess the effects of SBT on dynamic regulation of BP during orthostatic challenge and its impact in terms of OH prevalence in patients with CHF. A beneficial effect of slow breathing on orthostatic tolerance was demonstrated in a randomized crossover study on healthy volunteers. The authors postulated that this improvement is mediated by the generation of negative intrathoracic pressure during slow and deep breathing, increasing right venous return and in turn LV stroke volume, with resulting beneficial effects on the cardiovascular and autonomic systems [26]. Another suggested mechanism of the positive influence of slow breathing on OH is the possibility that the generation of greater negative pressure in the thorax accelerates blood flow through capillary beds owing to a vacuum effect and to maximization of the pressure gradient.

Orthostatic intolerance is an important issue in CHF. In a meta-analysis by Ricci et al., compared with the absence of OH, the occurrence of OH was associated with a significantly increased risk of heart failure (relative risk 2.25, 95% confidence interval 1.52–3.33) [27]. An impairment in autonomic regulation is frequent in this population [28] and may be further exacerbated by the use of some of the medications commonly prescribed in CHF, such as diuretics or vasodilators [29]. In this context, our study did not reveal any negative influence of SBT in terms of orthostatic tolerance, indicating that this technique represents an additional, potentially valuable therapeutic approach devoid of negative effects on OH in CHF patients. In fact, one could hypothesize that many CHF patients for whom OH is an issue may benefit from SBT, should it be able to reduce the need for the use of diuretics or vasodilators to control symptoms. This possibility was beyond the scope of the present study but it appears to be of clinical interest and should be explored in future research.

Finally, we observed an improvement in the QoL during the course of the study, between baseline and final assessment, in line with that reported by Parati et al. [9]. However, the pattern of MLHF changes in the two groups (improvement was observed in both the SBT and usual care phases) suggests that it was not specifically due to SBT, but rather that direct contact of patients with the staff involved in the trial, performing check-ups,

Table IV. Changes in blood pressure in the two study groups and in the different study phases after standing up.

| Group | Baseline SBP/DBP | At 12 weeks SBP/DBP | Final evaluation SBP/DBP | *p* |
|---|---|---|---|---|
| I | −2.6 ± 14.1/+2.4 ± 8.7 | +0.3 ± 10.5/−1.3 ± 8.5 | −0.4 ± 14.6/+4.3 ± 7.9 | 0.69/0.09 |
| II | −2.3 ± 12.2/+2.8 ± 10.1 | +0.3 ± 10.5/+0.7 ± 9.3 | −4.35 ± 14.6/+2.5 ± 9.5 | 0.70/0.97 |

SBP, systolic blood pressure; DBP, diastolic blood pressure.

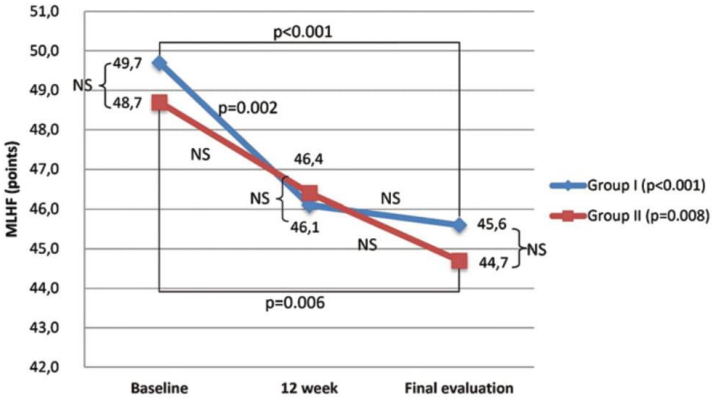


Figure 2. Results of the Minnesota Living with Heart Failure (MLHF) questionnaire according to group and study phase. NS, not significant.



increasing medical surveillance and showing interest in their problems, was probably the main cause of improved QoL. This emphasizes the need for appropriate control in studies on non-pharmacological interventions, where the effects of a close follow-up may be as important as those of the intervention itself, in particular when "soft" endpoints (such as QoL) are considered. However, it should be underlined that Ekman et al., in their well-controlled study on CHF patients, found that a positive effect of SBT on the QoL and severity of CHF symptoms was restricted to responding patients, i.e. those in whom SBT induced lasting changes in the breathing pattern [25]. In addition, owing to the crossover design of our study, we cannot completely exclude a carryover effect to explain the difference in QoL score between baseline and the end of the study.

Our study has several strengths, including having a sample size moderately larger than that of most previous studies [9,25], having a controlled design and using a device specifically designed for SBT (and approved by the US Food and Drug Administration for BP lowering), following a standardized exercise protocol. This device implements a series of features which make the exercise easier for the patient, including individualized acoustic guidance of breathing frequency, resulting in its gradual reduction, and visual feedback on the exercise performance. This is important as self-maintenance of a constantly low number of breaths by the patient is a difficult task and a rigid breathing pace could have negative effects on exercise performance.

There are also some limitations of our study which should be acknowledged. First, the BP measurement was performed using the traditional, non-continuous method. We therefore cannot completely exclude possible BP reductions between the scheduled measurements. Secondly, the number of subjects with OH was low and therefore the study may not be sufficiently powered to detect a small increase in OH prevalence. Nonetheless, the fact that the absolute values of orthostatic BP changes were virtually unchanged after SBT makes this possibility unlikely. Thirdly, for practical reasons we implemented a crossover rather than a parallel group design. Thus, we cannot exclude some carryover effect, as exemplified by the changes observed in the QoL. Finally, we cannot exclude the possible influence of coexisting morbidities (e.g. diabetes, hypertension) or that of concomitant drug therapy on OH, although drug treatment was kept stable during the study.

## Conclusions

Our data indicate that SBT does not increase the prevalence of OH, thereby supporting it as a feasible and safe method which may be used in CHF patients. Moreover, our data do not seem to support a significant impact on QoL by this intervention; however, given the cross-sectional design of our study, this finding needs to be confirmed by longitudinal trials with a controlled parallel group design. Further data from controlled studies are still necessary to confirm the clinical benefits of SBT in CHF patients, before it may be proposed as a novel and useful component of cardiorespiratory rehabilitation programs in CHF.

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## Declaration of interest

No potential conflict of interest was reported by the authors.

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ORIGINAL ARTICLE

# Effects of device-guided slow breathing training on exercise capacity, cardiac function, and respiratory patterns during sleep in male and female patients with chronic heart failure

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**KEY WORDS**

chronic heart failure, sleep apnea, slow breathing training

**ABSTRACT**

**INTRODUCTION** Slow breathing training (SBT) has been proposed as a new nonpharmacologic treatment in patients with chronic heart failure (CHF).

**OBJECTIVES** The aim of this study was to assess the effects of SBT on exercise capacity, hemodynamic parameters, and sleep respiratory patterns in a relatively large sample of CHF patients.

**PATIENTS AND METHODS** A crossover open study was conducted. Patients completed, in a random order, 10- to 12-week SBT, with 2 15-minute sessions of device-guided SBT each day, reaching 6 breaths/min, and a 10- to 12-week follow-up under standard care. Clinical data collection, polysomnography, echocardiography, 6-minute walk test (6MWT), and laboratory tests were performed.

**RESULTS** A total of 96 patients (74 men, 22 women) in New York Heart Association classes I–III, with an average age of 65 years and an ejection fraction (EF) of 31%, completed the study. Home-based SBT was safe. After training, EF and 6MWT distance improved (EF: 31.3% ±7.3% vs 32.3% ±7.7%; $P = 0.030$; 6MWT: 449.9 ±122.7 m vs 468.3 ±121.9 m; $P < 0.001$), and the apnea–hypopnea index decreased (5.6 [interquartile range (IQR), 2.1; 12.8] vs. 5.4 [IQR, 2.0; 10.8]; $P = 0.043$).

**CONCLUSIONS** SBT improved physical capacity and systolic heart function; it also diminished sleep disturbances. The results support the benefits of SBT as a novel component of cardiorespiratory rehabilitation programs in patients with CHF.

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**INTRODUCTION** Chronic heart failure (CHF) has become one of the most widespread diseases and a principal cause of morbidity and mortality, due to the high prevalence of its main causes in aging societies, namely, hypertension and coronary heart disease.[1,2] Despite unquestionable progress in pharmacologic and device-based treatment, the mortality of CHF patients has only slightly improved in recent years,[3,4] and frequent hospitalizations[4] and poor quality of life[5] of these patients remain major health care issues. Especially in this latter aspect, cardiac rehabilitation programs based on physical exercise might prove particularly beneficial. However, their use in clinical practice remains limited because of the time and resources needed to achieve a satisfactory outcome. New nonpharmacologic home-based treatment options may thus be of particular interest in this regard. Among these options, respiratory training aimed at slowing the breathing rate, was proposed some years ago. A device for slow breathing training (SBT) was developed (RESPeRATE) in order to facilitate the patient in the potentially difficult task of maintaining

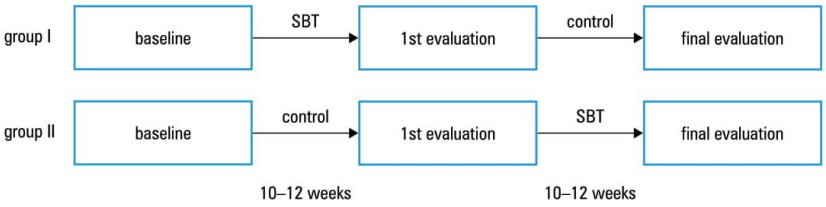


**FIGURE 1** Study design; group I, started with slow breathing training (SBT); group II, started with standard care

a constant number of breaths. This device guides the breathing exercise through visual and acoustic feedback, and its application has been recognized by the American Heart Association as a potentially useful nonpharmacologic approach for lowering blood pressure.[6]

The use of SBT has also been shown to be a feasible treatment option in the framework of the home-based rehabilitation of patients with CHF.[7] Our previously published data indicated that it is safe and does not significantly affect blood pressure values or the prevalence of orthostatic hypotension in these patients.[8] Moreover, preliminary data have demonstrated the usefulness of home-based rehabilitation in terms of improving both subjective (New York Heart Association [NYHA] class, breathlessness) and objective (exercise capacity, pulmonary function, and ventricular EF) parameters.[9-11] It was hypothesized that the favorable effects of SBT may be mediated by improved baroreflex sensitivity and respiratory mechanics.[9,10]

Respiratory abnormalities, from shallow breathing to Cheyne-Stokes periodicity, are very frequent in advanced CHF and their presence suggests a poor prognosis.[12] In particular, sleep-disordered breathing, mainly characterized by the presence of central apneas, is found in up to 76% of patients with systolic and diastolic heart failure[13] and, apparently, remains in a dose-dependent relationship with heart failure severity.[14] Intervention with positive airway pressure devices was shown to reduce the number of central apneas in CHF patients[15] and may improve some clinical parameters.[16] However, data from a recent trial suggest that adaptive servoventilation treatment is associated with higher mortality in CHF patients.[17]

Alternative therapeutic options to correct sleep-disordered breathing in CHF thus remain to be evaluated. In this context, no information is available on whether a training based on slow breathing during the day may improve abnormal patterns of respiration at night.

In summary, previous data indicate that SBT may be a simple and clinically useful adjunct to cardiac rehabilitation in CHF patients but stronger evidence is needed to support its clinical use. Therefore, we performed this study to assess the effects of SBT on clinical variables, including exercise capacity, hemodynamic parameters, and respiratory patterns during sleep in a relatively large sample of patients with CHF.

## PATIENTS AND METHODS

### Study design

The study, performed in 2 cardiology departments (Kraków, Poland and Milan, Italy), employed a crossover open trial design where patients, in a random order, underwent a 10- to 12-week SBT with the RESPeRATE device (InterCure Ltd., Lod, Israel) and a 10- to 12-week follow-up under standard care. Participants were identified by local investigators in the period between 2012 and 2015, and were consecutively assigned to intervention sequence starting with either SBT or standard care according to a previously prepared simple randomization list. In all patients, home sleep study, echocardiography, 6-minute walk test (6MWT), and laboratory tests were performed at baseline and after each study phase (FIGURE 1). Optimized pharmacologic treatment was maintained throughout the study. The study was performed in accordance with the 1975 Declaration of Helsinki for Human Research and approved by the Bioethical Committee of the participating institutions: Jagiellonian University Bioethical Committee and the Ethics Committee of Istituto Auxologico Italiano. Patients were included only if they gave their written informed consent. The study has been registered in the Polish National Science Centre (number 2011/03/B/NZ5/00 533).

### Study population

Adult patients with CHF fulfilling the following conditions were enrolled for this study: NYHA classes I–III; left ventricular EF (LVEF) lower than 40% in echocardiographic study; stable clinical conditions with no cardiovascular interventions over the previous 3 months; receiving stable pharmacologic treatment over the previous 4 weeks; sinus rhythm in 24-hour Holter monitoring; and ability to perform breathing exercises after supervised training. Patients after heart transplantation, patients who had received traditional cardiac rehabilitation within the previous 3 months, and patients presenting with serious chronic obstructive pulmonary disease, ventricular arrhythmias (tachycardia, fibrillation), or conduction abnormalities (second- and third-degree atrioventricular block) were excluded.

### Slow breathing training (the RESPeRATE device)

In the present study, patients were asked to undergo 2 separate 15-minute sessions of device-guided SBT with the RESPeRATE device throughout the 10- to 12-week period of SBT. The principles

of functioning of this device were described previously.[18] Briefly, after a "learning" phase of the patient's respiratory pattern, the device guides the patient's breathing by means of a musical pattern and gradually reduces breathing frequency to 6 breaths/min, while maintaining a desired inspiration/expiration time ratio.[8]

**Echocardiography** Echocardiography was performed using Vivid 7 Pro (General Electric, Fairfield, Connecticut, United States), with a 2.5-MHz probe by a single experienced operator who was blinded to the patients' allocation to experimental groups. One-dimensional, two-dimensional, pulse, and continuous Doppler, and pulsed-wave tissue Doppler imaging methods incorporating the measurement of individual phases of mitral annulus velocity were used. Each point of the protocol was recorded for at least 3 cardiac cycles during patients' steady breathing. The data were recorded, stored, and analyzed using the Echo-Pack system (General Electric). EF was calculated using the Simpson's formula. In the presence of tricuspid regurgitation, the tricuspid regurgitation pressure gradient and the value of right atrial pressure estimated on the basis of the width and the respiratory subsidence of the vena cava were used to assess the systolic pressure in the right ventricle. Right ventricular systolic pressure was calculated by adding the values of tricuspid regurgitation pressure gradient and right atrial pressure.[19]

**Home sleep study** Home sleep study was performed with Embletta Gold, an ambulatory overnight cardiorespiratory device (Embla, Broomfield, Colorado, United States), which recorded nasal/oral airflow (via a pressure cannula), chest and abdominal wall movements (via inductive belts), oxygen saturation (via a finger probe pulse-oximetry) and heart rate (via a CM5 device). A breathing event was defined as abnormal if: 1) a complete cessation of airflow lasting more than 10 seconds was present (apnea); or 2) a reduction in respiratory airflow greater than 50% and lasting more than 10 seconds and associated with a desaturation of 4% or higher (hypopnea) occurred. Obstructive apneas were defined by a reduction of respiratory airflow of over 50% for a minimum of 10 seconds, associated with paradoxical thoracic and abdominal motion and a desaturation of 4% or higher. Central apneas were defined by the absence/reduction of respiratory airflow for 10 seconds with an absence of thoracic and abdominal excursions and a desaturation of 4% or higher. The apnea–hypopnea index (AHI) was defined as the average number of apneas and hypopneas per hour of sleep. A sleep-related breathing disorder was diagnosed when the AHI was 5 or higher. Cheyne–Stokes respiration was characterized by the lack of air flow and respiratory effort followed by hyperventilation in a crescendo-decrescendo pattern.[20]

**Six-minute walk test** The 6MWT was performed in patients after a 10-minute resting period in a sitting position. Patients were asked to march at their own pace, on a flat and level surface in an empty corridor. They were informed about the progress of the test on regular basis; at the end of the 6-minute period, the total distance walked was measured. At baseline and after the test, blood pressure and oxygen saturation were also measured.[21]

**Statistical analysis** Considering the paucity of similar studies in the literature, the sample size was determined based on SBP effects on EF observed in the previous data from our group[9]: assuming a sample standard deviation of 8% and a correlation coefficient of 0.6 between EF before and after the intervention, 103 patients were needed to identify a 2% difference in EF with a power of 80%.

All data were analyzed using the Statistica PL v.12.0 software (StatSoft, Tulsa, Oklahoma, United States). Categorical variables were reported as percentages, while continuous variables—as means and standard deviations or median and interquartile ranges when data distribution differed from the normal. The $\chi^2$ test was applied for all categorical variables. For continuous variables, the analysis of variance for repeated measures was applied. If the assumptions were not met, a multidimensional approach or the Friedman test was used. For statistically significant results, detailed comparisons using the appropriate post hoc testing (Tukey tests) were conducted. To assess changes in only 2 measurements, the *t* test for paired samples or the Wilcoxon matched pairs test was used. The results for which the *P* value was lower than the assumed level of significance $\alpha = 0.05$ ($P < 0.05$) were considered significant.

**RESULTS** We included 110 patients (age, 23–87 years; 86 men and 24 women), of whom 14 did not complete the study for the following reasons: 2 sudden cardiac deaths; cardiac resynchronization therapy device implantation; 2 hospitalizations (myocardial infarction and limb fracture); alcohol addiction; overnight working; 4 changed the place of residence; 3 withdrew from further participation in the study (health reasons were excluded). Consequently, the trial ended after 96 subjects completed the study (74 in Kraków, 22 in Milan; age, 23–86 years; 74 men and 22 women).

Owing to a specific study design (crossover open trial), in order to verify the probability of a significant carryover effect, we preliminarily assessed the interactions between the intervention sequence (SBT first vs control first) and the observed effects, and found no significant interactions (*P* value always >0.4). Thus, the results could be safely pooled together.

The clinical characteristics of the patients are shown in TABLE 1, separately for male and female participants. Male participants had slightly higher body mass index and more frequent ischemic

**TABLE 1** Baseline characteristics of study participants

| Parameter | All participants (n = 96) | Male participants (n = 74) | Female participants (n = 22) | *P* value |
|---|---|---|---|---|
| age, y | 64.5 (57.0–71.5) | 64.5 (57.0–72.0) | 64.5 (56.0–69.0) | NS |
| BMI, kg/m² | 26.4 (24.4–29.1) | 26.9 (24.4–30.1) | 25.0 (21.8–27.1) | 0.036 |
| NYHA class I–III, n | 11/65/20 | 7/49/16 | 4/14/4 | NS |
| EF, % | 31.0 (25.0–37.0) | 30.0 (25.0–36.0) | 32.5 (27.0–38.0) | NS |
| sPAP, mmHg | 35.0 (30.0–44.5) | 35.0 (30.0–45.0) | 32.5 (30.0–44.0) | NS |
| office SBP, mmHg | 131.0 (118.0–140.0) | 131.5 (118.5–140.3) | 126.0 (112.0–138.0) | NS |
| office DBP, mmHg | 80.8 (72.0–87.0) | 81.0 (74.3–87.3) | 79.0 (68.5–85.0) | NS |
| 6MWT distance, m | 440.0 (360.0–521.0) | 459.0 (380.0–525.0) | 410.0 (324.0–462.0) | NS |
| AHI, 1/h | 6.6 (2.6–14.2) | 10.0 (3.0–16.0) | 4.9 (1.0–6.6) | 0.001 |
| central AHI | 0.1 (0.0–0.7) | 0.1 (0.0–1.0) | 0.0 (0.0–0.1) | 0.048 |
| obstructive AHI | 2.0 (0.4–4.3) | 2.3 (0.5–6.0) | 1.0 (0.3–2.3) | 0.038 |
| ischemic etiology, n (%) | 67 (69.1) | 56 (75.7) | 11 (50) | 0.021 |
| β-blockers, n (%) | 88 (91.7) | 67 (90.5) | 21 (95.5) | NS |
| ACEI/ARB, n (%) | 69 (71.9) | 54 (73.0) | 15 (68.2) | NS |
| diuretics, n (%) | 69 (71.9) | 52 (70.3) | 17 (77.3) | NS |

Data are presented as median (interquartile range) unless stated otherwise.

Abbreviations: 6MWT, 6-minute walk test; ACEI, angiotensin-converting enzyme inhibitor; AHI, apnea–hypopnea index; ARB, angiotensin receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; EF, ejection fraction; NYHA, New York Heart Association; NS, nonsignificant; SBP, systolic blood pressure; sPAP, systolic pulmonary artery pressure

etiology and sleep apneas, both central and obstructive. Of 96 patients, 20 had mild to moderate obstructive sleep apnea and 6 had mild to moderate central sleep apnea. On the other hand, there were no significant differences in baseline characteristics according to the intervention sequence (initial SBT versus initial control period).

The main clinical variables before and after the period of SBT are presented in TABLE 2. We observed a significant reduction in global AHI (from 5.6 [2.1–12.8] to 5.35 [2.0–10.8], $P = 0.043$), and a trend for a reduction in central apneas in the whole population ($P = 0.16$); central apneas were significantly reduced in men ($P = 0.039$) (even if the median values were close to 0 due to highly skewed distribution) but not in women ($P = 0.21$). No significant changes in obstructive apneas were observed (TABLE 2).

There was a significant improvement in LVEF after SBT (31.3% ±7.3% vs 32.3% ±7.7%; $P = 0.030$), accompanied by a reduction in end-diastolic diameter of the left ventricle and a trend for a reduction in the E/A ratio, while no change was observed in systolic pulmonary artery pressure (sPAP). The increase in LVEF was more evident in women (from 32.8% to 35.3%) than in men (from 30.8% to 31.4%; $P$ for interaction = 0.07), and in patients with NYHA class I (from 34.4% to 37.6%) compared with those with classes II (from 31.1% to 32.5%) and III (from 30.2% to 28.9%; $P$ for interaction = 0.018), while no effect of CHF etiology was observed (TABLE 2).

The 6MWT distance increased after SBT (449.9 ±122.7 m vs 468.3 ±121.9 m; $P < 0.001$; TABLE 2), regardless of the intervention sequence (FIGURE 2).

During the study, no patient reported safety issues related to study procedures and no adverse events attributable to the intervention occurred.

**DISCUSSION** Our study attempted to assess a number of clinically relevant parameters in a relatively large sample of patients with CHF before and after SBT. We indeed confirmed previous findings showing that SBT may improve cardiac function and functional performance. Furthermore, our study investigated for the first time the effects of SBT on sleep-disordered breathing in these patients.

Previous studies have suggested that slow breathing or SBT may be a useful adjunct to standard CHF treatment. Acute effects of slow breathing in patients with heart failure were assessed by Bernardi et al,[10] who reported an increase in blood oxygenation levels and improved exercise performance in participants who underwent 1-month training. Improvement in blood oxygenation seems to be related to an improved respiratory mechanics with increased alveolar ventilation[10] as shown also by a study in subjects exposed to hypoxia.[22]

The information on the beneficial effects of SBT was further extended by a pilot study by Parati et al,[9] in which SBT was performed with the same device as was used in the present study. These effects included reductions in both the NYHA class and sPAP, as well as improvement in EF, ventilatory parameters, and quality of life.

Furthermore, Ekman et al[11] found an improvement in NYHA class and breathlessness after 1 month of SBT with the RESPeRATE device.

**TABLE 2** Key clinical variables before and after slow breathing training

| Parameter | All participants (n = 96) | | | Male participants (n = 74) | | | Female participants (n = 22) | | |
|---|---|---|---|---|---|---|---|---|---|
| | before SBT | after SBT | *P* value | before SBT | after SBT | *P* value | before SBT | after SBT | *P* value |
| 6MWT, m | 449.9 ±122.7 | 468.3 ±121.9 | <0.001 | 461 (389–529) | 480 (402–574) | <0.001 | 420 ±134 | 427 ±135 | NS |
| sleep parameters | | | | | | | | | |
| AHI, 1/h | 5.6 (2.1–12.8) | 5.4 (2.0–10.8) | 0.043 | 7.2 (2.6–15.6) | 6.5 (2.5–12.4) | 0.013 | 4.0 ±4.3 | 4.8 ±4.8 | NS |
| AI central | 0.0 (0.0–0.7) | 0.0 (0.0–0.6) | NS | 0.1 (0.0–1.1) | 0.1 (0.0–0.7) | 0.039 | 0.0 (0.0–0.1) | 0.0 (0.0–0.4) | NS |
| AI obstructive | 1.6 (0.4–4.1) | 1.4 (0.5–4.6) | NS | 1.8 (0.5–5.3) | 1.6 (0.4–5.2) | NS | 1.2 ±1.6 | 1.9 ±2.1 | NS |
| echocardiography | | | | | | | | | |
| LVEDd, mm | 61 (56–65) | 60 (56–66) | 0.023 | 62 (58–66) | 61 (57–67) | 0.041 | 57 ±7 | 57 ±7 | NS |
| LVESd, mm | 49 (43–54) | 49 (43–55) | NS | 50 (44–54) | 50 (44–56) | NS | 45 (39–52) | 43 (40–47) | NS |
| E/A ratio | 0.80 (0.65–1.44) | 0.77 (0.67–1.20) | 0.061 | 0.79 (6.4–1.45) | 0.77 (0.63–1.22) | NS | 1.08 ±0.56 | 0.95 ±0.40 | NS |
| sPAP, mmHg | 35 (29–43) | 35 (28–40) | NS | 35 (27–43) | 35 (27–40) | NS | 33 (30–38) | 31 (30–43) | NS |
| LVEF,% | 31 ±7 | 32 ±8 | 0.030 | 31 ±7 | 31 ±7 | NS | 33 (26–38) | 35 (32–40) | 0.005 |

Data are presented as mean ± SD or median (interquartile range) as appropriate.

Abbreviations: AI, apnea index; E/A, early-to-late ventricular filling velocity ratio; LVEDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESd, left ventricular end-systolic diameter; SBT, slow breathing training; others, see TABLE 1

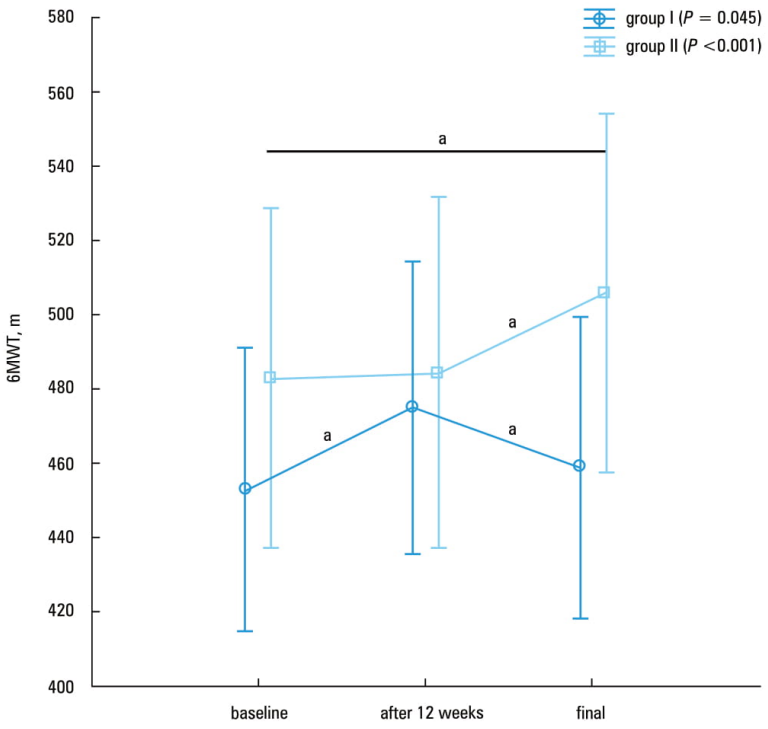


**FIGURE 2** Changes in the 6-minute walk test (6MWT) distance between study phases and treatment sequences; group I, started with slow breathing training; group II, started with standard care; data presented as mean ± standard error
**a** significant differences

In our study, we demonstrated that SBT led to a significant increase in LVEF in patients with CHF. This improvement might be the result of increasing the sensitivity of baroreceptor reflex and respiratory mechanics itself,[9] with a possible effect on respiratory muscles.[23] Our results are consistent with the results of the study by Parati et al,[9] although in the current study the increase in LVEF was less pronounced (Parati et al[9] reported an increase in LVEF from 32% ±6% to

39% ±9%). Similarly, in our population, we did not show a positive effect of SBT on the reduction of sPAP. These results differ from the results of the pilot study, where sPAP decreased from 49 ±17 mmHg to 38 ±9 mmHg after 10 weeks of SBT.

These discrepancies could be explained by the fact that the pilot study included patients with significantly higher baseline sPAP values: the baseline condition of more severely impaired pulmonary hemodynamics could have amplified a potentially favorable effect of slow breathing, less evident in the current study.[9] On the other hand, the controlled design of our study might also have reduced the foreseeable bias of a small uncontrolled study. Indeed, our data are in agreement with the results of a study by Fox et al[24] in patients with pulmonary hypertension, in whom 6 weeks of exercise training led to a significant improvement in the 6MWT distance despite nonsignificant changes in echocardiography parameters such as stroke volume and sPAP. Interestingly, the benefits in terms of LVEF improvement were mostly evident in female participants and in those with clinically milder CHF. Sex differences in response to exercise training in patients with CHF were previously reported by Pina et al,[25] who found greater benefits (measured by peak oxygen consumption and 6MWT) in women than in men with CHF. Although in our sample there was no significant difference between men and women in terms of a change in the 6MWT distance, the finding of improved LV function after SBT restricted to female sex may further support the usefulness of rehabilitation techniques in this group.

Sleep-disordered breathing is commonly seen in systolic and diastolic heart failure. Sleep apnea comprises several forms of sleep-disordered breathing. Although the pathophysiology of centrally driven apneas differs considerably compared with that of obstructive sleep apnea, they share multiple consequences. The differential diagnosis of the 2 forms of sleep apnea is based on polysomnographic studies where the presence or absence of respiratory movements distinguishes obstructive from central episodes. Apparently, there is a dose-dependent relationship between sleep disorders and the severity of heart failure, with a gradual increase in central sleep apnea occurrence along with the progression of cardiac failure.[14]

In our study, the AHI score equaled 6.6 (interquartile range, 2.6–14.2) at baseline. Nevertheless, the use of SBT resulted in an overall improvement in breathing stability during sleep as the AHI modestly decreased after active treatment (TABLE 2).

We observed a trend towards a reduced number of central apneas and hypopneas ($P = 0.16$), whereas no change was observed in obstructive episodes. Arguably, the absolute benefit in terms of improvement in sleep-disordered breathing was modest (the median central apnea index values equal to 0 derived from a highly skewed distribution of this variable with numerous participants having no central apneas). This was probably due to the fact that our intervention was not specifically aimed at reducing the burden of sleep apneas but rather at assessing clinical effects of SBT in a representative group of CHF patients followed in rehabilitation programs. Therefore, study participants had on average relatively mild CHF with good functional performance (79% of patients were classified as NYHA class II or lower), were in stable conditions, and had only modestly elevated body mass index (median, 26.4 kg/m$^2$). Therefore, since the prevalence of both central and obstructive sleep apneas was low, the conceivable benefits of SBT were limited. Also in this case we observed a difference between sexes; however, contrary to what was observed for the changes in LVEF, an improvement in central apneas was only evident in male participants, possibly due to a higher central apnea index at baseline.

The finding of the higher rate of central apneas in men is in line with an increase in the prevalence of central apneas in patients with CHF[26] and in healthy subjects exposed to high altitude where central apneas are common.[27] As a consequence of our findings, we believe that a study including specifically a sample of patients with CHF and sleep-disordered breathing would be justified. Considering that an optimization of heart failure treatment may alleviate central sleep apnea,[28,29] and in the wake of recent controversies regarding whether or not central sleep apnea should be specifically targeted in heart failure patients, a new therapeutic option targeting the pathophysiological basis of central apneas might be of particular interest.

In our previous analyses, we did not show significant changes in blood pressure values after SBT.[8] The RESPeRATE device has been successfully used to lower blood pressure in patients with hypertension. The lack of significant changes in blood pressure values in the studied group could be attributed to low prevalence of elevated blood pressure.

Our data showed an improvement in exercise capacity in the 6MWT after SBT. According to current guidelines, the 6MWT is easy to administer and provides strong indications for measuring the response to medical intervention in patients with heart failure.[21] In ambulatory patients with systolic heart failure, 6MWT provides prognostic utility comparable to that of cardiopulmonary exercise tests, which is the gold standard for the assessment of exercise capacity in this group of patients.[30]

The improvement in physical capacity on the basis of the bicycle cardiopulmonary exercise test in patients with heart failure treated with monthly respiratory training was reported by Bernardi et al.[10] After 1 month of respiratory muscle training, Mancini et al[31] found an improvement in exercise capacity based on the results of the 6MWT. Thus far, only the pilot study by Parati et al, which had similar duration and the same protocol as our study with the use of

the RESPeRATE device, showed an improvement in exercise capacity based on the bicycle cardiopulmonary test.[9] The meta-analysis by Montemezzo et al[32] of all studies on the use of respiratory rehabilitation in patients with heart failure confirms its beneficial effects on physical performance and usefulness in clinical practice, although it should be emphasized that the number of these studies is low.

Our study has several strengths. First, the respiratory profile after SBT with RESPeRATE had never been tested previously; second, the sample size was larger than in most previous studies[9,11]; third, the controlled design and the use of a device designed for SBT (and approved by the Food & Drug Administration for blood pressure lowering) followed a standardized exercise protocol. Furthermore, this device implements a series of features that make the exercise easier for the patient, including the individualized acoustic guidance of breathing frequency, which results in its gradual reduction, and visual feedback on the exercise performance. This is important as self-maintenance of a constant number of breaths by the patient is a difficult task, and rigid breathing pacing could have a negative effect on exercise performance.

There are also a few limitations. First, the majority of enrolled patients were in NYHA class II, thus the information on the tolerability and efficacy in more severe CHF is limited. Second, since for practical reasons we implemented a crossover rather than a parallel-group design, there might have been a carryover effect; however, the lack of interaction of the intervention sequence with the observed changes suggests that such an effect was not relevant. Third, a strict supervision of exercise quality in patients' homes was not performed, and the observed effect might have been diluted by participants who were not compliant with the training. Fourth, we did not assess breathing pattern during daytime and therefore have no data on the presence of central apneas in the awake period.[33] Finally, we could not exclude the possible influence of comorbidities (eg, diabetes, hypertension) or drugs on the results, although pharmacotherapy was kept stable during the study.

In conclusion, in patients with stable chronic systolic heart failure, SBT improved physical capacity and systolic left ventricular function, with a tendency to attenuate sleep disturbances, mainly central apnea. The latter results support the hypothesis that central sleep apnea may represent a consequence of heart failure or an adaptation mechanism to the complex neurohormonal abnormalities observed in these patients. We believe that device-guided SBT may be successfully implemented as a home-based rehabilitation tool in patients with CHF, leading to improvements in their clinical status and breathing patterns.

**Contribution statement** KS conceived the idea for the study. KS, DC, KK-J, and GP contributed to the design of the research. TD, DD-D, GK, KS, CL, AB, and SS were involved in data collection. GB, TD, and GK analyzed the data. KS and KK-J coordinated funding for the project. All authors edited and approved the final version of the manuscript.

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Original paper

# Renal denervation in patients with symptomatic chronic heart failure despite resynchronization therapy – a pilot study

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**Abstract**

**Introduction:** Renal denervation (RD) has been shown to decrease sympathetic function in patients with hypertension. Its efficacy in symptomatic chronic heart failure (CHF) patients not responding to cardiac resynchronization therapy (CRT) has not been evaluated.

**Aim:** To assess whether a less invasive treatment method – renal denervation – is safe in symptomatic heart failure patients despite optimal medical treatment and resynchronization therapy and whether it is associated with an improvement in clinical status, exercise capacity and hemodynamic parameters.

**Material and methods:** The study was an open-label, randomized, controlled clinical trial. Patients were divided into an intervention (RD) and a control group. Clinical data collection, blood pressure (BP) measurements, echocardiography, 6-minute walk test (6MWT) and laboratory tests were performed before, 6 and 12 months after RD. The patients were followed-up to 24 months.

**Results:** We included 20 patients aged 52.0 to 86.0 years (median age: 71.5 years), 15 males and 5 females with median left ventricular ejection fraction (LVEF) of 32.5%, body mass index 31.3 kg/m$^2$. Renal denervation was safe, no significant adverse effects were registered. There were no significant differences in LVEF, BP, 6MWT and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) concentration 6 and 12 months after RD or control.

**Conclusions:** Our results indicate that RD in CHF patients not responding to CRT is safe and does not worsen exercise capacity and hemodynamic parameters.

**Key words:** chronic heart failure, cardiac resynchronization therapy, renal denervation.

Summary

Renal denervation (RD) in symptomatic chronic heart failure patients not responding to cardiac resynchronization therapy has not been evaluated. In our patients RD was safe, no serious adverse effects were registered. We detected no significant relation between renal artery denervation and clinical status, exercise capacity and hemodynamic parameters in optimally treated heart failure patients with systolic blood pressure over 110 mm Hg. Renal denervation was a safe procedure in this population.

## Introduction

Currently, due to advances in treatment, we observe an increase in life expectancy in patients with hypertension and coronary artery disease. These diseases are among the leading causes of heart failure development and, as a result of better survival rate and longer lifespan in these patients, chronic heart failure (CHF) is increasing in prevalence [1–3]. Despite the unquestionable progress in treatment of these predisposing diseases the mortality rate of CHF patients has only slightly improved in recent years [4]. Cardiac resynchronization therapy (CRT) – a method of heart stimulation – was introduced into the treatment of heart failure almost 20 years ago [5]. The CRT is used in symptomatic patients with advanced stages of heart failure, despite optimal pharmacological therapy, with accompanying intraventricular conduction block. It is one of the most promis-

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ing therapies, with a confirmed beneficial effect on heart failure outcomes [6]. However, there still remains a group of patients in which CRT it is not effective. About one third of patients who receive CRT do not have a meaningful clinical improvement. The reasons for this are complex and still not fully understood [7]. To date in this group of patients only left ventricular assist devices and heart transplant remain possible therapeutic modalities, but the accessibility of these methods is still insufficient.

## Aim

We aimed to assess whether a less invasive treatment method – renal denervation – is safe in symptomatic heart failure patients despite optimal medical treatment and resynchronization therapy and whether it is associated with an improvement in clinical status, exercise capacity and hemodynamic parameters.

## Material and methods

### Study design

The study was conducted as an open-label, prospective, randomized, controlled clinical trial where patients were assigned to an intervention group undergoing the renal denervation procedure and a control group with no intervention based on the results of coin toss. Peripheral blood pressure (BP) measurements, transthoracic echocardiography, 6-minute walk test (6MWT), renal function assessment and biochemistry were performed at baseline and after 6 and 12 months. The patients were followed-up to 24 months. Optimal pharmacotherapy according to current European Society of Cardiology (ESC) guidelines was kept constant throughout the study [1, 2]. The echocardiographic optimization of atrioventricular and interventricular delay in CRT was performed for each patient before the study.

### Ethics

The study was performed in accordance with the 1975 Declaration of Helsinki for Human Research and approved by the Jagiellonian University Bioethical Committee. Patients were included only if they gave their informed consent. The study is registered in the ClinicalTrials.gov repository (id: NCT02329145).

### Study population

Adult CHF patients who met the following criteria were enrolled in this study: NYHA class II–IV; implanted resynchronization pacemaker according to current European guidelines at least 6 months prior to inclusion; persistent symptoms, defined as a lack of improvement in subjective dyspnea or exercise tolerance, despite stable pharmacological treatment over the previous 4 weeks (with ACE inhibitor and β-blocker unless contraindicated) and optimal biventricular (BIV) pacing (no less than 98% of paced QRS complexes); left ventricular ejection fraction (LVEF) equal to or lower than 35% in echocardiographic assessment prior to CRT implantation; estimated glomerular filtration rate (eGFR according to Modification of Diet in Renal Disease (MDRD) formula $\geq$ 30 ml/min/1.73 m$^2$).

We excluded patients with renal artery anatomy not eligible for denervation (< 4 mm diameter, < 20 mm in length) [8]; history of prior renal artery intervention; single functioning kidney; systolic BP < 110 mm Hg; acute coronary syndrome or cerebrovascular event within last 3 months; serious medical conditions which may adversely affect safety such as significant peripheral vascular disease, abdominal aortic aneurysm, bleeding disorders (thrombocytopenia, hemophilia, or significant anemia) or pregnancy.

### Renal denervation

Patients in the treatment group underwent renal artery denervation performed by an endovascular catheter-based approach in order to disrupt renal sympathetic nerves. A Symplicity radiofrequency renal-denervation catheter (Medtronic) was used. The central artery tree and renal artery were accessed by the femoral artery. The catheter was connected to a radiofrequency (RF) generator and multiple RF applications were performed in order to disrupt renal sympathetic nerves. We performed up to six radiofrequency ablations of up to 2 min duration that were separated both longitudinally and rotationally within each renal artery. Renal evaluations using duplex scan were performed in order to exclude baseline renovascular abnormalities and possible complications of the procedure, the main one being renal artery stenosis [8].

### Peripheral blood pressure measurement

Office BP measurement was performed according to standards of the Polish Society of Hypertension [9]. Twenty-four-hour peripheral blood pressure monitoring was performed with the SpaceLabs 90207 monitor (Redmond, WA, USA). BP measurements were performed daily every 15 min (6 a.m. to 22 p.m.) and every 30 min at night (22.00 p.m. to 6.00 a.m.). Based on the acquired recordings mean values for systolic, diastolic blood pressure was calculated for 24 h, day and night time.

### Echocardiography

Echocardiography was performed using the Vivid 7 Pro (General Electric, Fairfield, USA), with a 2.5 MHz probe by a single experienced operator who was blinded to the patients' allocation to experimental groups. Measurements were assessed according to the European Society of Echocardiography standards [10]. Left ventricle mass was calculated using the Devereux formula [10].

### Six-minute walk test (6MWT)

The 6-minute walk test was performed in patients after a 10-minute, seated rest period. Patients were asked to march at their own pace, on a flat and level surface in an empty corridor. Patients were informed about the progress of the test on a regular basis; at the end of the 6-minute period, the total distance walked was measured. At baseline and after the test blood pressure and oxygen saturation were also measured [11].

### Biochemistry

Biochemical parameters such as serum N-terminal prohormone of brain natriuretic peptide (NT-proBNP), creatinine (with the calculation of eGFR) and electrolytes were measured.

### End points of the study

Primary end points were: 1) number of hospitalizations due to heart failure worsening within 1 year; 2) change in NYHA class within 1 year; 3) change in 6-minute walk test distance within 1 year. Additionally we evaluated the change in LVEF, BP values and NT-proBNP concentrations.

### Safety

Safety parameters included death, stroke, myocardial infarction, renal artery stenosis or dissection, pseudoaneurysm at the femoral access site, bleeding, and reduction in eGFR.

### Statistical analysis

All data were analyzed using the Statistica PL v.12.0 software. Categorical variables are reported as percentages and continuous variables as median and interquartile ranges when data distribution differed from the normal. The $\chi^2$ tests were applied to all categorical variables. For continuous variables, the Mann-Whitney test, the *t*-test for paired samples or the Wilcoxon matched pairs test was used. Effects for which the *p*-value was lower than the assumed level of significance $\alpha = 0.05$ ($p < 0.05$) were considered significant.

## Results

### Patient cohort

We screened 24 patients for being eligible for inclusion. In 4 patients in abdominal computed tomography we found tumors with suspicion of malignancy. These patients were excluded from the study [12]. Twenty patients aged 52.0 to 86.0 years (median age: 71.5 years), 15 males and 5 females with median LVEF of 32.5%, in NYHA class II and III, median body mass index (BMI) 31.3 kg/m$^2$ were randomized. Secondary forms of cardiomyopathy were the most prevalent causes of CHF – 12 (60%) patients had ischemic cardiomyopathy. Eight (40%) patients had dilated cardiomyopathy of unknown etiology. The median QRS complex duration prior to CRT implantation was 150 ms and after the procedure 120 ms. Nineteen (95%) patients had left bundle branch block morphology and 1 patient had right bundle branch block. The median LVEF prior to CRT implantation was 27%. The clinical characteristics of enrolled patients are shown in Table I separately for the intervention and control groups. There were no significant differences in baseline characteristics according to group assignment.

The mean total time of denervation was 661 ±65 s for the right and 668 ±84 s for the left renal artery. The reduction of tissue resistance during ablation was 14.36 ±2.53 and 13.89 ±1.89%, respectively.

### Primary endpoints

During 12 months of observation 3 patients in the RD group and 2 in the control group were rehospitalized due to decompesation of heart failure ($p$ = NS) whereas during 24 months of observation 4 patients inthe RD and 5 patients incontrol group were rehospitalized ($p$ = NS).

In the intervention group during 12 months of observation two patients improved from NYHA class III to II. In the control in 12 months 1 patient deteriorated from class II to III. The changes in NYHA class are presented in Figures 1 and 2.

The median change in 6MWT distance in the RD group was bigger compared to the control group, but it did not reach statistical significance (+38.0 (–50.0; +90.0) vs. 0.0 (–100.0; +40.0) m, $p = 0.212$).

### Secondary endpoints

Table II reports the changes in main clinical variables 6 and 12 months after renal denervation or allocation to the control group. We did not observe any significant changes in median heart rate, office blood pressure values, 6MWT distance or NT-proBNP concentrations.

### Safety results

Renal denervation was safe, the procedure was done without complications in all of the patients and no significant periprocedural adverse effects (e.g. renal artery stenosis or dissection, pseudoaneurysm at the femoral access site, bleeding) were observed. After 6 and 12 months of observation we did not observe significant changes in eGFR in either the intervention or the control group. No patient developed renal-related symptoms.

In 2-year follow-up 1 (5%) patient from the intervention group (10%) died of an unknown cause. What could have influenced the death is the fact that he discontinued the vitamin K antagonist despite indications (persistent AF and self-contrast of blood in echocardiography). After the 2-year follow-up we received information about the second death of a patient from the intervention group.

There were no strokes or myocardial infarctions during the course of the study.

## Discussion

To the authors' knowledge this is the first report of a randomized controlled trial examining the role of renal denervation in patients with symptomatic heart failure with reduced ejection fraction not responding to resynchronization therapy. We found that the procedure of RD in patients with CHF is safe as no long-term adverse events resulted from the intervention. Especially, we did not observe any cases of renal artery stenosis or aneurysm. Furthermore, we observed no significant impairment of renal function according to the estimated glomerular filtration rate.

The activation of the sympathetic nervous system is one of the pathomechanisms responsible for the development and progression of heart failure. In chronic heart failure increased activity of the sympathetic and decreased activity of the parasympathetic system are present [13]. Based on previous studies involving renal denervation in patients with resistant hypertension, a decrease in the excessive activity of the sympathetic nervous system in heart failure patients after renal denervation might be expected [14]. This knowledge has generated an interest in renal denervation including catheter-based procedures as an attractive therapeutic approach in the therapy of resistant hypertension. Primary clinical data from two big trials – Symplicity HTN-1 and HTN-2 – demonstrated that catheter-based renal sympa-

**Table I.** Baseline characteristics of study participants

| Parameter | All ($n$ = 20) | Denervation ($n$ = 10) | Control ($n$ = 10) | $P$-value |
|---|---|---|---|---|
| NYHA Class | 3.0 (2.0–3.0) | 3.0 (3.0–3.0) | 2.5 (2.0–3.0) | NS |
| Age [years] | 71.5 (67.5–78.0) | 75.0 (65.0–81.0) | 71.0 (70.0–76.0) | NS |
| Sex, male, $n$ (%) | 15 (75) | 8 (80) | 7 (70) | NS |
| BMI [kg/m$^2$] | 31.3 (29.2–35.6) | 31.1 (29.5–32.0) | 32.1 (26.2–37.7) | NS |
| LVEF prior to CRT (%) | 27.0 (22.0–33.5) | 27.5 (22.0–35.0) | 27.0 (25.0–32.0) | NS |
| LVEF at RD (%) | 32.5 (27.5–37.5) | 33.5 (30.0–40.0) | 32.0 (25.0–36.0) | NS |
| Heart rate [/min] | 70 (63.0–75.0) | 64.0 (61.0–75.0) | 70.0 (64.0–75.0) | NS |
| Office SBP [mm Hg] | 125 (120–137) | 124 (120–130) | 132 (120–153) | NS |
| Office DBP [mm Hg] | 74 (70–80) | 73 (70–80) | 74 (70–78) | NS |
| 24 h SBP [mm Hg] | 111 (102–118) | 113 (100–118) | 111 (102–119) | NS |
| 24 h DBP [mm Hg] | 63 (55–68) | 59 (56–68) | 65 (54–69) | NS |
| 6MWT distance [m] | 330 (270–415) | 320 (240–330) | 380 (300–440) | NS |
| NT-proBNP [pg/ml] | 1116 (491–2132) | 1116 (445–1878) | 1148 (537–2387) | NS |
| $HbA_{1c}$ (%) | 6.1 (5.8–6.4) | 6.3 (6.0–6.5) | 5.8 (5.6–6.4) | NS |
| Infarction, $n$ (%) | 8 (40) | 5 (50) | 3 (30) | NS |
| Diabetes, $n$ (%) | 9 (45) | 5 (50) | 4 (40) | NS |
| Hypertension, $n$ (%) | 15 (75) | 7 (70) | 8 (80) | NS |
| History of stroke, $n$ (%) | 3 (15) | 1 (10) | 2 (20) | NS |
| Hypercholesterolemia, $n$ (%) | 17 (85) | 8 (40) | 9 (45) | NS |
| CKD, $n$ (%) | 6 (30) | 4 (40) | 2 (20) | NS |
| CABG, $n$ (%) | 1 (5) | 0 (0) | 1 (10) | NS |
| PCI, $n$ (%) | 4 (20) | 4 (40) | 0 (0) | NS |
| AF, $n$ (%) | 16 (80) | 8 (80) | 8 (80) | NS |
| β-Blocker, $n$ (%) | 20 (100) | 10 (100) | 10 (100) | NS |
| ACEI/ARB, $n$ (%) | 17 (85) | 8 (80) | 9 (90) | NS |
| MRA, $n$ (%) | 17 (85) | 8 (80) | 9 (90) | NS |
| Diuretic, $n$ (%) | 19 (95) | 9 (90) | 10 (100) | NS |
| Digoxin, $n$ (%) | 5 (25) | 1 (10) | 40 (40) | NS |

*Values presented as median (interquartile range) or percentage. BMI – body mass index, LVEF – left ventricular ejection fraction, CRT – cardiac resynchronization therapy, RD – renal denervation, SBP – systolic blood pressure, DBP – diastolic blood pressure, 6MWT – 6-minute walk test, NT-proBNP – N-terminal prohormone of brain natriuretic peptide, $HbA_{1c}$ – glycated hemoglobin, CKD – chronic kidney disease, CABG – coronary artery bypass graft, PCI – percutaneous coronary intervention, AF – atrial fibrillation, ACEI – angiotensin-converting enzyme inhibitor, ARB – angiotensin receptor blocker, MRA – mineralocorticoid receptor antagonist, NYHA – New York Heart Association.*

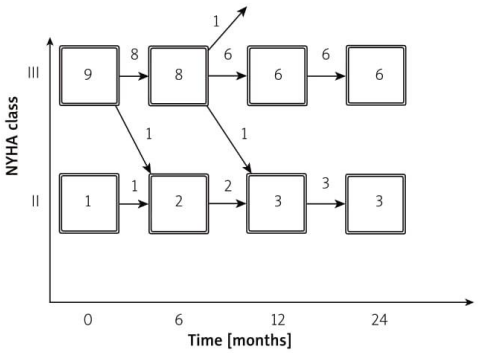


**Figure 1.** Changes in New York Heart Association (NYHA) class in the denervation group

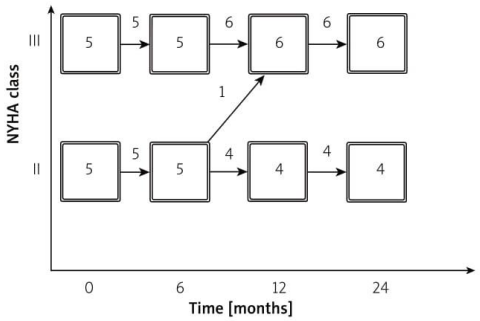


**Figure 2.** Changes in New York Heart Association (NYHA) class in the control group

**Table II.** Change in clinical variables at baseline and after 6 and 12 months

| Parameter | From baseline to 6th month | | | From baseline to 12th month | | |
|---|---|---|---|---|---|---|
| | RD (*n* = 10) | Control (*n* = 10) | *P*-value | RD (*n* = 10) | Control (*n* = 10) | *P*-value |
| LVEF (%) | 0.0 (0.0–3.0) | 2.0 (0.0; 7.0) | NS | 0.0 (–3.0; 7.0) | 2.0 (–3.0; 8.0) | NS |
| Heart rate [/min] | –1.5 (–4.0; –1) | 1.0 (0.0–5.0) | NS | 1.0 (–3.0; 4.0) | 4.5 (2.0; 6.0) | NS |
| Office SBP [mm Hg] | –1.0 (–4.0; 20.0) | 0.0 (–13.0; 15) | NS | 17.5 (10.0–28.0) | –5.0 (–16.0; 22.0) | NS |
| Office DBP [mm Hg] | 0.0 (–2.0; 14.0) | 0.0 (–5.0; 3.0) | NS | 8.0 (2.0–18.0) | 1.5 (–1.0; 5.0) | NS |
| 24 h SBP [mm Hg] | 3.0 (–9.0; 15.0) | –9.0 (–15.0; 5.0) | NS | 7.5 (6.0; 17.0) | –1.5 (–8.0; 3.0) | NS |
| 24 h DBP [mm Hg] | 5.0 (–1.0; 9.0) | –3.0 (–9.0; 7.0) | NS | 4.5 (3.0; 10.0) | 2.5 (–6.0; 6.0) | NS |
| 6MWT distance [m] | 20.0 (0.0; 90.0) | 2.0 (–20.0; 60.0) | NS | 38.0 (–50.0; 90.0) | 0.0 (–100.0; 40.0) | NS |
| NT-proBNP [pg/ml] | 31 (–450; 906) | –69 (–347; 48) | NS | –11(–1059; 462) | 211 (–22; 735) | NS |
| eGFR [ml/min/1.73 m$^2$] | 0.70 (–6.0; 17.1) | –0.6 (–11.2; 14.8) | NS | –4.1 (7.9; 0.0) | 0.4 (–7.4; 6.7) | NS |

*Values presented as median (interquartile range). RD – renal denervation, LVEF – left ventricular ejection fraction, SBP – systolic blood pressure, DBP – diastolic blood pressure, 6MWT – 6-minute walk test, eGFR – estimated glomerular filtration rate.*

thetic denervation can be safely used to reduce blood pressure within 24 months' observation [15, 16]. However, the results of the Symplicity HTN-3 trial have not confirmed the blood-lowering effect of renal denervation [17]. However, several factors had a substantial impact on the results of the HTN-3 trial [18]. Later studies, like the multicenter, international, single-blind, randomized, sham-controlled SPYRAL HTN-OFF MED study showed in 80 patients a significant reduction in both office and 24-h ambulatory blood pressure values in the intervention group with no effect in the control group. There were no major adverse events in either group [19].

Renal denervation studies in hypertension have shown a positive effect of RD on cardiac remodeling such as a reduction in left atrial volume index [20], reduction in mean interventricular septum thickness, LV mass index (LVMI) and LV filling pressures and an increase in LVEF [21 22].

There have been several studies that evaluated the effect of renal denervation in patients with CHF. One such study is the REACH study, which showed that RD in patients with CHF is safe. No episodes of syncope, hypotension or other significant hemodynamic dysfunction were recorded during the acute phase after RD and renal function remained stable. Furthermore, 6 months after RD a non-significant blood pressure reduction and an improvement in 6-minute walk distance ($\Delta$ = 27.1 ±9.7 m, $p$ = 0.03) were observed [23]. According to current guidelines, 6MWT is easy to administer and provides strong indications for measuring the response to medical intervention in patients with heart failure [11]. In ambulatory patients with systolic heart failure, 6MWT provides prognostic utility comparable to cardiopulmonary exercise tests, which is the gold standard for the assessment of exercise capacity in this group of patients [24]. In our study we found a non-significant improvement in 6MWT in patients 6 months after RD (320 (240; 330) vs. 335 (280; 360) m, $p$ = NS).

In a randomized, controlled pilot study by Chen *et al.* 60 symptomatic patients with CHF and reduced

EF (< 40%) were randomized to RD plus optimal medical therapy (OMT) or only OMT. Throughout the study no severe adverse events were observed. Blood pressure was stable in both groups. Patients 6 months after RD showed a significant improvement in LVEF (31.1 ±5.7 vs. 41.9 ±7.9%, $p < 0.001$) and 6-minute walk test distance (285.5 ±84.3 vs. 374.9 ±91.9 m, $p = 0.043$) and quality of life. NT-proBNP after RD was significantly reduced ($p < 0.001$). No significant changes in estimated glomerular filtration and no renal complications were found [25]. Compared to our study, the patients examined by Chen *et al.* were significantly younger, with less prevalent ischemic etiology and no stimulation.

Gao *et al.* in a study on 14 patients with CHF and ejection fraction < 45%, who received bilateral RD, observed, 6 months after the procedure, a significant increase in 6MWT distance (152.9 ±38.0 vs. 334.3 ±94.4 m, $p < 0.001$) and EF (36.0 ±4.1 vs. 43.8 ±7.9%, $p = 0.003$). On the other hand, systolic BP decreased from 138.6 ±22.1 to 123.2 ±10.5 mm Hg ($p = 0.026$) and diastolic BP from 81.1 ±11.3 to 72.9 ±7.5 mm Hg ($p = 0.032$). The authors did not observe adverse results or worsening of renal function. However, one of the limitations of this study was the lack of a control group [26].

The RDT-PEF study aimed at assessing the effect of RD with the Symplicity catheter vs standard therapy on several clinical parameters (Minnesota Living with Heart Failure Questionnaire score, peak oxygen uptake ($VO_2$) on exercise, BNP, E/e', LA volume index or LV mass index). Due to recruitment difficulties, the study was terminated after inclusion of only 25 patients and was underpowered to detect whether RD influenced the defined endpoints. Changes in eGFR were comparable in the two groups, but 2 patients required balloon angioplasty during the RD to treat renal artery wall edema [27].

In a study by Hopper *et al.* on 40 HF patients RD was associated with small reductions in NT-proBNP and 120-minute glucose tolerance at 12 months with no RD-associated adverse effect, except for 1 case of renal artery occlusion [28].

These previously described beneficial effects of RD on BP may also extend to the preservation of renal function. Kiuchi *et al.* reported beneficial effects of RD in 24 patients with chronic kidney disease and refractory hypertension on kidney function. A significant improvement in eGFR (85.4 ±34.9 vs. 64.4 ±23.9 ml/min/1.73 $m^2$, $p < 0.0001$) and a decrease in the median urine albumin/creatinine ratio (15.7 (10.3–34.2) vs. 48.5 (35.8–157.2) mg/g, $p = 0.0017$) at 6 months of follow-up were present [29]. There were also reports of a reduction in albuminuria after RD in patients with resistant hypertension [30]. Furthermore, a reduction in Doppler sonographic renal resistive index, which reflects systemic and renal hemodynamics, has been associated with progression of renal impairment and which could be a potential noninvasive predictor of lack of response to RD, has been observed [31]. In our study we observed a non-significant increase in eGFR after RD proving its safety in CHF patients in regard to renal function. Unfortunately we did not evaluate microalbuminuria.

Throughout the study one of the patients from the intervention group died of an unknown cause at home. We could not associate the death with the procedure of RD, as no acute and follow-up disturbances have been noted. The studied population consisted of patients with severe heart failure that did not respond to optimal pharmaco- and electrotherapy and the worsening of the underlying disease was the most probable cause of death.

Our study has several strengths. Firstly, it is the first study regarding renal denervation in patients with CHF not responding to CRT. To date, there have been several ongoing studies concerning RD in CHF, but there are no studies evaluating this intervention in severe stages of CHF that do not benefit from CRT. So far in this scientific area only limited data are available. Thus the above study has a pilot character.

There are also a few limitations. First, the small number of patients may have resulted in the study being underpowered to show significant change in evaluated parameters. One may speculate that RD could counteract the progression of CHF in these patients. Thus, the observed improvement in exercise capacity was small and did not reach statistical significance. Second, the use of a single-electrode catheter might have led to an inability to create a circumferential lesion effortlessly, which unfortunately cannot reliably be assessed during the procedure. In a 2017 position paper on the autonomic nervous system as a therapeutic target in heart failure from the Translational Research Committee of the Heart Failure Association of the ESC the use of such catheters is discouraged. However, when the protocol of this study was created and introduced, newer catheters and the aforementioned data were not yet available [32]. Furthermore, despite the increase in CRT implantation in recent years, the population of patients with this device who are eligible for RD is still limited due to hypotension or atherosclerosis of renal arteries. The lack of a sham procedure also limits the power of the results.

## Conclusions

We detected no significant relation between renal artery denervation and clinical status, exercise capacity and hemodynamic parameters in optimally treated heart failure patients with systolic blood pressure over 110 mm Hg. Renal denervation was a safe procedure in this population.

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## Conflict of interest

The authors declare no conflict of interest.

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## 6. Wyniki

*Publikacja 1*

Przebadano grupę czterdziestu pacjentów z niewydolnością serca z obniżoną frakcją wyrzutową lewej komory (*left venticular ejection fraction*, LVEF). Pacjentów randomizowano do dwóch grup: rozpoczynającej od treningu wolnego oddychania (*slow breathing training*, SBT) oraz rozpoczynającej od braku interwencji, następnie zamieniano grupy (cross-over). Każda faza badania trwała 10-12 tygodni. Oceniano wpływ SBT z użyciem urządzenia RESPeRATE na zmiany ciśnienia tętniczego, częstość hipotonii ortostatycznej (OH) oraz zmianę jakości życia (QoL). OH zdefiniowano jako spadek ciśnienia skurczowego krwi o ≥ 20 mmHg lub rozkurczowego o ≥ 10 mmHg w ciągu 3 minut stania. QoL była oceniana kwestionariuszem Minnesota. Częstość OH była niska i nie zmieniła się w trakcie badania (10% vs 10%). W grupie rozpoczynającej od SBT obserwowano spadek wyniku w MLHF (49,7 vs 46,1 pkt; p=0,002).

*Publikacja 2*

Przebadano 96 pacjentów z NS z obniżoną LVEF. Oceniano wpływ SBT na wydolność wysiłkową, parametry hemodynamiczne i wzorce oddechowe podczas snu w badaniu naprzemiennym (10 do 12 tygodni SBT z użyciem urządzenia RESPeRATE i, odpowiednio, kontroli). SBT był bezpieczny. Po treningu poprawiły się LVEF (31,3% ± 7,3% vs 32,3% ± 7,7%; p=0,030), a także dystans w teście 6-minutowego marszu (449,9 ± 122,7 m vs 468,3 ± 121,9 m; p <0,001). Zmniejszył się także wskaźnik bezdechów i spłyceń oddechów (mediana 5,6 [rozstęp międzykwartylowy (IQR), 2,1; 12,8] vs. 5,4 [IQR, 2,0; 10,8]; p=0,043).

*Publikacja 3*

U pacjentów z objawową przewlekłą NS z obniżoną LVEF nie odpowiadających na terapię resynchronizującą oceniano, czy denerwacja tętnic nerkowych jest bezpieczna i czy prowadzi do poprawy stanu klinicznego, wydolności wysiłkowej i parametrów hemodynamicznych. 20 pacjentów zrandomizowano 1:1 do interwencji (RDN) i grupy

kontrolnej. Denerwacja tętnic nerkowych była bezpieczna, nie stwierdzono istotnych działań niepożądanych. Nie było istotnych różnic pomiędzy grupami w zakresie frakcji wyrzutowej lewej komory, wartości ciśnień, dystansu w teście 6-minutowego marszu czy stężeniach NT-proBNP po 12 miesiącach.

## 7. Wnioski

W *Publikacji 1* potwierdzono bezpieczeństwo stosowania treningu wolnego oddychania przy użyciu urządzenia RESPeRATE w populacji pacjentów z niewydolnością serca z obniżoną frakcją wyrzutową w zakresie braku nasilenia zjawiska hipotonii ortostatycznej. Ponadto stwierdzono tendencję do poprawy jakości życia.

Zastosowanie treningu wolnego oddychania u pacjentów z NS z obniżoną LVEF w *Publikacji 2* prowadziło do poprawy wydolności fizycznej (definiowanej jako dystans w teście 6-minutowego marszu), poprawy czynności skurczowej lewej komory serca oraz do zmniejszenia zaburzeń oddychania w trakcie snu.

Denerwacja tętnic nerkowych u pacjentów z objawową NS nie reagującą na terapię resynchronizującą oraz optymalną farmakoterapię w *Publikacji 3* była bezpieczna, nie prowadziła do pogorszenia wydolności wysiłkowej, parametrów hemodynamicznych czy funkcji nerek. Niestety, metoda ta nie przyniosła istotnej poprawy w zakresie najważniejszych parametrów oceniających nasilenie niewydolności serca. Z obserwacji nie wynika aby zastosowanie denerwacji nerek mogło przynieść dodatkowe korzyści pacjentom z objawową przewlekłą niewydolnością serca.

Wyniki powyższych badań potwierdzają korzyści płynące z treningu wolnego oddychania jako nowego elementu programów rehabilitacji krążeniowo-oddechowej u pacjentów z NS. Przydatność techniki denerwacji tętnic nerkowych wymaga jednak dalszych badań.

## 8. Streszczenie pracy doktorskiej w języku polskim

Niewydolność serca (NS) staje się coraz bardziej rozpowszechnioną chorobą wraz ze zwiększaniem się długości życia oraz skuteczniejszym leczeniem nadciśnienia tętniczego i choroby wieńcowej, jej wiodących przyczyn. Leczenie NS, obok farmakoterapii obejmuje metody niefarmakologiczne (m.in. rehabilitację fizyczną) oraz inwazyjne. Istotne znaczenie mogą mieć zwłaszcza nowe metody niefarmakologiczne. Zaburzenia oddychania, takie jak centralne bezdechy, często występują w przebiegu zaawansowanej NS i świadczą o gorszym rokowaniu. Z drugiej strony zmniejszona w przebiegu treningu oddychania częstość oddechów może mieć korzystny wpływ na pracę układu sercowo-naczyniowego, zwłaszcza w niewydolności serca. Samodzielne utrzymanie zmniejszonej częstości oddechów jest jednak trudne. Z pomocą może przyjść urządzenia RESPeRATE, wspomagające zwolnienie oddychania poprzez sygnały wizualne i akustyczne, które było skuteczne w obniżaniu ciśnienia tętniczego w przebiegu nadciśnienia. Do leczenia NS około 20 lat temu wprowadzono nową metodę stymulacji – terapię resynchronizującą (CRT). Wciąż jednak pozostaje grupa chorych, u których nie przynosi ona spodziewanych rezultatów i nie następuje poprawa kliniczna, co może mieć związek z nadmierną aktywacją współczulnego układu nerwowego. Denerwacja tętnic nerkowych, metoda badana w leczeniu opornego nadciśnienia tętniczego może natomiast prowadzić do zmniejszenia ogólnoustrojowej aktywności układu współczulnego.

Celem pracy była ocena bezpieczeństwa i wpływu na wydolność fizyczną, parametry hemodynamiczne oraz jakość życia u objawowych pacjentów z NS z obniżoną frakcją wyrzutową lewej komory: a) treningu wolnego oddychania (SBT); b) denerwacji tętnic nerkowych (RDN) u pacjentów z objawami NS pomimo terapii resynchronizującej (CRT).

W pierwszej pracy zbadano 40 pacjentów z NS z obniżoną frakcją wyrzutową lewej komory (LVEF). Pacjenci naprzemiennie wykonywali SBT z użyciem urządzenia RESPeRATE

lub stosowali tylko standardową terapię w fazach 10-12 tygodniowych. Oceniano wpływ SBT na zmiany ciśnienia tętniczego, częstość hipotonii ortostatycznej (OH, spadek skurczowego o ≥ 20 mmHg lub rozkurczowego ciśnienia tętniczego o ≥ 10 mmHg w ciągu 3 minut stania) oraz zmianę jakości życia (kwestionariusz Minnesota - MLHF). Częstość OH była niska i nie zmieniła się w trakcie badania (10% vs 10%). W grupie rozpoczynającej od SBT obserwowano poprawę jakości życia - spadek wyniku w MLHF (49,7 vs 46,1 pkt; p=0,002)..

W drugiej pracy przebadano 96 pacjentów z NS z obniżoną LVEF. Oceniano wpływ SBT na wydolność wysiłkową, parametry hemodynamiczne i wzorce oddechowe podczas snu w badaniu naprzemiennym (10 do 12 tygodni SBT z użyciem urządzenia RESPeRATE i, odpowiednio, kontroli). SBT był bezpieczny. Po treningu poprawiły się LVEF (31,3% ± 7,3% vs 32,3% ± 7,7%; P = 0,030), a także dystans w teście 6-minutowego marszu (449,9 ± 122,7 m vs 468,3 ± 121,9 m; P <0,001). Zmniejszył się także wskaźnik bezdechów i spłyceń oddechów (mediana 5,6 [rozstęp międzykwartylowy (IQR), 2,1; 12,8] vs. 5,4 [IQR, 2,0; 10,8]; P = 0,043).

W trzeciej pracy zbadano 20 pacjentów w wieku od 52 do 86 lat, z objawową, pomimo terapii resynchronizującej, NS, których randomizowano do grupy ablacji tętnic nerkowych (RDN) i kontrolnej. Średnia LVEF wyniosła 32,5%, badani byli w klasach NYHA II i III. Oceniano, czy RDN jest bezpieczna i czy prowadzi do poprawy stanu klinicznego, wydolności wysiłkowej i parametrów hemodynamicznych. Wykonano ocenę układu autonomicznego, echokardiografię, badanie jakości życia z zastosowaniem kwestionariusza Minnesota, test 6-minutowego marszu, ocenę funkcji nerek i wybrane badania biochemiczne (NT-proBNP). RDN była bezpieczna, nie stwierdzono istotnych działań niepożądanych. Nie było istotnych różnic pomiędzy grupami w zakresie badanych parametrów po 12 miesiącach.

Wyniki badań potwierdziły, że metoda domowej rehabilitacji oparta na treningu wolnego oddychania jest bezpieczna i łatwa do stosowania przez pacjentów i nie prowadzi do pogorszenia

jakości życia. Trening wolnego oddychania wpłynął korzystnie na wydolność wysiłkową mierzoną dystansem marszu, funkcję skurczową serca ocenianą echokardiograficzne oraz zmniejszył liczbę zaburzeń oddechowych w czasie snu, w tym występowanie epizodów bezdechu centralnego. Wyniki dowodzą, że trening wolnego oddychania może być nową metodą niefarmakologicznego leczenia niewydolności serca.

Według dostępnej wiedzy badanie było pierwszą próbą oceny RDN u pacjentów z wszczepionym CRT. Denerwacja nerek u pacjentów z przewlekłą objawową niewydolnością serca leczoną optymalnie farmakologicznie i z zastosowaniem terapii resynchronizującej nie przyniosła istotnej poprawy w zakresie najważniejszych parametrów oceniających nasilenie niewydolności serca. Sama procedura okazała się być bezpieczna i nie powodowała istotnego spadku wartości ciśnienia tętniczego krwi (objawowej hipotonii). Z obserwacji nie wynika aby zastosowanie denerwacji nerek mogło przynieść dodatkowe korzyści pacjentom z objawową przewlekłą niewydolnością serca.

**9. Streszczenie pracy doktorskiej w języku angielskim**

Heart failure (HF) is becoming a more prevalent disease with the increasing life expectancy and more effective treatment of hypertension and coronary artery disease, its leading causes. The treatment of HF, apart from pharmacotherapy, includes non-pharmacological (e.g. physical rehabilitation) and invasive methods. In particular, new non-pharmacological methods may be of significant importance. Breathing disorders, such as central apnea, are common in advanced HF and indicate a worse prognosis. On the other hand, the reduced respiratory rate in the course of breathing training may have a beneficial effect on the cardiovascular system, especially in heart failure. However, self-maintaining of reduced breathing rate is difficult. RESPeRATE devices which help to slow breathing through visual and acoustic signals were effective in reducing blood pressure in the course of hypertension. About 20 years ago, a new method of stimulation – cardiac resynchronization therapy (CRT) was introduced to treat HF. However, there is still a group of patients in whom it does not lead to clinical improvement, which may be related to excessive activation of the sympathetic nervous system. Renal artery denervation, a method studied in the treatment of resistant hypertension, may lead to a reduction in systemic sympathetic activity.

The aim of the study was to evaluate the safety and influence on physical capacity, haemodynamic parameters and quality of life in symptomatic HF patients with reduced left ventricular ejection fraction of: a) slow breathing training (SBT); b) renal artery denervation (RDN) in patients with symptoms of NS despite resynchronization therapy (CRT).

In the first study, 40 patients with HF with reduced left ventricular ejection fraction (LVEF) were examined. Patients alternated between performing SBT with the RESPeRATE device or using only standard therapy in 10-12 week phases. The effect of SBT on changes in blood pressure, rate of orthostatic hypotension (OH, decrease in systolic blood pressure of ≥ 20 mmHg or diastolic blood pressure of ≥ 10 mmHg within 3 minutes of standing) and change in

the quality of life (Minnesota questionnaire - MLHF) were assessed. The OH frequency was low and did not change during the study (10% vs 10%). In the group starting with SBT, an improvement in the quality of life was observed - a decrease in the MLHF score (49.7 vs 46.1 points; p=0.002).

In the second study, 96 patients with HF with reduced LVEF were examined. The effect of SBT on exercise capacity, hemodynamic parameters, and breathing patterns during sleep was assessed in a cross-over study (10 to 12 weeks of SBT using the RESPeRATE device and control, respectively). SBT was safe. After training, LVEF improved (31.3% ± 7.3% vs 32.3% ± 7.7%; p=0.030), as well as the distance in the 6-minute walk test (449.9 ± 122.7 m vs. 468.3 ± 121.9 m; p<0.001). The apnea and hypopnea index also decreased (median 5.6 [interquartile range (IQR), 2.1; 12.8] vs. 5.4 [IQR, 2.0; 10.8]; p=0.043).

In the third study 20 patients aged 52 to 86 years with symptomatic HF despite resynchronization therapy were randomized to either renal artery ablation (RDN) or control. The mean LVEF was 32.5%, the subjects were in NYHA II and III classes. The safety of RDN and whether it leads to an improvement in the clinical condition, exercise capacity and hemodynamic parameters was assessed. Assessment of the autonomic system, echocardiography, quality of life with the Minnesota questionnaire, 6-minute walk test, kidney function and selected biochemical tests (NT-proBNP) were performed. The RDN was safe and there were no significant side effects. There were no significant differences between the groups in the studied parameters after 12 months.

The results of the research confirmed that home rehabilitation based on slow breathing training is safe and easy to use by patients and does not lead to a deterioration in the quality of life. Slow breathing training had a positive effect on exercise capacity measured by walking distance and cardiac systolic function assessed in echocardiography, and reduced the number of

respiratory disorders during sleep, including the occurrence of central apneas. The results show that slow breathing training may be a new method of non-pharmacological treatment of heart failure.

According to the available knowledge, the study was the first attempt to assess RDN in patients with implanted CRT. Renal denervation in patients with chronic symptomatic heart failure treated optimally with pharmacology and with the use of cardiac resynchronization therapy did not bring any significant improvement in the most important parameters assessing the severity of heart failure. The procedure itself was safe and did not cause a significant decrease in blood pressure (symptomatic hypotension). The observations do not show that the use of renal denervation could bring additional benefits in patients with symptomatic chronic heart failure despite resynchronization therapy.

**10. Piśmiennictwo:**


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## 11. Oświadczenia współautorów prac

Lek. Tomasz Drożdż
I Klinika Kardiologii i Elektrokardiologii Interwencyjnej
oraz Nadciśnienia Tętniczego
(stopień/tytuł, imię i nazwisko, afiliacja)

Kraków dnia 30.09.2020 r.

**OŚWIADCZENIE**

Jako współautor pracy*:

**Drozdz T, Bilo G, Debicka-Dabrowska D, Klocek M, Malfatto G, Kielbasa G, Styczkiewicz K, Bednarek A, Czarnecka D, Parati G, Kawecka-Jaszcz K. Blood pressure changes in patients with chronic heart failure undergoing slow breathing training. Blood Press. 2016;25(1):4-10.**

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji wynosi 40 % i polegał na**:

- stworzeniu hipotezy badawczej
- opracowaniu koncepcji badań
- rekrutacji pacjentów
- wykonywaniu pomiarów kontrolnych
- opracowaniu i interpretacji wyników tej pracy
- przygotowaniu manuskryptu pracy

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Tomasza Drożdż jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Drożdż

.....

(podpis współautora)

*należy podać tytuł, nazwę czasopisma, wolumen, rok, strony

**np. opracowywaniu pomysłu badań, stworzeniu hipotezy badawczej, opracowaniu koncepcji badań, wykonywaniu określonych eksperymentów i/lub pomiarów (najlepiej wskazać których), opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.

Lek. Grzegorz Kiełbasa
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Kraków dnia 24.08.2020

## OŚWIADCZENIE

Jako współautor pracy*:

**Drozdz T, Bilo G, Debicka-Dabrowska D, Klocek M, Malfatto G, Kielbasa G, Styczkiewicz K, Bednarek A, Czarnecka D, Parati G, Kawecka-Jaszcz K. Blood pressure changes in patients with chronic heart failure undergoing slow breathing training. Blood Press. 2016;25(1):4-10.**

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji wynosi 10 % i polegał na**:

- rekrutacji pacjentów
- wykonywaniu pomiarów kontrolnych
- przygotowaniu manuskryptu pracy

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Tomasza Drożdż jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek. Tomasza Drożdż polegający na**:

- stworzeniu hipotezy badawczej
- opracowaniu koncepcji badań
- rekrutacji pacjentów
- wykonywaniu pomiarów kontrolnych
- opracowaniu i interpretacji wyników tej pracy
- przygotowaniu manuskryptu pracy

.....
(podpis współautora)

*należy podać tytuł, nazwę czasopisma, wolumen, rok, strony

**np. opracowywaniu pomysłu badań, stworzeniu hipotezy badawczej, opracowaniu koncepcji badań, wykonywaniu określonych eksperymentów i/lub pomiarów (najlepiej wskazać których), opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.

Dr n. med. Agnieszka Bednarek
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Kraków dnia 29.09.2020 r.

**OŚWIADCZENIE**

Jako współautor pracy*:

**Drozdz T, Bilo G, Debicka-Dabrowska D, Klocek M, Malfatto G, Kielbasa G, Styczkiewicz K, Bednarek A, Czarnecka D, Parati G, Kawecka-Jaszcz K. Blood pressure changes in patients with chronic heart failure undergoing slow breathing training. Blood Press. 2016;25(1):4-10.**

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji wynosi 5 % i polegał na**:

- wykonywaniu pomiarów kontrolnych
- przygotowaniu manuskryptu pracy

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Tomasza Drożdż jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek. Tomasza Drożdż polegający na**:

- stworzeniu hipotezy badawczej
- opracowaniu koncepcji badań
- rekrutacji pacjentów
- wykonywaniu pomiarów kontrolnych
- opracowaniu i interpretacji wyników tej pracy
- przygotowaniu manuskryptu pracy

Agnieszka Bednarek

(podpis współautora)

*należy podać tytuł, nazwę czasopisma, wolumen, rok, strony

**np. opracowywaniu pomysłu badań, stworzeniu hipotezy badawczej, opracowaniu koncepcji badań, wykonywaniu określonych eksperymentów i/lub pomiarów (najlepiej wskazać których), opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.

Prof. dr hab. med. Kalina Kawecka-Jaszcz
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Kraków dnia 30.09.2020 r.

**OŚWIADCZENIE**

Jako współautor pracy*:

**Drozdz T, Bilo G, Debicka-Dabrowska D, Klocek M, Malfatto G, Kielbasa G, Styczkiewicz K, Bednarek A, Czarnecka D, Parati G, Kawecka-Jaszcz K. Blood pressure changes in patients with chronic heart failure undergoing slow breathing training. Blood Press. 2016;25(1):4-10.**

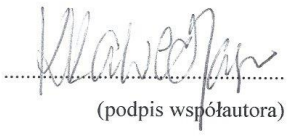
oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji wynosi 20 % i polegał na**:

- stworzeniu hipotezy badawczej
- opracowaniu koncepcji badań
- opracowaniu i interpretacji wyników tej pracy
- przygotowaniu manuskryptu pracy

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Tomasza Drożdż jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek. Tomasza Drożdż polegający na**:

- stworzeniu hipotezy badawczej
- opracowaniu koncepcji badań
- rekrutacji pacjentów
- wykonywaniu pomiarów kontrolnych
- opracowaniu i interpretacji wyników tej pracy
- przygotowaniu manuskryptu pracy



(podpis współautora)

*należy podać tytuł, nazwę czasopisma, wolumen, rok, strony

**np. opracowywaniu pomysłu badań, stworzeniu hipotezy badawczej, opracowaniu koncepcji badań, wykonywaniu określonych eksperymentów i/lub pomiarów (najlepiej wskazać których), opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.

Prof. dr hab. med. Danuta Czarnecka
I Klinika Kardiologii i Elektrokardiologii Interwencyjnej
oraz Nadciśnienia Tętniczego
(stopień/tytuł, imię i nazwisko, afiliacja)

Kraków, dnia 29.09.2020 r.

## OŚWIADCZENIE

Jako współautor pracy*:

**Drozdz T, Bilo G, Debicka-Dabrowska D, Klocek M, Malfatto G, Kielbasa G, Styczkiewicz K, Bednarek A, Czarnecka D, Parati G, Kawecka-Jaszcz K. Blood pressure changes in patients with chronic heart failure undergoing slow breathing training. Blood Press. 2016;25(1):4-10.**

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji wynosi 10 % i polegał na**:

- stworzeniu hipotezy badawczej
- opracowaniu koncepcji badań
- przygotowaniu manuskryptu pracy

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Tomasza Drożdż jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek. Tomasza Drożdż polegający na**:

- stworzeniu hipotezy badawczej
- opracowaniu koncepcji badań
- rekrutacji pacjentów
- wykonywaniu pomiarów kontrolnych
- opracowaniu i interpretacji wyników tej pracy
- przygotowaniu manuskryptu pracy

Danuta Czarnecka
.....

(podpis współautora)

*należy podać tytuł, nazwę czasopisma, wolumen, rok, strony

**np. opracowywaniu pomysłu badań, stworzeniu hipotezy badawczej, opracowaniu koncepcji badań, wykonywaniu określonych eksperymentów i/lub pomiarów (najlepiej wskazać których), opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.

Lek. Tomasz Drożdż
I Klinika Kardiologii i Elektrokardiologii Interwencyjnej
oraz Nadciśnienia Tętniczego
(stopień/tytuł, imię i nazwisko, afiliacja)

Kraków dnia 30.09.2020 r.

**OŚWIADCZENIE**

Jako współautor pracy*:

**Kawecka-Jaszcz K, Bilo G, Drożdż T, Dębicka-Dąbrowska D, Kiełbasa G, Malfatto G, Styczkiewicz K, Lombardi C, Bednarek A, Salerno S, Czarnecka D, Parati G. Effects of device-guided slow breathing training on exercise capacity, cardiac function, and respiratory patterns during sleep in male and female patients with chronic heart failure. Pol Arch Intern Med. 2017;127(1):8-15.**

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji wynosi 25% i polegał na**:

- stworzeniu hipotezy badawczej
- opracowaniu koncepcji badań
- rekrutacji pacjentów
- wykonywaniu pomiarów kontrolnych
- opracowaniu i interpretacji wyników tej pracy
- przygotowaniu manuskryptu pracy

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Tomasza Drożdż jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

.....

(podpis współautora)

*należy podać tytuł, nazwę czasopisma, wolumen, rok, strony

**np. opracowywaniu pomysłu badań, stworzeniu hipotezy badawczej, opracowaniu koncepcji badań, wykonywaniu określonych eksperymentów i/lub pomiarów (najlepiej wskazać których), opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.

Lek. Grzegorz Kiełbasa
I Klinika Kardiologii i Elektrokardiologii Interwencyjnej
oraz Nadciśnienia Tętniczego
(stopień/tytuł, imię i nazwisko, afiliacja)

Kraków dnia..24.08.2020 r.

**OŚWIADCZENIE**

Jako współautor pracy*:

**Kawecka-Jaszcz K, Bilo G, Drożdż T, Dębicka-Dąbrowska D, Kiełbasa G, Malfatto G, Styczkiewicz K, Lombardi C, Bednarek A, Salerno S, Czarnecka D, Parati G. Effects of device-guided slow breathing training on exercise capacity, cardiac function, and respiratory patterns during sleep in male and female patients with chronic heart failure. Pol Arch Intern Med. 2017;127(1):8-15.**

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji wynosi 10 % i polegał na**:

- rekrutacji pacjentów
- wykonywaniu pomiarów kontrolnych
- przygotowaniu manuskryptu pracy

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Tomasza Drożdż jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek. Tomasza Drożdż polegający na**:

- stworzeniu hipotezy badawczej
- opracowaniu koncepcji badań
- rekrutacji pacjentów
- wykonywaniu pomiarów kontrolnych
- opracowaniu i interpretacji wyników tej pracy
- przygotowaniu manuskryptu pracy

.....
(podpis współautora)

*należy podać tytuł, nazwę czasopisma, wolumen, rok, strony

**np. opracowywaniu pomysłu badań, stworzeniu hipotezy badawczej, opracowaniu koncepcji badań, wykonywaniu określonych eksperymentów i/lub pomiarów (najlepiej wskazać których), opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.

Dr n. med. Agnieszka Bednarek
I Klinika Kardiologii i Elektrokardiologii Interwencyjnej
oraz Nadciśnienia Tętniczego
(stopień/tytuł, imię i nazwisko, afiliacja)

Kraków dnia 29.09.2020 r.

**OŚWIADCZENIE**

Jako współautor pracy*:

**Kawecka-Jaszcz K, Bilo G, Drożdż T, Dębicka-Dąbrowska D, Kiełbasa G, Malfatto G, Styczkiewicz K, Lombardi C, Bednarek A, Salerno S, Czarnecka D, Parati G. Effects of device-guided slow breathing training on exercise capacity, cardiac function, and respiratory patterns during sleep in male and female patients with chronic heart failure. Pol Arch Intern Med. 2017;127(1):8-15.**

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji wynosi 5 % i polegał na**:

- wykonywaniu pomiarów kontrolnych
- przygotowaniu manuskryptu pracy

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Tomasza Drożdż jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek. Tomasza Drożdż polegający na**:

- stworzeniu hipotezy badawczej
- opracowaniu koncepcji badań
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- wykonywaniu pomiarów kontrolnych
- opracowaniu i interpretacji wyników tej pracy
- przygotowaniu manuskryptu pracy

Agnieszka Bednarek

(podpis współautora)

*należy podać tytuł, nazwę czasopisma, wolumen, rok, strony

**np. opracowywaniu pomysłu badań, stworzeniu hipotezy badawczej, opracowaniu koncepcji badań, wykonywaniu określonych eksperymentów i/lub pomiarów (najlepiej wskazać których), opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.

Prof. dr hab. med. Kalina Kawecka-Jaszcz
I Klinika Kardiologii i Elektrokardiologii Interwencyjnej
oraz Nadciśnienia Tętniczego
(stopień/tytuł, imię i nazwisko, afiliacja)

Kraków dnia 30.09.2020 r.

**OŚWIADCZENIE**

Jako współautor pracy*:

**Kawecka-Jaszcz K, Bilo G, Drożdż T, Dębicka-Dąbrowska D, Kiełbasa G, Malfatto G, Styczkiewicz K, Lombardi C, Bednarek A, Salerno S, Czarnecka D, Parati G. Effects of device-guided slow breathing training on exercise capacity, cardiac function, and respiratory patterns during sleep in male and female patients with chronic heart failure. Pol Arch Intern Med. 2017;127(1):8-15.**

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji wynosi 30 % i polegał na**:

- stworzeniu hipotezy badawczej
- opracowaniu koncepcji badań
- opracowaniu i interpretacji wyników tej pracy
- przygotowaniu manuskryptu pracy

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Tomasza Drożdż jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

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- stworzeniu hipotezy badawczej
- opracowaniu koncepcji badań
- rekrutacji pacjentów
- wykonywaniu pomiarów kontrolnych
- opracowaniu i interpretacji wyników tej pracy
- przygotowaniu manuskryptu pracy

.....
(podpis współautora)

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**np. opracowywaniu pomysłu badań, stworzeniu hipotezy badawczej, opracowaniu koncepcji badań, wykonywaniu określonych eksperymentów i/lub pomiarów (najlepiej wskazać których), opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.

Prof. dr hab. med. Danuta Czarnecka
I Klinika Kardiologii i Elektrokardiologii Interwencyjnej
oraz Nadciśnienia Tętniczego
(stopień/tytuł, imię i nazwisko, afiliacja)

Kraków, dnia 29.09.2020 r.

## OŚWIADCZENIE

Jako współautor pracy*:

**Kawecka-Jaszcz K, Bilo G, Drożdż T, Dębicka-Dąbrowska D, Kiełbasa G, Malfatto G, Styczkiewicz K, Lombardi C, Bednarek A, Salerno S, Czarnecka D, Parati G. Effects of device-guided slow breathing training on exercise capacity, cardiac function, and respiratory patterns during sleep in male and female patients with chronic heart failure. Pol Arch Intern Med. 2017;127(1):8-15.**

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji wynosi 10 % i polegał na**:

- stworzeniu hipotezy badawczej
- opracowaniu koncepcji badań
- przygotowaniu manuskryptu pracy

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Tomasza Drożdż jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

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- opracowaniu koncepcji badań
- rekrutacji pacjentów
- wykonywaniu pomiarów kontrolnych
- opracowaniu i interpretacji wyników tej pracy
- przygotowaniu manuskryptu pracy

Danuta Czarnecka

(podpis współautora)

*należy podać tytuł, nazwę czasopisma, wolumen, rok, strony

**np. opracowywaniu pomysłu badań, stworzeniu hipotezy badawczej, opracowaniu koncepcji badań, wykonywaniu określonych eksperymentów i/lub pomiarów (najlepiej wskazać których), opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.

lek. Tomasz Drożdż
I Klinika Kardiologii i Elektrokardiologii Interwencyjnej
oraz Nadciśnienia Tętniczego
(stopień/tytuł, imię i nazwisko, afiliacja)

Kraków dnia 29.09.2020 r.

## OŚWIADCZENIE

Jako współautor pracy*:

**Drożdż T, Jastrzębski M, Moskal P, Kusiak A, Bednarek A, Styczkiewicz K, Jankowski P, Czarnecka D. Renal denervation in patients with symptomatic chronic heart failure despite resynchronization therapy - a pilot study. Postepy Kardiol Interwencyjnej. 2019;15(2):240-246.** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji wynosi 40% i polegał na**:

- stworzeniu hipotezy badawczej
- opracowaniu koncepcji badań
- rekrutacji pacjentów
- wykonywaniu pomiarów kontrolnych
- opracowaniu i interpretacji wyników tej pracy
- przygotowaniu manuskryptu pracy

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Tomasza Drożdż jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

.....

(podpis współautora)

*należy podać tytuł, nazwę czasopisma, wolumen, rok, strony

**np. opracowywaniu pomysłu badań, stworzeniu hipotezy badawczej, opracowaniu koncepcji badań, wykonywaniu określonych eksperymentów i/lub pomiarów (najlepiej wskazać których), opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.

Dr n. med. Aleksander Kusiak
I Klinika Kardiologii i Elektrokardiologii Interwencyjnej
oraz Nadciśnienia Tętniczego
(stopień/tytuł, imię i nazwisko, afiliacja)

Kraków dnia...29.08.2020...

**OŚWIADCZENIE**

Jako współautor pracy*:

**Drożdż T, Jastrzębski M, Moskal P, Kusiak A, Bednarek A, Styczkiewicz K, Jankowski P, Czarnecka D. Renal denervation in patients with symptomatic chronic heart failure despite resynchronization therapy - a pilot study. Postepy Kardiol Interwencyjnej. 2019;15(2):240-246.** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji wynosi 10 % i polegał na**:

- rekrutacji pacjentów
- wykonywaniu pomiarów kontrolnych
- przygotowaniu manuskryptu pracy

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Tomasza Drożdż jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek. Tomasza Drożdż polegający na**:

- stworzeniu hipotezy badawczej
- opracowaniu koncepcji badań
- rekrutacji pacjentów
- wykonywaniu pomiarów kontrolnych
- opracowaniu i interpretacji wyników tej pracy
- przygotowaniu manuskryptu pracy

AK

.....

(podpis współautora)

*należy podać tytuł, nazwę czasopisma, wolumen, rok, strony

**np. opracowywaniu pomysłu badań, stworzeniu hipotezy badawczej, opracowaniu koncepcji badań, wykonywaniu określonych eksperymentów i/lub pomiarów (najlepiej wskazać których), opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.

Dr n. med. Agnieszka Bednarek
I Klinika Kardiologii i Elektrokardiologii Interwencyjnej
oraz Nadciśnienia Tętniczego
(stopień/tytuł, imię i nazwisko, afiliacja)

Kraków dnia 29.09.2020 r.

**OŚWIADCZENIE**

Jako współautor pracy*:

**Drożdż T, Jastrzębski M, Moskal P, Kusiak A, Bednarek A, Styczkiewicz K, Jankowski P, Czarnecka D. Renal denervation in patients with symptomatic chronic heart failure despite resynchronization therapy - a pilot study. Postepy Kardiol Interwencyjnej. 2019;15(2):240-246.** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji wynosi 5 % i polegał na**:

- wykonywaniu pomiarów kontrolnych
- przygotowaniu manuskryptu pracy

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Tomasza Drożdż jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek. Tomasza Drożdż polegający na**:

- stworzeniu hipotezy badawczej
- opracowaniu koncepcji badań
- rekrutacji pacjentów
- wykonywaniu pomiarów kontrolnych
- opracowaniu i interpretacji wyników tej pracy
- przygotowaniu manuskryptu pracy

Agnieszka Bednarek

(podpis współautora)

*należy podać tytuł, nazwę czasopisma, wolumen, rok, strony

**np. opracowywaniu pomysłu badań, stworzeniu hipotezy badawczej, opracowaniu koncepcji badań, wykonywaniu określonych eksperymentów i/lub pomiarów (najlepiej wskazać których), opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.

lek. Paweł Moskal
I Klinika Kardiologii i Elektrokardiologii Interwencyjnej
oraz Nadciśnienia Tętniczego
(stopień/tytuł, imię i nazwisko, afiliacja)

Kraków dnia 29.09.2020 r.

## OŚWIADCZENIE

Jako współautor pracy*:

**Drożdż T, Jastrzębski M, Moskal P, Kusiak A, Bednarek A, Styczkiewicz K, Jankowski P, Czarnecka D. Renal denervation in patients with symptomatic chronic heart failure despite resynchronization therapy - a pilot study. Postepy Kardiol Interwencyjnej. 2019;15(2):240-246.** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji wynosi 5% i polegał na**:

- wykonywaniu pomiarów kontrolnych
- przygotowaniu manuskryptu pracy

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Tomasza Drożdż jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek. Tomasza Drożdż polegający na**:

- stworzeniu hipotezy badawczej
- opracowaniu koncepcji badań
- rekrutacji pacjentów
- wykonywaniu pomiarów kontrolnych
- opracowaniu i interpretacji wyników tej pracy
- przygotowaniu manuskryptu pracy

Paweł Moskal

.....

(podpis współautora)

*należy podać tytuł, nazwę czasopisma, wolumen, rok, strony

**np. opracowywaniu pomysłu badań, stworzeniu hipotezy badawczej, opracowaniu koncepcji badań, wykonywaniu określonych eksperymentów i/lub pomiarów (najlepiej wskazać których), opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.

Prof. dr hab. med. Danuta Czarnecka
I Klinika Kardiologii i Elektrokardiologii Interwencyjnej
oraz Nadciśnienia Tętniczego
(stopień/tytuł, imię i nazwisko, afiliacja)

Kraków dnia 29.09.2020 r.

## OŚWIADCZENIE

Jako współautor pracy*:

**Drożdż T, Jastrzębski M, Moskal P, Kusiak A, Bednarek A, Styczkiewicz K, Jankowski P, Czarnecka D. Renal denervation in patients with symptomatic chronic heart failure despite resynchronization therapy - a pilot study. Postepy Kardiol Interwencyjnej. 2019;15(2):240-246.** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji wynosi 20% i polegał na**:

- stworzeniu hipotezy badawczej
- opracowaniu koncepcji badań
- opracowaniu i interpretacji wyników tej pracy
- przygotowaniu manuskryptu pracy

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Tomasza Drożdż jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek. Tomasza Drożdż polegający na**:

- stworzeniu hipotezy badawczej
- opracowaniu koncepcji badań
- rekrutacji pacjentów
- wykonywaniu pomiarów kontrolnych
- opracowaniu i interpretacji wyników tej pracy
- przygotowaniu manuskryptu pracy

Danuta Czarnecka

(podpis współautora)

*należy podać tytuł, nazwę czasopisma, wolumen, rok, strony

**np. opracowywaniu pomysłu badań, stworzeniu hipotezy badawczej, opracowaniu koncepcji badań, wykonywaniu określonych eksperymentów i/lub pomiarów (najlepiej wskazać których), opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.