Comparison the effects of recanalisation of chronic total occlusion of the right and left coronary arteries on the autonomic nervous system function

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Abstract

Background: Recanalisation of the chronic total occlusion (CTO) of coronary artery is not a routine procedure. The benefits of CTO recanalisation have not yet been definitively established. This may be due to inappropriate identification of patients who benefit the most from the CTO recanalisation.

Aim: To assess the autonomic nervous system (ANS) parameters and left ventricular ejection fraction (LVEF) changes after the recanalisation of the left anterior descending (LAD) and right coronary artery (RCA).

Methods: Twenty three patients with CTO, stable angina and a positive exercise test result were included in the study. All subjects were admitted to the hospital for elective recanalisation of CTO. One day before the recanalisation, within the first 24 h and three months after the procedure, LVEF, baroreceptor sensitivity (WBA_BRS) and heart rate variability (HRV) measures: mRR, SDNN, pNN50, LF/HF were assessed. Results before and after recanalisation were compared.

Results: In the LAD group, initial LVEF, WBA_BRS and LF/HF values were significantly lower than in the RCA group (43 ± 11 vs. 52 ± 4%, p = 0.005; 3.1 ± 1.9 vs. 7.9 ± 5.0 ms/mmHg, p = 0.008; 1.3 ± 1.9 vs. 3.7 ± 2.6, p = 0.02, respectively). During first 24 h after the recanalisation, LVEF increase was observed in both groups. In the LAD group additional LVEF improvement was found during a long-term follow up (LVEF in the RCA group: 52 ± 4%, 56 ± 2%, 56 ± 2%; in the LAD group: 43 ± 11%, 47 ± 10%, 54 ± 9%). In the RCA group a transient decrease of WBA_BRS during first 24 h after the procedure was found (7.9 ± 5.0 vs. 5.0 ± 2.8 ms/mmHg, p = 0.09), while in the LAD group this effect was not observed. Moreover, in the LAD group a trend towards an increase of WBA_BRS was found three months after the recanalisation (3.1 ± 1.9 vs. 5.0 ± 2.8 ms/mmHg, p = 0.09). Similar trends were observed for HRV.

Conclusions: CTO recanalisation results in increased LVEF in all patients, but is more pronounced following LAD rather than RCA recanalisation. Also, the changes in the ANS parameters were more beneficial after LAD than RCA recanalisation. These findings may suggest that recanalisation of LAD is more beneficial than that of RCA.

Key words: chronic total occlusion, baroreflex sensitivity, recanalisation, autonomic nervous system

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Introduction

Chronic total occlusion (CTO) is diagnosed in as many as 30-40% patients with coronary artery disease (CAD) [1]. The prognosis of patients with CTO is comparable to the prognosis of patients with significantly stenosed coronary artery – annual mortality rate amounts to 2% [2]. However, recanalisation of CTO constitutes only 10% of all percutaneous coronary interventions [3]. The CTO recanalisation is not performed on a routine basis mainly due to a lack of its fully documented benefits. Some studies showed that opening of CTO is associated with significantly lower mortality than leaving chronic total occlusion, though other reports did not confirm these observations [4-8]. It has been stated in many studies that after recanalisation of CTO, left ventricular ejection fraction (LVEF) gets better – the primary risk factor of death in patients after myocardial infarction (MI) – however, in this situation as well, the results are not entirely uniform [4, 9-12].

Assessment of baroreflex sensitivity (BRS) and heart rate variability (HRV) has a thoroughly confirmed value in prediction of cardiac death and life-threatening ventricular arrhythmia risk in MI survivors. The patients with markedly

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decreased BRS and HRV are at higher risk of death than those with relatively well preserved BRS and HRV [13]. Currently, only few studies addressed the issue whether CTO recanalisation has a beneficial impact on autonomic nervous system (ANS) activity and the risk of sudden cardiac death. In a few studies HRV and BRS were evaluated in patients with occluded coronary artery as compared to they profile in patient with open infarct related artery [14-18]. So far, no assessment of BRS and HRV was made before and after recanalisation in one patient group.

A lack of well-documented benefits from recanalisation of CTO may result from imperfect identification of patients with CTO, who benefit the most. It seems that the best results from restoring patency of CTO coronary artery are likely to be gained in the group with preserved viability of myocardial area supplied by this artery and in those at higher risk, e.g., subjects after anterior MI and low LVEF [11, 12, 19].

Our study enrolled patients with angina and positive stress test which indirectly confirmed viability of an area supplied by CTO artery (there were no stenoses in other coronary arteries). Because we expected to obtain greater benefits from CTO recanalisation in patients after anterior MI, we carried out a separate analysis of BRS and HRV parameter profile in patient after restoring patency of the left or right coronary artery.

Methods

Patients

Consecutive 61 patients with CTO were admitted to perform an elective CTO recanalisation. All patients had single vessel CAD, stable angina pectoris (CCS I-III) and positive stress test – exercise test, or in some cases, echocardiographic dobutamine test. The CTO was defined as an occlusion with TIMI flow 0, occurring for > 4 weeks. No significant stenoses were found in the remaining coronary arteries.

The following exclusion criteria were used: age > 80 years, significant valvular defect, ventricular or supraventricular ectopic beats totaling over 5% of all heartbeats, permanent atrial fibrillation, sick sinus syndrome, the second and third degree atrioventricular block, presence of pacemaker, insulin-dependent diabetes mellitus, coronary and hemodynamic instability and patient's severe general or psychophysical condition preventing unassisted arrival for examination and lack of patient's consent for the participation in the study. Twenty six subjects failed to meet the study inclusion/exclusion criteria. The most frequent causes of patients' ineligibility were as follows: insulin-dependent diabetes mellitus – 6 subjects, severe general or psychophysical condition preventing unassisted arrival for examination – 5 subjects, lack of consent for participation in the study – 5 subjects, and numerous premature beats in the ECG at rest – 4 subjects (the remaining reasons – in single cases). Thus, 35 patients entered the study.

Recanalisation of CTO

The procedure of CTO recanalisation was successful (TIMI 3) in 30 (86%) patients. In all cases coronary stent was inserted if indicated. Following an attempt of CTO recanalisation, either successful or not, no serious complications were recorded, including no elevation of myocardial necrosis markers' levels in any patient.

Among 30 patients who underwent recanalisation of CTO, the target coronary artery was left anterior descending (LAD) in 8 (27%) and right coronary artery (RCA) in 15 (50%) patients. The remaining 7 patients had recanalisation of the left circumflex artery (4 subjects), obtuse marginal branch (2 subjects) and antero-lateral branch (1 subject).

Twenty three patients who underwent recanalisation of LAD or RCA formed two groups that were compared.

Analysis of ANS activity

Evaluation of BRS and HRV was performed three times: a day before CTO recanalisation, on day 1 after recanalisation, and then at month 3 after recanalisation. Activity of ANS was examined each time after the procedure in the morning, in a quiet, shadowed, warm room, according to the protocol thoroughly described in earlier publications [20]. Arterial BRS was assessed using algorithm suggested by Pinna to calculate WBA_BRS index. This parameter is calculated with the use of spectral analysis of spontaneous changes of systolic blood pressure and heart rate in the entire low frequency band of 0.04-0.15 Hz [21]. Besides, common HRV parameters were measured as well: mean RR interval (mRR), standard deviation of all normal RR intervals (SDNN), percentage of consecutive RR differences > 50 ms (pNN50) and low frequency/high frequency ratio (LF/HF).

Echocardiographic assessment of LVEF was performed at the same time-points as BRS analysis.

Following calculation of WBA_BRS, HRV parameters and LVEF, they were reevaluated after CTO recanalisation (on day 1 and month 3) and compared to the pre-recanalisation values, both for RCA and LAD groups.

The study was approved by the Independent Ethics Committee for Clinical Trials at the Medical University in Gdańsk.

Statistical analysis

Data are presented as means and standard deviations (in case of continuous variables of normal distribution) or as numbers and percentages in case of categorised variables. Normal distribution of individual parameters was determined with Kołomogrow-Smirnow test with Liliefors's modification. The significance of differences between pre-

and post-procedural variables were assessed using Wilcoxon signed-rank test, as majority of variables failed to meet normal distribution pattern, or t-test. The Rs Spearman coefficient was applied to verify correlations. The results were found significant if p value was lower or equal to 0.05. No corrections were implemented for multiplicity of comparisons.

Results

Table I presents clinical characteristics of 23 study patients (57 ± 10 years old, male to female ratio: 7 : 3), with distinction of two groups – with LAD recanalisation and RCA recanalisation.

There were no differences between patients from both groups with respect to age, history of previous MI, time from infraction to CTO recanalisation, concomitant diseases and majority of taken drugs (except for diuretics which were more often administered in the LAD group as opposed to RCA group as a result of more severe myocardial damage in the former one).

Mean LVEF before the procedure was significantly lower in patients with LAD occluded as compared to patients with CTO of RCA (Table I). Similarly, mean baseline WBA_BRS was significantly lower in the LAD group than in the RCA group (3.1 ± 1.9 vs. 7.9 ± 5.0 ms/mmHg, p = 0.008). The HRV parameters (mRR, SDNN and pNN50) did not differentiate the analysed groups, however LF/HF values were significantly lower in the LAD group in comparison with the RCA group (1.3 ± 1.9 vs. 3.7 ± 2.6, p = 0.02).

Changes of LVEF, WBA_BRS and HRV after RCA recanalisation

A significant improvement of LVEF was observed as soon as on the first day after the procedure: 56 ± 3 vs. 52 ± 4%; p = 0.01. Through further follow-up the mean LVEF value remained stable – three months after recanalisation it was comparable to the value determined on the first day after the procedure: 56 ± 4 vs. 56 ± 3%; (NS) (Figure 1 C).

The ANS function deteriorated temporarily, that could be best reflected by WBA_BRS, which was 7.9 ± 5.0 before the procedure compared to 4.5 ± 3.1 ms/mmHg on day 1 (p < 0.05) (Figure 1 A). Also some HRV parameters tended to worsen one day after procedure (Table II).

Changes of WBA_BRS on day 1 after RCA recanalisation compared to values prior to the procedure for individual patients are shown in Figure 2 (left panel). In 9 of 15 patients a decrease in WBA_BRS was observed. It is worth emphasising that in 5 (33%) patients the WBA_BRS values, which were initially normal, on day 1 decreased up to ≤ 3 ms/mmHg, which is well-confirmed borderline value of high risk of sudden cardiac death.

At month 3, following transient decrease on the first day, WBA_BRS returned to its baseline values – 8.7 ± 7.2 and 7.9 ± 5.0 ms/mmHg, respectively; p = 0.91 (Figure 3, left panel). The HRV parameters also normalised (Table II).

Table I. Clinical characteristics of patients with successful recanalisation

	LAD (n = 8)	RCA (n = 15)
Age [years]	60 ± 10	56 ± 9
Males n (%)	4 (50%)	12 (80%)
History of MI, n (%)	6 (75%)	10 (67%)
Time from MI [months]	2 ± 1	2 ± 2
Non-STEMI, n (%)	1 (13%)	1 (7%)
STEMI, n (%)	5 (63%)	9 (60%)
LVEF [%]*	43 ± 11	52 ± 4
Medication, n (%)		
beta-blockers	8 (100%)	13 (87%)
angiotensin-converting enzyme inhibitors	7 (88%)	12 (80%)
acetylosalicylic acid	8 (100%)	15 (100%)
statins	8 (100%)	15 (100%)
calcium channel blockers	2 (25%)	5 (33%)
diuretics*	5 (62%)	0 (0%)
Co-morbidities, n (%)		
arterial hypertension	7 (88%)	10 (67%)
hypercholesterolemia	8 (100%)	15 (100%)
type 2 diabetes mellitus	1 (13%)	2 (13%)

** p < 0.05*

Changes of LVEF, WBA_BRS and HRV after recanalisation of LAD

In the LAD group, alike in RCA one, significant increase of LVEF on the first day after recanalisation was observed as compared to the baseline values: 47 ± 10 vs. 43 ± 11%; p = 0.03. In addition, further improvement of LVEF was seen over the long-term follow-up – at month 3 mean LVEF was 54 ± 9% (Figure 1 D).

Regarding ANS function, no significant changes of BRS (Figure 2, right panel) and HRV values (Table III) were documented on the first day following recanalisation of LAD. However, three months after the procedure there was a significant trend towards an improvement of mean WBA_BRS compared to its mean values prior to LAD recanalisation – 5.0 ± 2.8 and 3.1 ± 1.9 ms/mmHg, respectively (p = 0.09) (Figure 1 B). The increase of WBA_BRS was confirmed in 7 of 8 patients with recanalised LAD (Figure 3, right panel).

Generally, mean HRV parameters did not change significantly after three months of restoration of LAD patency. Only pNN50 tended to improve compared to its baseline value (Table III).

Correlation between WBA_BRS and LVEF

All studied correlations between WBA_BRS and LVEF were poor – Pearson correlation coefficient was significantly lower than 0.3 (rs = 0.01–0.21) (NS).

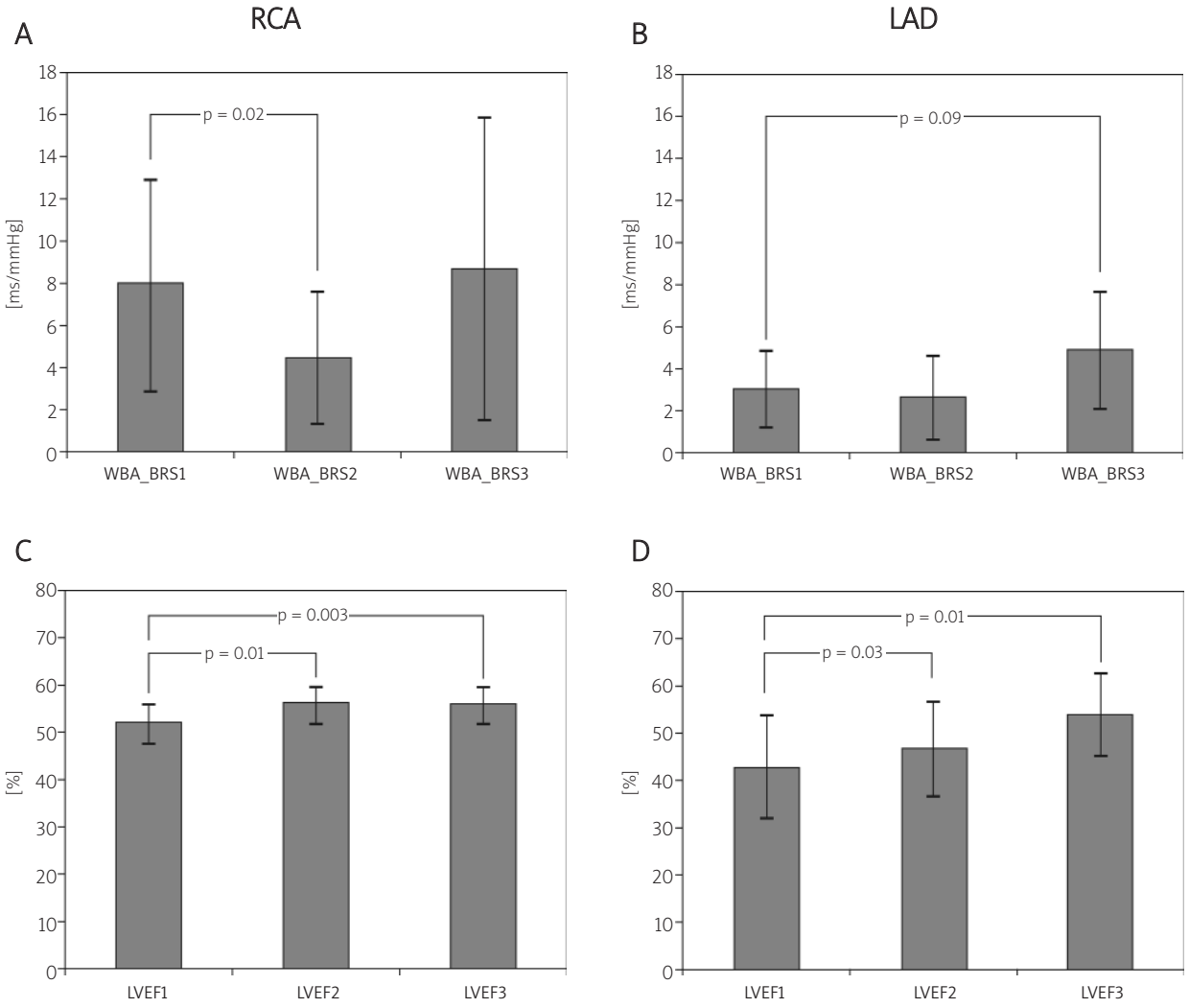

Figure 1. Comparison of WBA_BRS and LVEF before recanalisation, on Day 1 and at Month 3 in RCA and LAD groups. **A** – values of WBA_BRS in RCA group before recanalisation (WBA_BRS1), on Day 1 (WBA_BRS2) and at Month 3 (WBA_BRS3). **B** – values of WBA_BRS in LAD group before recanalisation (WBA_BRS1), on Day 1 (WBA_BRS2) and at Month 3 (WBA_BRS3). **C** – values of LVEF in RCA group before recanalisation (LVEF1), on Day 1 (LVEF2) and at Month 3 (LVEF3). **D** – values of LVEF in LAD group before recanalisation (LVEF1), on Day 1 (LVEF2) and at Month 3 (LVEF3)

Table II. Comparison of HRV parameters in the RCA group

	Before recanalisation	Day 1 after recanalisation	Month 3 after recanalisation
mRR [ms]	1007 ± 118	1000 ± 132	1073 ± 123
pNN50 [%]	4.3 ± 4.4	1.1 ± 1.1	3.0 ± 3.9
SDNN [ms]	28 ± 9	22 ± 12	29.8 ± 10.7
LF/HF	3.7 ± 2.6	1.9 ± 2.0	1.8 ± 1.4

All comparisons NS

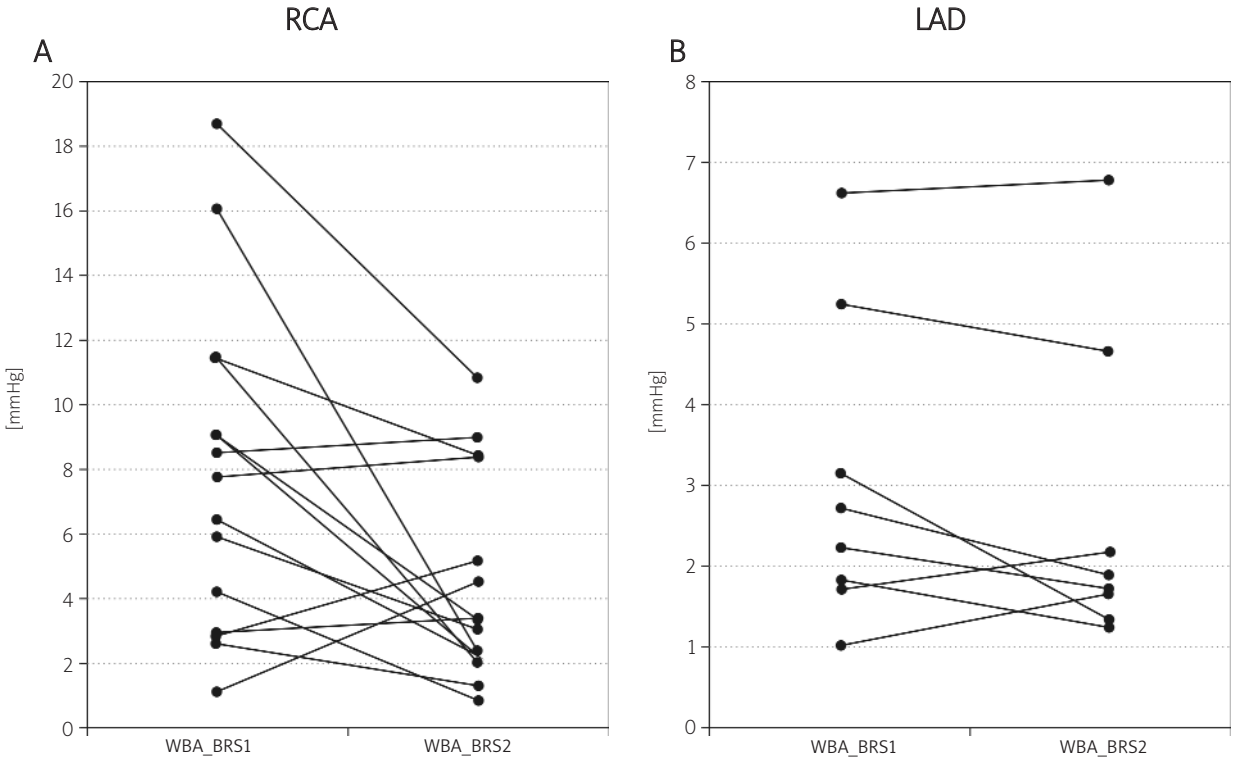

Figure 2. Left panel: individual values of WBA_BRS on Day 1 after recanalisation of CTO compared to the baseline values in patients with recanalised RCA. Right panel: individual values of WBA_BRS on Day 1 after recanalisation of CTO compared to the baseline values in patients with recanalised LAD

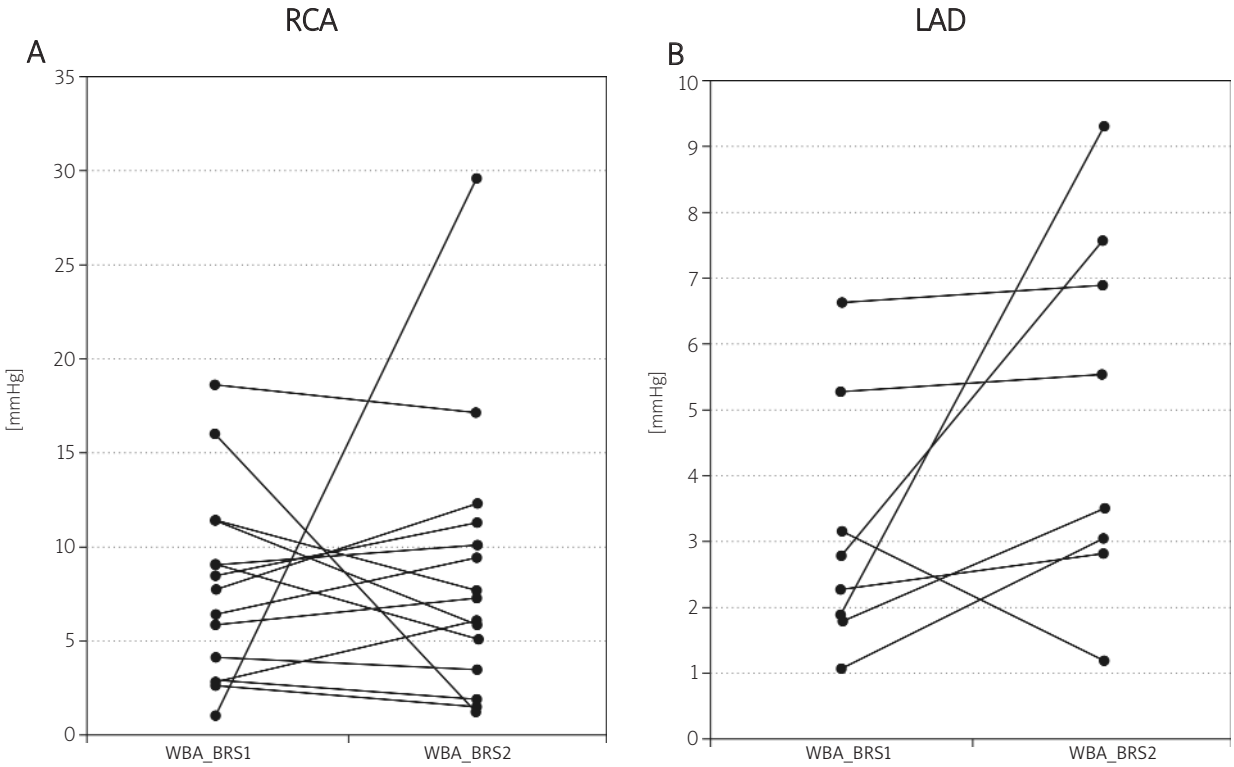

Figure 3. Left panel: individual values of WBA_BRS at Month 3 after recanalisation of CTO compared to the baseline values in patients with recanalised RCA. Right panel: individual values of WBA_BRS at Month 3 after recanalisation of CTO compared to the baseline values in patients with recanalised LAD

Table III. Comparison of HRV parameters in the LAD group

	Before recanalisation	Day 1 after recanalisation	Month 3 after recanalisation
mRR [ms]	974 ± 183	1073 ± 123	1020 ± 155
pNN50 [%]	4.2 ± 7.3	1.9 ± 1.4	6.3 ± 9.4
SDNN [ms]	22 ± 14	27 ± 9	25.6 ± 9.4
LF/HF	1.3 ± 1.9	2.2 ± 1.9	1.6 ± 2.45

All comparisons NS

Discussion

In this study, we observed significant variability of ANS parameters in patients with recanalised RCA and LAD. In the first group, higher baseline LVEF and WBA_BRS were found than in the other one. Following recanalisation, this group experienced improvement of LVEF (both on day 1 and during further follow-up), with accompanying transient decrease in WBA_BRS resolving later during the follow-up; however, not exceeding the baseline values. Patient with LAD recanalisation did not present with transient decrease in BRS parameter, having its marked increase during long-term follow-up.

Evaluation of baseline parameters revealed significantly lower LVEF in patients with chronic occlusion of LAD as compared to RCA group. This supports the commonly recognised fact that occlusion of a larger vessel supplying considerable parts of myocardium leads to greater systolic dysfunction than occlusion of a smaller coronary artery. Lower baseline BRS and some of HRV parameters in the LAD group than in RCA group are associated with lower LVEF in the former group of patients. This relationship was described by number of investigators [13, 17].

The post-recanalisation analysis showed increase of LVEF in both groups, which is consistent with number of publications [9-11]. A new finding is better improvement of LVEF after LAD recanalisation than after RCA recanalisation.

There is lack of papers on the effects of CTO recanalisation on BRS, which requires both, pre- and post-procedural analysis, as well as evaluation of direct and long-term changes. So far, only single papers are available comparing BRS in subjects with CTO and patent infarct-related coronary artery, showing higher values in the latter group [17, 18].

Several studies provided separate analysis of BRS in patients after anterior or inferior MI, however the revascularisation impact has not been addressed. Furthermore, results of those studies are divergent. La Rovere et al. [22] and Bigger et al. [23] showed lower BRS values in patients with inferior than anterior MI. Studies of Farrell et al. [18], Schwartz et al. [24] and Osculati et al. [25] did not reveal differences in BRS in those groups. On the other hand, Webb et al. [26] showed more compromised BRS after anterior rather than inferior MI.

In our study lower BRS was found in the LAD group, which is obvious as associated with lower LVEF in this group of patients. Moreover, LAD and RCA recanalisation groups had different BRS changes profile. However, these findings should be interpreted with caution, in particular in the light of Airaksinen et al. study, who assessed ANS reaction to short occlusions of the right or left coronary artery and found that those reactions are only present in part of patients, and their direction and severity are not dependent on the occlusion site [27]. Pomidossi et al. stated that decreased BRS observed during coronary angioplasty was not dependent on location of ischemia (anterior vs. inferior wall), which applied also to the silent ischemia episodes [28]. On the other hand, in the ATRAMI population, restoration of LAD patency gave significantly higher benefit regarding BRS than that of RCA [13]

Transient decrease in BRS following recanalisation of RCA may be associated with sympathetic instability related to the procedure performed. The most important conclusion of our study is that fact that LAD group, which is at higher risk, was found to have long-term improvement of autonomic reactivity; this was not seen in the RCA group. Higher increase of BRS in the LAD group than in RCA one may be associated with more evident improvement of LVEF in the former group. In fact, assessment of individual patients parameters does not show strict correlation between BRS and LVEF [17, 18, 22]; however, higher mean LVEF in the entire study population was associated with higher mean BRS [13, 17]. These findings seem to support the thesis that beneficial improvement of ANS function following complete myocardial revascularisation is present in patients at higher risk at baseline, i.e., after anterior MI, with lower LVEF and BRS [17], while it is not observed in subjects with good LVEF and preserved BRS.

In our study, WBA_BRS values better differentiated both study groups than HRV parameters, which showed similar profile of changes. This may results from different methodology of HRV analysis. In our study, short-term HRV was assessed (10 min intervals) in laboratory conditions and in supine patient. This was done to standardise and simplify methodology. It also allowed for good evaluation of parasympathetic system which predominates in those conditions, but could lead to underestimation of sympathetic activity. The HRV trend observed in our study was confirmed by research based on 24-hour monitoring of HRV [14-16, 29].

Conclusions

The CTO recanalisation caused improvement of LVEF in all patients, although more evident after restoration of LAD patency. More beneficial changes in the ANS acitivity were observed after recanalisation of LAD rather than RCA.

Our results may suggest additional benefit of recanalisation of chronically occluded LAD, not only through limitation of the infarction zone, but also through potential antiarrhythmic effect resulting from shifting the autonomic balance in favor of parasympathetic nervous system.

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Porównanie wpływu rekanalizacji przewlekle zamkniętej prawej i lewej tętnicy wieńcowej na czynność autonomicznego układu nerwowego

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Streszczenie

Wstęp: Rekanalizacja przewlekle zamkniętej tętnicy wieńcowej (CTO) nie jest rutynowo wykonywana ze względu na brak jednoznacznych korzyści z tego zabiegu. Wynika to prawdopodobnie z niedostatecznego wyodrębnienia spośród chorych z CTO grupy, w której efekty rekanalizacji są największe.

Cel: Ocena zachowania wskaźników czynności autonomicznego układu nerwowego (AUN) i frakcji wyrzutowej lewej komory (LVEF) w dwóch grupach chorych: po rekanalizacji lewej (grupa LAD) i prawej tętnicy wieńcowej (grupa RCA).

Metody: Badaniami objęto 23 chorych ze stabilną chorobą wieńcową i dodatnim wynikiem testu obciążeniowego, przyjętych na oddział kardiologii w celu wykonania planowej rekanalizacji CTO. U wszystkich chorych dzień przed rekanalizacją, w pierwszej dobie po rekanalizacji oraz 3 miesiące po zabiegu oznaczano LVEF oraz obliczano spektralny wskaźnik WBA_BRS i wskaźniki HRV: mRR, SDNN, pNN50, LF/HF. Następnie dokonano porównań tych wskaźników oznaczanych po rekanalizacji CTO w stosunku do wartości przed zabiegiem.

Wyniki: W grupie LAD wyjściowe wartości LVEF, WBA_BRS i LF/HF były istotnie niższe niż w grupie RCA (odpowiednio: 43 ± 11 *vs* 52 ± 4%, p = 0,005; 3,1 ± 1,9 *vs* 7,9 ± 5,0 ms/mmHg, p = 0,008; 1,3 ± 1,9 *vs* 3,7 ± 2,6, p = 0,02). Pod wpływem rekanalizacji, już w pierwszej dobie w obu grupach obserwowano wzrost LVEF, ale w grupie LAD stwierdzono dalszą poprawę LVEF w obserwacji odległej (LVEF w trzech punktach czasowych w grupie RCA wynosiła: 52 ± 4, 56 ± 4, 56 ± 2%, a w grupie LAD: 43 ± 11, 47 ± 10, 54 ± 9%). W grupie RCA wystąpiło przejściowe pogorszenie wartości WBA_BRS w pierwszej dobie po zabiegu (7,9 ± 5,0 *vs* 4,5 ± 3,1 ms/mmHg, p < 0,05). W grupie LAD nie obserwowano przejściowego obniżenia wartości WBA_BRS, natomiast po trzech miesiącach stwierdzono jego zauważalny wzrost (3,1 ± 1,9 *vs* 5,0 ± 2,8 ms/mmHg, p = 0,09). Podobne trendy obserwowano w odniesieniu do HRV, bez osiągnięcia znamienności statystycznej.

Wnioski: Rekanalizacja CTO powoduje poprawę LVEF u wszystkich chorych, aczkolwiek wyraźniejsze zmiany obserwowano po udrożnieniu LAD. W zakresie czynności AUN stwierdzono bardziej korzystne zmiany po rekanalizacji LAD niż RCA, ponieważ nie wykazano przejściowego spadku BRS w pierwszej dobie po zabiegu, natomiast w obserwacji odległej wzrost parametrów był silniej wyrażony. Biorąc pod uwagę zarówno zmiany LVEF, jak i czynności AUN, wydaje się, że rekanalizacja CTO jest szczególnie wskazana u osób z zamkniętą LAD.

Słowa kluczowe: przewlekłe zamknięcie tętnicy wieńcowej, wrażliwość baroreceptorów tętniczych, rekanalizacja, czynność AUN

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