

# The effect of chronically occluded coronary artery recanalisation on baroreflex sensitivity and left ventricular systolic function

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## Abstract

**Background:** Recanalisation of chronic total occlusion (CTO) of a coronary artery can be reflected by improvements in various clinical parameters. Revealing increased parasympathetic activity would constitute an additional argument for performing this procedure.

**Aim:** To assess the effect of CTO recanalisation on baroreflex sensitivity (BRS) and left ventricular ejection fraction (LVEF) in stable symptomatic patients with coronary artery disease.

**Methods:** BRS (spectral analysis, transfer function, Blackman-Tukey algorithm, 0.03 Hz bandwidth Parzen window) and LVEF (echocardiography, Simpson's method) were analysed in 23 patients: one day (R1) before, one day (R2) after, and three months (R3) after CTO recanalisation. Patients were divided into two groups: those with depressed ( $\leq 3$  ms/mm Hg) or preserved ( $> 3$  ms/mm Hg) BRS.

**Results:** Significant BRS changes were observed in the study group compared to baseline values ( $p = 0.016$ ). In the patients with a depressed reflex, BRS in R2 was similar to R1 and almost doubled in R3 ( $p = 0.018$ ). In the patients with a preserved reflex, BRS significantly decreased in R2 ( $p = 0.024$ ) and returned to the baseline value in R3. The behaviour of LVEF was homogenous in the groups, showing an increase from R1 to R3.

**Conclusions:** The improvement in autonomic nervous system activity after successful CTO recanalisation is reflected by an increase in BRS, and the changes are dependent on the baseline value of the measurement: patients with a depressed BRS before recanalisation present a greater BRS improvement than patients with a preserved BRS. The CTO recanalisation leads to the improvement of LVEF in both groups.

**Key words:** recanalisation, baroreflex sensitivity, ejection fraction

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## INTRODUCTION

While recanalisation of a coronary artery in the setting of an acute coronary syndrome (ACS) is unequivocally recommended [1], recanalisation of a chronic total occlusion (CTO) remains a matter of controversy. There is no indication to perform CTO recanalisation in all asymptomatic patients

with coronary artery disease (CAD). On the other hand, this procedure plays a vital role in symptomatic patients and in cases where the occluded vessel supplies a large myocardial area with preserved viability [1]. In appropriately selected patients, the CTO opening procedure delays, or even eliminates, the need for further revascularisation and is associated

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with significantly fewer subsequent by-pass procedures [2, 3]. Furthermore, successful recanalisation improves left ventricular ejection fraction (LVEF) and exercise tolerance [4–7].

Increasing attention is being paid to the relationship between coronary artery status and autonomic nervous system (ANS) function [8–10]. It has been established that ANS dysfunction reduces myocardial electrical stability and increases the risk of life-threatening ventricular arrhythmias and sudden cardiac death (SCD) [11–14]. Demonstrating improvement of ANS function after CTO recanalisation could be considered an additional argument in favour of this procedure. It is worth mentioning, however, that studies concerning this issue are scarce and inconclusive [8]. Furthermore, the majority of available studies have been focused on patients with ACS [15–20]. Research concerning the assessment of ANS function after successful CTO recanalisation is incomplete. The nature of the relationship between ANS and LVEF changes after CTO recanalisation also remains unclear. Moreover, in the majority of the published studies, heart rate variability (HRV) parameters are assessed [21–26], whereas only a few studies have referred to the effect of CTO recanalisation on baroreflex sensitivity (BRS) [27, 28]. The impact of successful CTO recanalisation on BRS and its potential relation to the baseline value of the measurement has not been fully clarified [29, 30].

Accordingly, the aim of this study was to assess the effect of CTO recanalisation on BRS and LVEF in stable symptomatic patients with CAD and to determine whether these effects are related to baseline ANS dysfunction. Having in mind the importance of patient homogeneity in such circumstances, we chose to include only single-vessel CAD patients with an angiographically confirmed CTO.

## METHODS

Twenty-three consecutive patients with stable angina (class 1–3 according to the Canadian Classification), positive exercise testing, single vessel CAD, and CTO (of more than four weeks' duration) suitable for revascularisation were included in the study. Exclusion criteria were as follows: age > 70 years, premature ventricular contractions more than 5% of all recorded QRS complexes, chronic atrial fibrillation/flutter, atrioventricular block (2<sup>nd</sup> or 3<sup>rd</sup> degree), permanent cardiac pacemaker, peripheral diabetic neuropathy (as documented in in-hospital or outpatient medical records) and a lack of patient consent. In each included patient, BRS and LVEF were examined one day before CTO recanalisation (R1), and one day (R2) and three months (R3) after the procedure.

### *Assessment of BRS function*

The tests were performed in the morning. All patients had been in a fasting state for at least 4 h and refrained from smoking cigarettes, drinking coffee and alcohol for at least 12 h prior to the examination. The recordings were conducted in a quiet

room, with the patient relaxed in the supine position with head elevated by 30°. We recorded ECG (MINGOGRAF 720C) and beat-by-beat systolic arterial pressure (SAP) (Finapres 2300, Ohmeda). The SAP measurements were non-invasive and taken at the finger with the pressure cuff wrapped around the middle phalanx of the third finger of the right hand. The BRS values were analysed with equipment and software which is widely recommended and used in expert centres.

The first 15 min were used for signal stabilisation, and then a 10-min recording of SAP and ECG was performed for each patient. From the ECG and SAP signals, we obtained a time series of heart period (resolution: 1 ms) and SAP using POLYAN software [31]. SAP and heart period were plotted together and the widest sub-record free from artifacts, large transients or marked changes in the fluctuation pattern of the signals was selected interactively. Recordings shorter than 240 s were excluded from subsequent analysis. Isolated ectopic beats were corrected by linear interpolation. BRS was evaluated automatically in order to reduce the subjectivity of the analysis. Briefly, bivariate spectral analysis between SAP and heart period time series was performed using Blackman-Tukey algorithm with a 0.03 Hz bandwidth Parzen window, and BRS was obtained by averaging the estimated gain function in the 0.04–0.15 Hz range [32]. All patients were divided into two groups: those with a severely depressed BRS ( $\leq 3$  ms/mm Hg) and those with BRS > 3 ms/mm Hg. The cut-off level of reduced BRS was adopted from the ATRAMI study [13].

### *Echocardiographic measurements*

Standard M-mode and two-dimensional echocardiography followed by colour flow imaging and pulses and continuous wave Doppler ultrasound study was performed in all patients (SONOS 2500, Hewlett Packard, 2.5 MHz transducer). Left ventricular end-systolic and end-diastolic volume were calculated by the biplane area-length method, and LVEF was obtained from the average of three consecutive cardiac cycles taken from apical four-chamber views using Simpson's rule [33].

This study was undertaken as part of a wider research programme examining the effect of CTO recanalisation of a coronary artery on ANS activity. The entire programme was approved by the Independent Bioethical Committee for Scientific Research of the Medical University of Gdansk (NKEBN/10/2003). Written informed consent was obtained from all the studied patients.

### *Statistical analysis*

Patients were grouped into those with depressed reflex (BRS  $\leq 3$  ms/mm Hg) and those with preserved reflex (BRS > 3 ms/mm Hg). Continuous variables were analysed by a two-factor (time and group) ANOVA, with repeated-measures on the factor time (levels: baseline, next day after the procedure and three months thereafter). Predefined contrasts

Table 1. Patients' clinical characteristics

	All (n = 23)	Subjects with preserved BRS (> 3 ms/mm Hg; n = 16)	Subjects with depressed BRS (≤ 3 ms/mm Hg; n = 7)	P*
Mean age [years]	55 ± 8	54 ± 9	56 ± 6	0.5
Men	16 (70%)	11 (70%)	5 (71%)	0.7
History of MI:				
NSTEMI	2 (9%)	2 (13%)	0 (0%)	0.9
STEMI	12 (52%)	8 (50%)	4 (57%)	0.8
Infarct-related artery:				
Left anterior descending coronary artery	7 (30%)	4 (25%)	3 (43%)	0.7
Left circumflex coronary artery	2 (9%)	0 (0%)	1 (14%)	0.7
Right coronary artery	13 (57%)	11 (69%)	3 (43%)	0.5
Other	1 (4%)	1 (6%)	0 (0%)	0.7
Left ventricular ejection fraction [%]	50 ± 8	51 ± 7	48 ± 10	0.5
Drugs**:				
Beta-adrenolitics	21 (94%)	15 (94%)	6 (86%)	0.9
ACEI/ARB	18 (78%)	13 (81%)	5 (71%)	1.0
Acetylsalicylic acid	23 (100%)	16 (100%)	7 (100%)	–
Statins	23 (100%)	16 (100%)	7 (100%)	–
Nitrates	7 (30%)	4 (25%)	3 (43%)	0.7
Comorbidities:				
Arterial hypertension	16 (70%)	12 (75%)	4 (57%)	0.7
Hypercholesterolaemia	23 (100%)	16 (100%)	7 (100%)	–
Type 2 diabetes	10 (43%)	7 (44%)	3 (43%)	0.8
Chronic kidney disease (GFR < 60 mL/min)	10 (43%)	7 (44%)	3 (43%)	0.8

Data is presented as the mean ± SD or numbers and percentages; \*p value between subjects with preserved and depressed BRS; \*\*all the patients were given clopidogrel before and 30 days after the procedure; ACEI/ARB — angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; BRS — baroreflex sensitivity; GFR — glomerular filtration ratio; MI — myocardial infarction; NSTEMI — non-ST segment elevation myocardial infarction; STEMI — ST-segment elevation myocardial infarction

of interest were: next day after the procedure vs. baseline (early or acute effect of CTO recanalisation) and three months after the procedure vs. baseline (long-term effect). A value of  $p \leq 0.05$  was considered statistically significant, and all tests were two-sided. Continuous variables were expressed as mean values ± standard deviations (SD), and categorical variables as counts and percentages.

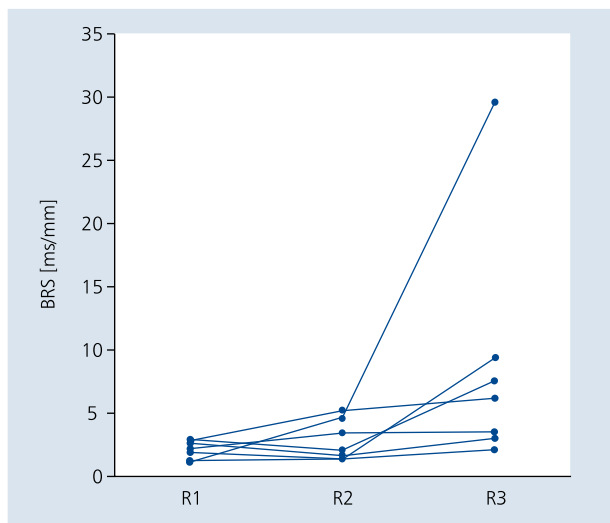
## RESULTS

Clinical characteristics of the study patients are presented in Table 1. No statistically significant differences in the clinical characteristics and pharmacological treatment between patients with  $BRS \leq 3$  ms/mm Hg and  $BRS > 3$  ms/mm Hg were noted. The CTO recanalisation was successful in all patients (grade 3 coronary flow according Thrombolysis in Myocardial Infarction [TIMI]). Standard techniques were followed for the recanalisation procedure: in 75% of patients by radial artery approach, and in the remaining 25% by femoral access. In each case, a stent was implanted in line with the current standard CTO treatment (in all patients bare metal stents

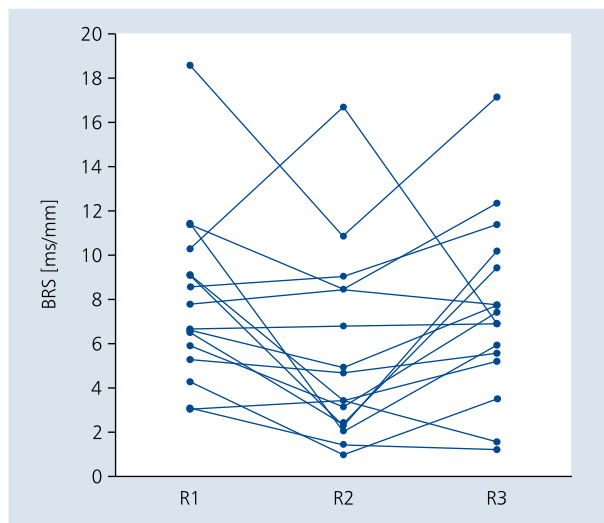
were implanted). No clinical, neurological or biochemical (troponin elevation) complications were observed in any of the patients. Medication adjustments (including beta-blocker increase) that were done at one month in some patients ( $n = 13$ ) could have potentially influenced our results. However, additional analysis performed in a group with no dose adjustments revealed no significant changes compared to the entire study population. Complete post-procedural resolution of angina was noted in all patients.

### *Effect of CTO recanalisation on BRS*

The full protocol of ANS activity assessment was completed for all patients. As shown in the case profile plots (Figs. 1, 2), and in Table 2, the time course of BRS was significantly different in the two groups of patients with either depressed or preserved BRS ( $p$  value for the interaction between the factor group and the factor time: 0.016). Specifically, in the patients with a depressed reflex, mean BRS one day after CTO recanalisation was similar to the baseline value and almost doubled after three months. Conversely, in the patients with



**Figure 1.** Baroreflex sensitivity (BRS) before (R1), and one day (R2) and three months (R3) after chronic total occlusion recanalisation among the patients with depressed BRS



**Figure 2.** Baroreflex sensitivity (BRS) before (R1), and one day (R2) and three months (R3) after chronic total occlusion recanalisation among the patients with preserved BRS

**Table 2.** Baroreflex sensitivity (BRS) before (R1), and one day (R2) and three months (R3) after chronic total occlusion recanalisation

	R1	R2	R3
Subjects with depressed BRS ( $\leq 3$ ms/mm Hg, n = 7)	2.1 $\pm$ 0.7	2.7 $\pm$ 1.6	5.3 $\pm$ 2.6*
Subjects with preserved BRS ( $> 3$ ms/mm Hg, n = 16)	8.0 $\pm$ 3.9	5.5 $\pm$ 4.3†	7.5 $\pm$ 4.1

Data is presented as the mean  $\pm$  SD; \*p = 0.018 vs. R1; †p = 0.024 vs. R1

**Table 3.** Left ventricular ejection fraction before (R1), and one day (R2) and three months after chronic total occlusion recanalisation (R3) in patients with depressed and preserved baroreflex sensitivity (BRS)

	R1	R2	R3
Subjects with depressed BRS ( $\leq 3$ ms/mm Hg, n = 7)	47.9 $\pm$ 9.9	50.0 $\pm$ 9.6	55.0 $\pm$ 10.0*
Subjects with preserved BRS ( $> 3$ ms/mm Hg, n = 16)	51.0 $\pm$ 7.1	54.0 $\pm$ 6.6†	55.7 $\pm$ 8.0‡

Data is presented as the mean  $\pm$  SD; \*p = 0.025 vs. R1, †p = 0.007 vs. R1, ‡p = 0.0005 vs. R1

a preserved reflex, mean BRS significantly decreased one day after the procedure and returned to the baseline value after three months.

#### **Effect of CTO recanalisation on LVEF**

LVEF behaviour was inconsistent with BRS behaviour over time, and was substantially homogenous in the two groups of patients with depressed and preserved reflex, showing an increase from baseline as early as one day post as well as three months after the procedure (Table 3). This finding was supported by a largely non-significant group-by-time interaction effect (p = 0.33). In patients with preserved BRS, the increase in mean LVEF from baseline, both one day and three months after the procedure, was statistically significant; whereas, in patients with depressed BRS it was borderline non-significant (p = 0.08), probably due to the small sample

size. Baseline LVEF values were not significantly different in the two groups (p = 0.40).

#### **DISCUSSION**

The most important finding of this study is the observation that in the case of patients with initially depressed BRS, i.e. those particularly at risk of SCD, CTO recanalisation results in a significant increase in BRS value at three-month follow-up. This suggests a shift in ANS balance towards the parasympathetic component.

The relationship between ischaemia and autonomic function has long been recognised. In a study by Pomidossi et al. [34], ischaemic episodes during angioplasty, including asymptomatic ischaemia, were related to unequivocal BRS reduction (measured invasively). On the other hand, angiographic subanalysis of the ATRAMI population (n = 359) by Mortara et al. [8] directly documented the relation of

coronary artery patency status to autonomic function. Mean BRS values in patients with an occluded infarct-related artery were lower than in patients with patent arteries. The exact mechanisms of these relationships are complex and require further elucidation. To the best of our knowledge, in the group of patients with severely reduced BRS, this paper is the first to contribute the above mentioned findings. Its clinical value could be substantial, as data from literature suggests that a higher BRS value can be related to a lower risk of malignant ventricular arrhythmias and SCD [13]. It should be mentioned that in a recently published study [35], CTO recanalisation did not improve the overall prognosis. However, malignant arrhythmia and SCD (i.e. end points that are appropriate for ANS analysis), were not separately referred to in this work. We demonstrated that successful CTO recanalisation can be reflected by an increase in BRS, suggestive of ANS function improvement. Furthermore, the change was related to the baseline value of the measurement: patients with depressed BRS ( $\leq 3$  ms/mm Hg) before CTO recanalisation exhibited a larger BRS improvement than patients with preserved BRS ( $> 3$  ms/mm Hg). The reliability of our results is supported by the homogeneity of our group (symptomatic patients with single-vessel CAD who underwent successful CTO recanalisation resulting in TIMI-3 coronary flow). As to the current definition of CTO (duration of  $\geq$  three months), we would like to point out that at the time of our study initiation (i.e. prior to the 2005 consensus document by Stone et al. [36]), this definition was far from being formulated, and occlusions of variable duration (i.e. from less than four weeks to over six months) were termed CTOs and reported on in the literature.

Although published evidence of changes in ANS resulting from recanalisation of the coronary vessels in chronic CAD is sparse and based on HRV parameters, previously reported findings were similar to those observed in our study [22–25]. For instance, Osterhues et al. [22] studied patients with single-, bi- and tri-vessel CAD, documenting insignificant increases in some HRV indices six to eight months after revascularisation. Tseng et al. [23] analysed various HRV parameters in patients with regional systolic dysfunction in the area supplied by a stenosed vessel and reported a significant improvement in some of them within two months after successful elective angioplasty. Bonaduce et al. [24] reported similar findings. Gajos et al. [25] observed normalisation of standard deviation of normal-to-normal R-R interval after revascularisation in patients whose baseline values of this parameter were below 94 ms threshold assumed by the authors.

Our study revealed a similar direction of changes in the BRS in a subgroup of individuals with initially depressed reflex. A significant increase in BRS values was observed in these patients at three months following the procedure, from  $2.1 \pm 0.7$  to  $5.3 \pm 2.6$  ms/mm Hg ( $p = 0.018$ ). The clinical significance of our results is even more important, since we analysed the patients with BRS  $\leq 3$  ms/mm Hg. Such patients

can potentially benefit the most from ANS function improvement in terms of SCD risk. This finding could constitute an additional argument for performing recanalisation of CTO coronary vessels in a properly selected group of patients.

Conversely, no significant long-term changes were documented in a subgroup of patients with baseline BRS  $> 3$  ms/mm Hg. Kanadasi et al. [26] reported similar findings but in regards to HRV parameters. Based on our study, one cannot explain why the improvement in BRS was observed only in patients whose baseline values of this parameter were  $\leq 3$  ms/mm Hg. A larger reserve of reflex available in this group of patients could be one possible reason. Earlier studies suggest that changes in the ANS parameters are more beneficial after left than after right coronary artery recanalisation [27]. However, subgroups compared in our study did not differ with regard to the artery that was recanalised.

While a long-term increase in BRS could be considered a favourable phenomenon, it is hard to define the exact importance of the reduction in this parameter (from  $8.0 \pm 3.9$  to  $5.5 \pm 4.3$  ms/mm Hg) observed in some patients one day after the procedure, possibly suggesting a shift in ANS balance towards the sympathetic system. Similar results were presented in previous studies [27, 28], especially with regard to patients in whom the right coronary artery was recanalised [27]. It is worth noting that this phenomenon, relatively consistently reported by various authors, has a transient character [22, 26, 27]. It has been suggested that the changes observed during the early period after the procedure could potentially be the result of the influence of modified conditions of myocardial perfusion on transient disturbance of sympathetic-parasympathetic balance [15, 17]. Additionally, the effects of extra-coronary factors, such as the co-existence of mechanical intervention in the vascular system with the necessity of prolonged immobilisation in the supine position, and exposure to stress and pain, have been implicated [37]. These factors may explain some of the ANS instability observed one day after the CTO recanalisation. Although the exact clinical importance of these changes is hard to define, they constitute an additional argument for careful monitoring of patients during the early post-procedural period.

It has been demonstrated that the revascularisation of the coronary vessel is accompanied by LVEF improvement [4–7]. This phenomenon was also confirmed in our study. Noticeably, an increase in LVEF was observed as early as one day after the procedure, irrespective of depressed BRS documented in a subgroup of patients with baseline BRS  $> 3$  ms/mm Hg. At three months, a further improvement in LVEF was documented in both studied subgroups. According to the literature, effective myocardial perfusion obtained as a result of epicardial artery recanalisation is vital for LVEF improvement; this objective was achieved in all participants in our study [15].

One should note that favourable changes in LVEF markedly preceded the changes observed in BRS. Although obtaining



effective perfusion of an occluded vessel may lead to a marked increase in LVEF as early as one day after the procedure, it may also be associated with disturbed dynamic balance of ANS. This may be also related to the fact that improvement in LVEF and BRS are determined by a different spectrum of factors, e.g. LVEF is most closely related to restored perfusion and, in terms of ANS function, more sensitive to sympathetic rather than parasympathetic changes, whereas BRS is more closely related to vagal responses, that may be disturbed early after a vascular intervention. As mentioned previously, time is required to stabilise ANS function at a more favourable level [23].

### Limitations of the study

The studied group was relatively small. Moreover, no long term analysis of malignant arrhythmia and SCD is available. Detailed analysis of CTO including the length and vessel diameter in the groups with initially depressed and preserved BRS was not performed. We present data from a pilot study, constituting part of a larger research programme on the effect of successful CTO recanalisation on BRS. However, our initial results seem interesting from a clinical standpoint, which was a reason for presenting this preliminary report. Another limitation is related to the threshold BRS value of  $BRS \leq 3$  ms/mm Hg, adopted from the ATRAMI study, in which a different method (i.e. phenylephrine test) was used in patients who survived acute myocardial infarction. We have adopted the ATRAMI BRS value due to the lack of recommended cut-off values for the method used in our study. Another limitation of the work is related to the fact that only BRS values are presented.

### CONCLUSIONS

The improvement in ANS after a successful CTO recanalisation is reflected by an increase in BRS, and changes are dependent on the baseline value of the measurement: patients with depressed BRS before recanalisation present a larger BRS improvement (probably due to greater BRS reserve) than patients with a preserved BRS. CTO recanalisation leads to an improvement of LVEF as early as one day after the procedure, and a further LVEF increase was observed at three months in both groups.

**Conflict of interest:** none declared

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# Wpływ udroźnienia przewlekle zamkniętej tętnicy wieńcowej na wrażliwość odruchu z baroreceptorów tętnicznych i funkcję skurczową lewej komory

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## Streszczenie

**Wstęp:** Rekanalizacja przewlekle zamkniętego naczynia wieńcowego (CTO) może prowadzić do poprawy wielu parametrów klinicznych. Wykazanie wzmożenia aktywności przywspółczulnej autonomicznego układu nerwowego stanowiłoby kolejny argument do przeprowadzenia takich zabiegów.

**Cel:** Celem niniejszej pracy była ocena wpływu udroźnienia CTO na wrażliwość baroreceptorów tętnicznych (BRS) oraz frakcję wyrzutową lewej komory (LVEF) u pacjentów ze stabilną objawową chorobą wieńcową.

**Metody:** Wartości BRS (metoda spektralna, funkcja przejścia, algorytm Blackmana-Tukeya, okna Parzena 0,03 Hz) oraz LVEF (echokardiografia metodą Simpsona) oceniono u 23 pacjentów: w dniu poprzedzającym zabieg rekanalizacji CTO (R1), następnego dnia (R2) i 3 miesiące (R3) po zabiegu. Dodatkowo pacjenci byli podzieleni na 2 grupy: z istotnie obniżoną BRS ( $\leq 3$  ms/mm Hg) oraz z zachowaną BRS ( $> 3$  ms/mm Hg).

**Wyniki:** Stwierdzono istotne zmiany z zakresu BRS na skutek CTO w porównaniu z wartościami wyjściowymi ( $p = 0,016$ ). Wśród chorych z BRS  $\leq 3$  ms/mm Hg wartości tego parametru, nie wykazując istotnych zmian w rejestracji R2, uległy istotnemu wzrostowi w rejestracji R3 ( $p = 0,018$ ). U pacjentów z BRS  $> 3$  ms/mm Hg wartości tego parametru znamiennie się zmniejszyły w rejestracji R2 ( $p = 0,024$ ) i powróciły do wartości wyjściowych w rejestracji R3. W zakresie LVEF zaobserwowano istotny wzrost w rejestracji R2, a następnie R3.

**Wnioski:** Na skutek rekanalizacji CTO dochodzi do zmian w zakresie aktywności autonomicznego układu nerwowego, wyrażonych wzrostem BRS, zależnych od wyjściowych wartości tego parametru. U pacjentów z upośledzonym odruchem z baroreceptorów tętnicznych dochodzi do wyraźnej poprawy tego parametru, podczas gdy u chorych z zachowaną wartością BRS nie stwierdzono poprawy w zakresie tego parametru. Poprawę dotyczącą LVEF zaobserwowano już następnego dnia po zabiegu w obu analizowanych grupach.

**Słowa kluczowe:** rekanalizacja, odruch z baroreceptor tętnicznych, frakcja wyrzutowa

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