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# Comparative analysis of cardioprotective effects of two renal denervation techniques

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**Aim.** To compare cardioprotective effects of two renal denervation (RD) techniques: main renal artery or its branches after bifurcation in patients with resistant hypertension (RH).

**Material and methods.** This randomized double-blind clinical (ClinicalTrials.gov. identifier: NCT02667912) study with a follow-up of 12,3±1,6 months included 55 patients with RH, which was divided into 2 groups: group 1 (n=27) — main renal artery denervation; group 2 — RD of branches. Mean age of patients was 57,3±9,5 and 56,4±9,3 years, respectively. We assessed structural and functional cardiac characteristics using two-dimensional speckle-tracking echocardiography (STE).

**Results.** Initially, the patients in the groups did not differ in terms of studied parameters and therapy. After RD in both groups, the levels of myocardial stress significantly decreased; 95% confidence interval: after main renal artery denervation — systolic [-4802; -2896], diastolic [-3264; -2032] dyne/cm$^2$; after RD of branches — [-6324; -5328] and [-4021; -2521] dyne/cm$^2$, respectively (p=0,001 and 0,024, respectively). After main renal artery denervation, there was a decrease in the left ventricular (LV) wall thickness (interventricular septum [1,06; -0,62] and posterior wall [0,12; -0,62]) in comparison with RD of branches ([-0,68; -1,28] and [-0,68; -1,06], respectively). These differences were significant: p=0,023 and 0,021, respectively. After distal RD, decrease in the LV mass was observed more often by 21,2%, an increase in the LV mass was 2 times less frequent. Restoration of diastolic function was more common in patients after distal RD than main renal artery denervation (26% vs 13%, respectively). According to pilot analysis, STE parameters was also improved.

**Conclusion.** Twelve months after distal RD, compared with the main renal artery denervation, the LV wall thickness, number of patients with LV hypertrophy, and diastolic dysfunction decreased significantly greater. Two-dimensional STE revealed improvement of cardiac parameters. The results require further research.

**Keywords:** heart, hypertension, renal denervation, diastolic function.

**Relationships and Activities.** State assignment of Tomsk National Medical Research Center (state registration: AAAA-A17-117052310076-7 dated 23.05.2017).

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According to the May Measurement Month global campaign, where 1,5 million people were examined in 2018, 33,4% were diagnosed with hypertension (HTN). Of 60% of participants observed for HTN, target blood pressure (BP) levels were achieved only in 33,2% [1]. The problem of reaching target pressure levels is an independent task for reducing the risk of cardiovascular events, which has not yet been resolved. For its implementation, in addition to drug therapy for HTN, novel therapy options (device-based treatment) are currently being proposed and actively studied [2]. Among them, the most widespread is the method of endovascular renal denervation (RDN) [3]. Various approaches to radiofrequency ablation are of great interest: conventional RD (CRD), used until 2016, with the application of ablation points in the renal artery trunk, and distal RD (DRD) when the ablation is carried out in its distal part and branches after the bifurcation. It was proved that it is in the distal renal artery and its branches the concentration of sympathetic nerve endings is maximal [4]. This was followed by studies that showed a more pronounced antihypertensive effect of DRD compared to CRD [5]. In this connection, there are grounds to believe that organ protection after DRD will be more beneficial, since the association between heart disorders and increased activity of the sympathetic nervous system [6], HTN and related myocardial stress (MS) is obvious. Beneficial CRD effects on the heart have been demonstrated previously in experimental and clinical studies [7-9]. There are practically no comparative studies concerning the cardioprotective effects of the two approaches. Therefore, the aim of this prospective randomized double-blind study was to compare the cardioprotective effects of CRD and DRD in patients with resistant hypertension (RH) in parallel groups.

## Material and methods

This clinical (ClinicalTrials.gov.identifier: NCT02667912), single-center, randomized, double-blind, controlled in parallel groups study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The study protocol and informed consent, which was signed by each participant prior to study initiation, were approved by the Ethics Committees of all participating clinical centers.

There were following inclusion criteria: adult male and female patients aged 18-80 year with systolic blood pressure (SBP) ⩾160 mm Hg or diastolic blood pressure (DBP) ⩾100 mm Hg received the therapy (at least 3 months) with three antihypertensive drugs, including a diuretic. Exclusion criteria were as follows: glomerular filtration rate <30 ml/min/1,73 $m^2$, 24-hour mean SBP <135 mm Hg, secondary HTN, severe arterial abnormalities, pregnancy, significant failure of organs or systems (neurological, hematological, metabolic, cardiac, hepatic, pulmonary, etc.). Standard echocardiographic and left ventricular (LV) diastolic function (DF) indices, as well as two-dimensional strain speckle tracking echocardiographic (STE) parameters were evaluated [10-12]. LV MS was calculated as follows: $MS_{syst}$ ($MS_{diast}$) = SBP (DBP) × LV end-systolic (diastolic) dimension / 4 × LV posterior wall thickness (PWT) × (1 + LV PWT / LV end-systolic (diastolic) dimension), dyn/$cm^2$. The technique of performing ORD and DRD in this study was described in detail earlier [13].

The study design is shown in Figure 1. The composition of drug groups and the doses prescribed were monitored at each visit to the center. Patients with RH (n=55), meeting the selection criteria, after angiography with ruling out of exclusion criteria disorders before the initiation of the RD were randomized in a 1:1 ratio into groups for radiofrequency ablation by the DRD or CRD. The type of intervention remained unknown to patients, researchers, and others involved in evaluating treatment outcomes throughout the study period. By the end of the study, four patients died for reasons unrelated to the procedure, while three patients refused to repeat examinations.

Statistical analysis was carried out using Statistica for Windows 10.0 software. The quality of the data was assessed using distribution histograms. In the case of pronounced deviations from the random distribution, the data were checked for errors in values and patient selection criteria. The hypothesis of a Gaussian distribution was tested using the Kolmogorov-Smirnov test. The main methods of statistical analysis were parametric Student's t test and the nonparametric Wilcoxon test for quantitative variables. The statistical significance of qualitative differences was assessed using the goodness of fit test; for values <10, the Yates' correction was used. When comparing the distributions of qualitative traits in dependent samples, the McNemar's test was used. The results are presented with the correct distribution: as mean ± standard deviation (M±SD) or as Me (median), confidence intervals (CI) or min-max values for informative presentation of data in case of incorrect distribution. The difference was considered significant at p<0,05.

## Results

Patients in the groups did not initially differ in analyzed, anthropological indices, as well as in parameters of fundamental importance for the study (Tables 1, 2).

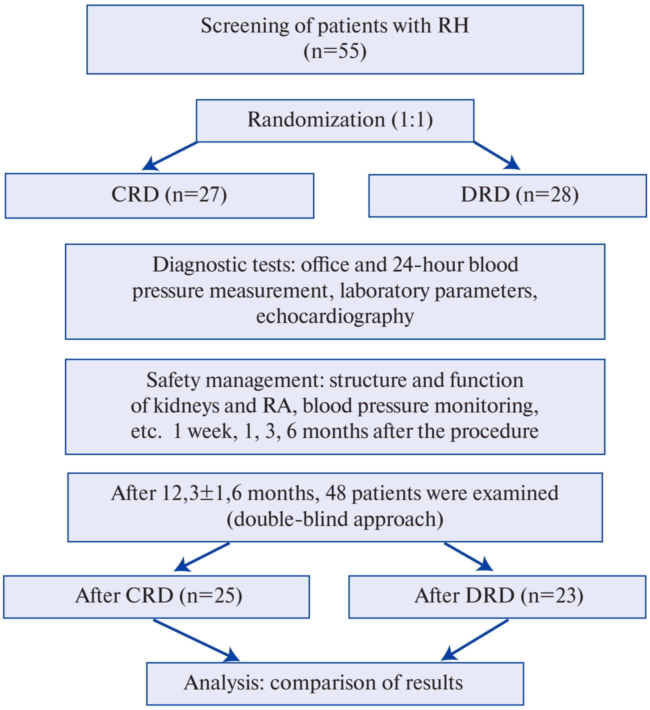


**Figure 1.** Study design.
**Abbreviations:** BP — blood pressure, DRD — distal renal denervation, CRD — conventional renal denervation, RA — renal artery, RH — resistant hypertension.

**Table 1**

**Clinical characteristics of patients in a randomized trial**

| | CRD group | DRD group | P |
|---|---|---|---|
| Mean 24-hour SBP, mm Hg | 158,0±15,2 | 166,3±24,2 | 0,122 |
| Mean 24-hour DBP, mm Hg | 87,9±17,6 | 90,8±18,6 | 0,781 |
| Age, years | 57,3±9,5 | 56,4±9,3 | 0,909 |
| Sex, female % | 62,0 | 60,0 | 0,248 |
| Race, white % | 100 | 100 | 1,000 |
| Body mass index | 32,3±4,2 | 31,2±5,3 | 0,623 |
| COVID-19, % | 11,4 | 12,7 | 0,522 |
| Hypercholesterolemia, % | 63,1 | 65,7 | 0,674 |
| HR, bpm | 71,1±9,8 | 69,7±12,0 | 0,308 |
| GFR, ml/min/1,73 $m^2$ | 72,4±12,1 | 80,7±23,0 | 0,064 |

**Abbreviations:** DBP — diastolic blood pressure, DRD — distal renal denervation, CRD — conventional renal denervation, SBP — systolic blood pressure, GFR — glomerular filtration rate, HR — heart rate.

The initial values indicated the increase of interventricular septum (IVS) and LV PWT in patients with LV dimensions closer to the upper boundaries or exceeding the norm. Attention was drawn to a slight increase in the left atrial dimension and volume, which is typical for patients with RH. It should be noted that the analysis of 2D strain STE parameters was carried out as a pilot in a little part of the participants under CRD (n=4) and DRD (n=6). Nevertheless, initially there was a slight decrease in STE parameters relative to the general healthy population or approaching the lower normal limits (Table 2).

Patients used different groups of drugs, but without significant differences in the main classes at baseline (Table 3). The doses in the study groups were focused on the maximum tolerated for each participant. The researchers did not change therapy during follow-up.

To avoid duplication, previously published data on a more pronounced antihypertensive effect of DRD as compared to CRD on office and 24-hour BP are not presented here [13], which were used to calculate MS. When analyzing the parameters of systolic and diastolic MS, there was a positive trend in both groups (95% CI, systolic MS [-4802; -2896], diastolic MS [-3264; -2032] after CRD vs. [-6324; -5328] and [-4021; -2521] dyn/$cm^2$ after DRD, p=0,001 and 0,024, respectively), with a significantly greater decrease in systolic MS in the DRD group, which is clearly shown in Figure 2 with their median values.

A less significant decrease in LV wall thickness after CRD was noted (Me is shown in the figure): IVS min-max [-0,62; 1,06] and LVPW [-0,62; 0,12] compared with DRD: [-1,28; -0,68] and [-1,06; -0,68] (Figure 3).

Therefore, a more pronounced regression of estimated value is natural — LV mass with a tendency to superiority of DRD vs. CRD, but without a significant advantage. LV mass dynamics were as follows: -36,10 [-111,43; 23,42] and -5,46 [-86,39; 23,34], p=0,114, respectively. An illustration of LV mass distribution in the groups is presented in Figure 4, where the decrease in LV mass after DRD occurred more often by 21,2% (p=0,023). After DRD, an increase in LV mass occurred 2 times less often (patients with LV mass dynamics >0 g).

LV DF was analyzed with total assessment of diastolic dysfunction signs and showed improvement in both groups (Figure 5), but normalization of DF was achieved 2 times more often after DRD vs. CRD (26% vs. 13%, respectively). It should be noted that there was no high-grade (grade 3) dysfunction in the groups at baseline, and it was not detected after a 1-yearf follow-up.

Figure 6 A shows changes in 2D strain STE parameters for standard LV segments. Significant positive changes in of global longitudinal strain were detected, evident for the basal and apical segments, and the radial strain, where significant differences were observed in most segments after

**Table 2**

**Comparative characteristics of initial echocardiography parameters during randomization**

| | CRD group, Mean±SD or Mean [5-95%] | DRD group, Mean±SD or Mean [5-95%] | P |
|---|---|---|---|
| Left atrial dimension, mm | 43,17±5,14 | 43,04±3,78 | 0,521 |
| Left atrial volume, ml | 77,91±19,19 | 84,14±15,89 | 0,394 |
| LV EDD, mm | 47,19±5,14 | 47,53±2,95 | 0,325 |
| LV ESD, mm | 29,93±4,34 | 30,52±2,43 | 0,242 |
| IVS, mm | 14,2 [13,1-15,3] | 14,1 [13,3-14,9] | 0,184 |
| LVPW, mm | 12,8 [12,0-13,8] | 12,8 [12,0-13,7] | 0,389 |
| LV mass, g | 259,8 [236,4-293,2] | 264,1 [240,0-288,7] | 0,136 |
| Global longitudinal strain, % | -13,9±5,01 | -14,1±5,01 | 0,647 |
| Strain in radial direction, % | 46,43±14,88 | 44,11±9,91 | 0,521 |
| Strain in circumferential direction, % | -15,72±6,61 | -16,21±8,13 | 0,512 |
| Strain rate longitudinal, sec $^{-1}$ | 1,137±0,286 | 0,992±0,230 | 0,385 |

**Abbreviations:** DRD — distal renal denervation, LVPW — left ventricular posterior wall, EDD — end-diastolic dimension, ESD — end-systolic dimension, LV — left ventricle, IVS — interventricular septum, CRD — conventional renal denervation.

**Table 3**

**Characteristics of antihypertensives' groups used during the follow-up period**

| | Proportion of use (%) | | p |
|---|---|---|---|
| | CRD group | DRD group | |
| ACE inhibitors | 53,0 | 49,0 | 0,921 |
| ARBs | 47,0 | 51,0 | 0,134 |
| CCB | 77,6 | 77,1 | 0,947 |
| Diuretics | 100 | 100 | 1,000 |
| Central-acting agents | 51,0 | 42,9 | 0,513 |
| β-blockers | 78,6 | 66,8 | 0,079 |
| α-blockers | 8,2 | 6,9 | 0,476 |
| Direct-acting vasodilators | 7,2 | 6,9 | 0,391 |

**Abbreviations:** DRD — distal renal denervation, ACE — angiotensin-converting enzyme, ARBs — angiotensin II receptor blockers, CCBs — calcium channel blockers, CRD — conventional renal denervation.

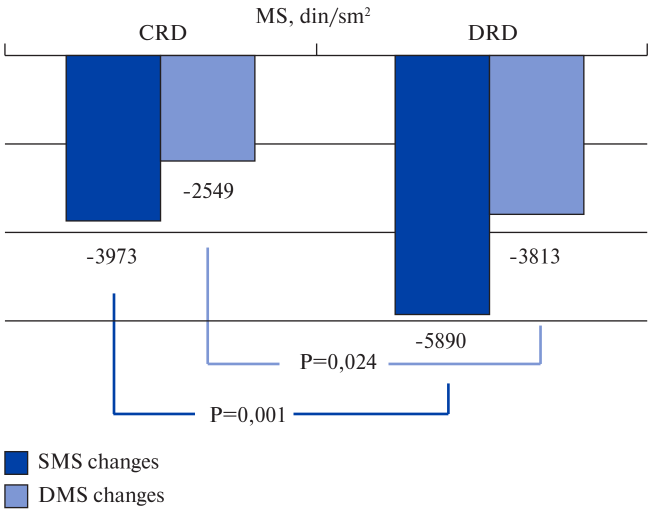


**Figure 2.** Comparison of changes in MS after CRD and DRD in patients after 12 months.
**Abbreviations:** DRD — distal renal denervation, DMS — diastolic myocardial stress, MS — myocardial stress, SMS — systolic myocardial stress, CRD — conventional renal denervation.

DRD (Figure 6 B). There was no significant difference between the analyzed techniques in circumferential strain (Figure 6 C).

## Discussion

It is well known that studies on RD, especially distal, are still very small in number and samples in them due to some objective reasons: the method has been introduced into clinical practice only in a number of countries and has a rather high cost; new equipment requires licensing by local health authorities and others, but the relevance of research is obvious at the present time [3]. Therefore, the world has a very careful and interested attitude to each clinical trial on RD. To date, some of its cardioprotective effects have been proven in sham-control experimental studies. The researchers noted an increase in LVEF and a decrease in LV end-diastolic volume in models of heart failure, an increase in ventricular diastolic dimension against the background of suppression of LV remodeling substrates (BNP, Ang II, aldosterone, TGF-β expression). A number of clinical studies have also shown a significant decrease in IVS thickness, LV

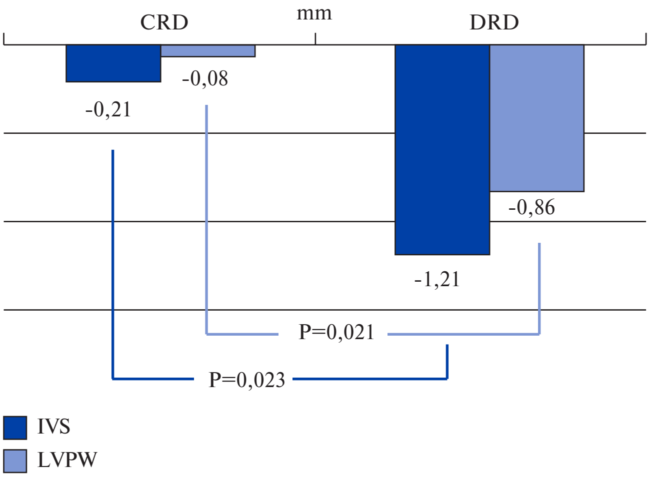


**Figure 3.** Comparison of changes in LV walls after CRD and DRD in patients after 12 months.
**Abbreviations:** DRD — distal renal denervation, LVPW — left ventricular posterior wall, IVS — interventricular septum, CRD — conventional renal denervation.

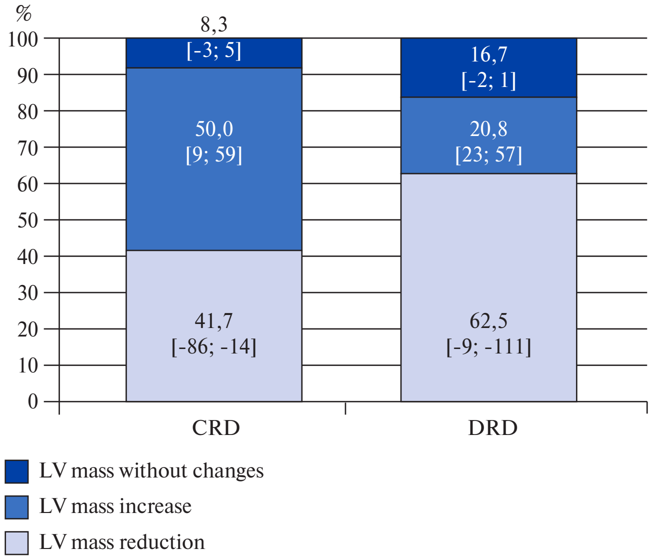


**Figure 4.** Comparison of changes in LV in the groups after CRD and DRD.
**Note:** upper figure — intragroup changes presented as %, lower figures — range of changes [min; max].
**Abbreviations:** DRD — distal renal denervation, LV — left ventricle, CRD — conventional renal denervation.

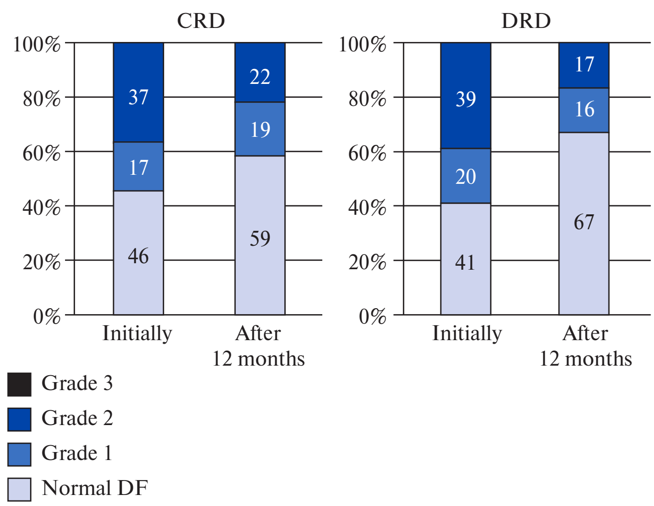


**Figure 5.** Changes in DD grade and restoration of LV DF after CRD and DRD.
**Abbreviations:** DRD — distal renal denervation, CRD — conventional renal denervation, DD — diastolic dysfunction, DF — diastolic function.

mass index and normalization of LV DF parameters [7-9]. These data were obtained after CRD. It is very likely that a more targeted effect on the sympathetic nervous system endings in the renal arteries causes a more pronounced antihypertensive effect after DRD. Since in this study, a more pronounced and cardioprotective effect was observed, this may be explained by a decrease in LV wall stress. In addition, a more directed effect on sympathetic nervous system fibers with the afferent response of greater strength should be expected to be realized in the beneficial effects of reducing LV mass But the detailed pathophysiological mechanisms of these processes should still be studied. Our data in 2018-2019 were presented for wide discussion at the congresses on hypertension and cardiology (ESH, ISH, ESC), where one of the frequently asked questions was: why did we not use the LV mass index in our estimations? We would like to give an explanation that this was applied deliberately and reasonably. Since during statistical processing of LV mass index, where each value (IVS, LVPW, end-diastolic size), together with the measurement error, is raised to the third power [10], plus the inspection error of body surface area during follow-up, then, therefore, this significantly increases the total error of calculated LV mass index and, accordingly, requires a much larger number of investigated values to determine the significance of the differences.

Special attention should be paid to the analysis of a pilot study of 2D strain STE parameters for standard LV segments. It is logical to assume that a more pronounced change in the longitudinal and circumferential strain after DRD is associated with a MS change and a decrease in sympathetic nerve activity. At the same time, it is not yet clear why not all LV segments responded equally? Given the small size of sample, of course, this requires further accumulation and verification of data.

**Study limitations.** The study was single-center, with no comparison to the sham-control group, with a small number of participants and a limited follow-up period.

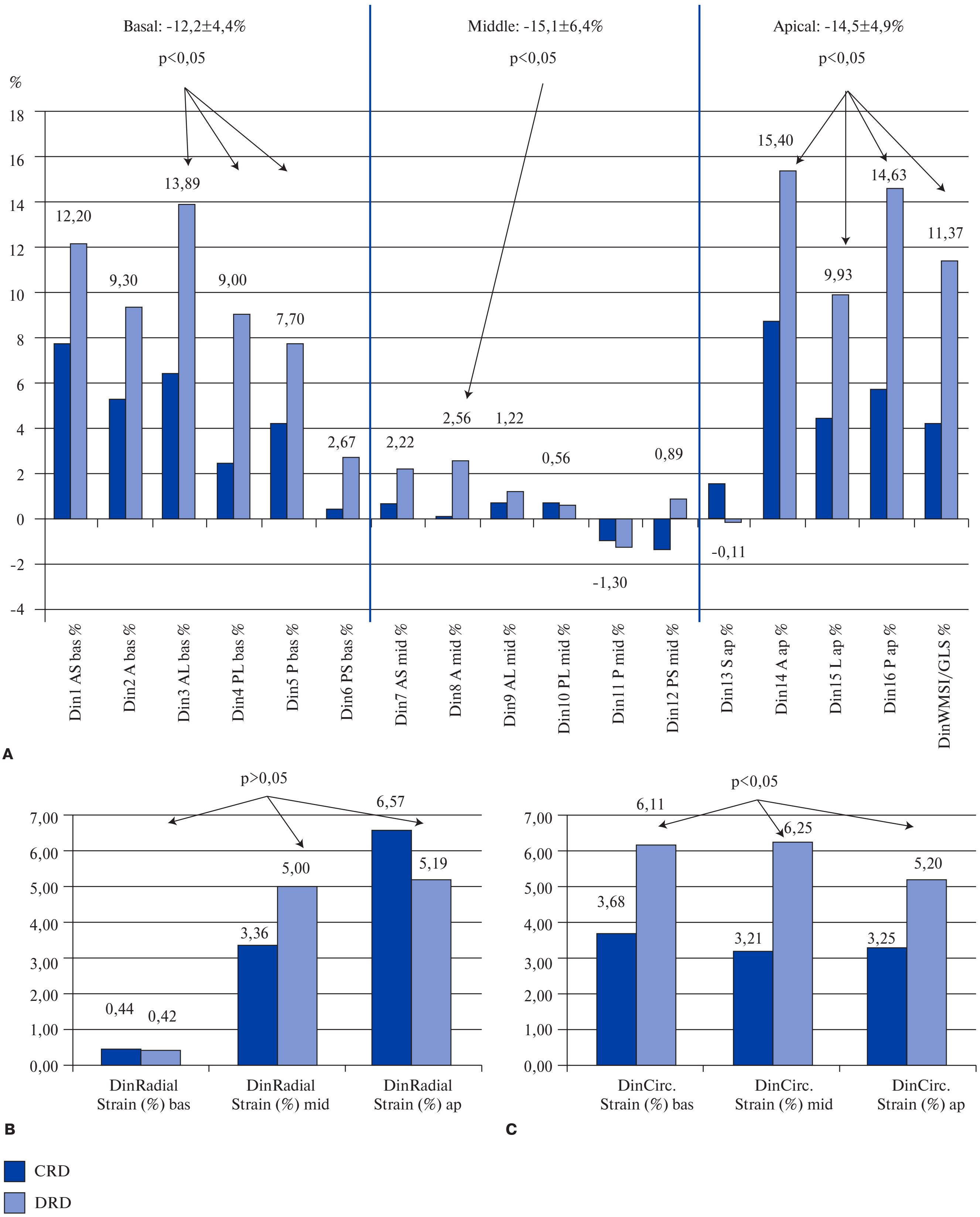


**Figure 6.** Comparison of changes in LV strain parameters in standard segments 12 months after CRD and DRD: **A** — LV global longitudinal strain, **B** — radial strain, **C** — circumferential strain.

**Abbreviations:** DRD — distal renal denervation, CRD — conventional renal denervation, A — anterior, AL — anterolateral, ap — apical, AS — anteroseptal, bas — basal, Circ. — circumferential, L — lateral, mid — middle, PL — posterolateral (inferolateral), P — posterior (inferior), PS — posteroseptal (inferoseptal), S — septal, WMSI/GLS — Wall motion score index/Global longitudinal strain.

## Conclusion

Twelve months after distal RD, compared with the main renal artery denervation, the LV wall thickness, number of patients with LV hypertrophy, and diastolic dysfunction decreased significantly greater. Two-dimensional STE revealed improvement of cardiac parameters. The results require further research.

**Acknowledgments.** The authors are grateful to the resident Bukharova E. K. for partially done work with speckle-tracking echocardiography.

**Relationships and Activities.** State assignment of Tomsk National Medical Research Center (state registration: AAAA-A17-117052310076-7 dated 23.05.2017).

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