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Surgical Technique of Angiogenesis Stimulation (Extracardial Myocardial Revascularization) in Patients with Coronary Artery Disease

Shevchenko YuL[1], Borshchev GG[1], Ulbashev DS[1]*

Abstract

Background: Coronary artery disease (CAD) remains one of the main causes of morbidity, early disability, and mortality in the adult population, despite significant achievements in the diagnosis and treatment of coronary blood flow disorders. An undoubted achievement at the present stage is the improvement of conservative and X-ray endovascular treatment methods; however, this has led to an increase in the number of patients with diffuse coronary lesions. We have developed a method of combination treatment for CAD through direct myocardial revascularization (CABG) in combination with the method YurLeon, which improves the results in such patients.

Materials and Methods: This study included 1,080 CAD patients with FC III–IV angina pectoris, who underwent surgical revascularization of the myocardium at Pirogov National Medical and Surgical Center, Russian Federation. A total of 650 men (60.19%) and 430 women (39.81%) aged 50 to 75 years were enrolled. Of them, 586 patients underwent coronary bypass surgery (CABG), whereas 494 patients underwent coronary bypass surgery supplemented with indirect revascularization using the YurLeon technique (CABG+YurLeon). Patients underwent gated-SPECT, echocardiography, computer tomography, coronary angiography and assessment of the quality of life using the SF-36 questionnaire.

Results: At the intraoperative stage and in the early postoperative period, there were no significant differences in complication rates between the two groups ($p>0.05$). One year postoperatively, we observed statistically significant differences in functional class of angina pectoris (Me[Q1-Q3]): 2[1-2] (after CABG), 1[1-2] (after CABG+YurLeon); $p<0,05$; left ventricular ejection fraction (M±SD): 50.12±6.20% (after CABG), 56.10±5.81% (after CABG+YurLeon); $p<0.05$; rest extent (M±SD): 15.56±9.56% (after CABG) and 8.38±5.79% (after CABG+YurLeon); $p < 0.05$; quality of life: 75±14.15 (PF after CABG), 87±10.32 (PF after CABG+YurLeon); $p<0.05$; 79±7.01 (RP after CABG), 90.01±10.50 (RP after CABG+YurLeon), $p<0.05$; 80±5.21 (BP after CABG), 93.10±6.37 (BP after CABG+YurLeon), $p<0.05$. After CABG, myocardial infarction associated with bypass dysfunction in the late postoperative period was registered in 17 of 150 patients (11.3%), whereas after CABG+YurLeon, it was observed only in 2 of 52 patients (3.8%) ($p = 0.001$).

Conclusion: Coronary bypass surgery, supplemented with the YurLeon method, is an effective and safe method of surgical treatment of patients with CAD, particularly in those with diffuse lesions of the coronary arteries, since it ensures additional blood supply to the myocardium.

Affiliation:

[1]St. George Clinic of Thoracic and Cardiovascular Surgery, Pirogov National Medical and Surgical Center; 70 Nizhnyaya Pervomayskaya St., Moscow, 105203, Russia

Corresponding author:

Daniil S Ulbashev, St. George Clinic of Thoracic and Cardiovascular Surgery, Pirogov National Medical and Surgical Center; 70 Nizhnyaya Pervomayskaya St., Moscow, 105203, Russia.

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Keywords: angiogenesis; coronary artery disease; coronary bypass surgery; indirect revascularization; YurLeon

Background

In spite of the advances made in the prevention and treatment of coronary artery disease (CAD), it remains one of the leading causes of morbidity and mortality [1-3]. Improved pharmacotherapy significantly reduced mortality and increased the quality of life of CAD patients in recent decades. Surgery is the most commonly used method to treat CAD [1]. However, there is a substantial group of patients in whom conservative treatments have proved ineffective, while complete surgical revascularization is technically impossible. This group includes patients with diffuse coronary artery lesions, distal occlusion, small diameter of coronary vessels, and those with recurrent, progressive angina, in whom repeated surgery is impossible [4]. Indirect revascularization has long been used in cardiac surgery for CAD patients. To form a vascular network, surgeons used the omentum, lung, muscles and other highly vascularized organs and tissues, attached them to the myocardium, ligated the internal thoracic arteries, and formed adhesive pericarditis [5-8]. During multiple repeated cardiac surgeries performed at different time-points after the first operation, as well as surgeries for different forms of compressive pericarditis, we noticed abundant growth in the adhesions between the pericardium and epicardium. Moreover, the intensity of blood flow in them was so high that even with careful hemostasis, patients developed bleeding postoperatively and required urgent opening of the wound to stop bleeding. We also noticed that postoperative wound suppuration (pericarditis, mediastinitis, osteomyelitis) increased heart vascularization, which was detected at repeated surgery. These findings encouraged our investigations of extracardial revascularization and development of methods for its stimulation in CAD patients, especially in those with diffuse lesions of the coronary vessels. In 2007, the team of St. George Clinic of Thoracic and Cardiovascular Surgery, N.I.Pirogov National Medical and Surgical Center launched special systematic studies aimed explore this issue. The analysis of various vascular growth factors in tissues of CAD patients showed that their highest concentration was observed in the discharge from the pericardial and retrosternal drains installed after the main stage of surgery. We have developed a special technique of drainage fluid collection, bacterial control, storage, and injection into the residual pericardial cavity.

Materials and Methods

This study included 1,080 patients diagnosed with CAD and functional class (FC) III or IV exertional angina who had undergone surgical revascularization of the myocardium. The study population included 650 men (60.19%) and 430 women (39.81%) aged 50 to 75 years. Patients in group I (n = 586) underwent coronary artery bypass grafting (CABG). Patients in group II (n = 494) underwent CABG plus indirect revascularization of the myocardium using the YurLeon method (CABG + YurLeon).

YurLeon method

Intraoperative Stage

- After completion of the main CABG stage, the pericardium and epicardium are treated with abrasive material (special glove, sponge) (Figure 1);
- Then mediastinal tissues (pericardial adipose tissue, involuted thymus) are prepared by being separated from the pericardium with subtotal or partial pericardectomy over the anterior and lateral LV wall (Figure 2);
- The next stage includes lipocardiopexia. The heart is wrapped in a prepared mediastinal fat flap and fixed to the epicardium with a Prolene 7/0 thread (Figure 3);
- A special thin drainage tube is installed along the diaphragmatic surface under the heart. Through this tube, an aspirate with vascular growth factors will be injected in the postoperative period (Figure 3). All other drainage tubes are connected to a sterile vessel with an active aspiration system;

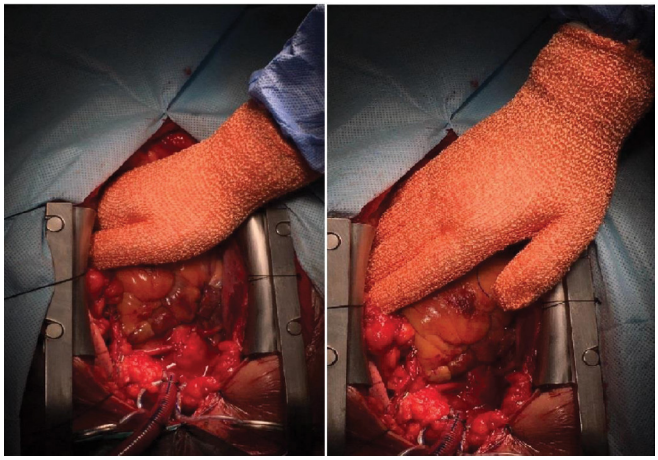

Figure 1: Mechanical treatment of the epicardium and pericardium with a sterile abrasive glove.

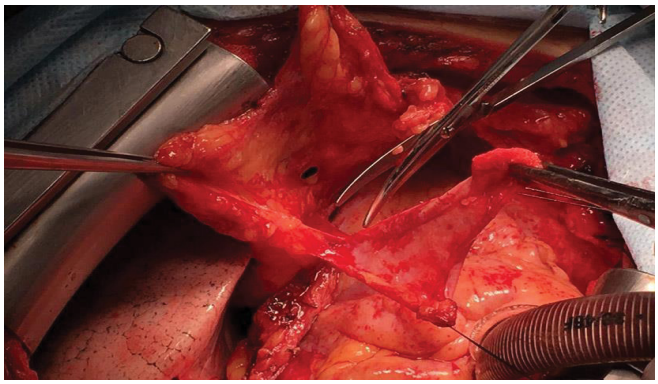

Figure 2: Subtotal pericardectomy.

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Postoperative Stage

- Fluid collected during the first day (approximately 80–100 mL) is stored in a sterile vessel at +4C°. This fluid contains many growth factors, such as vascular endothelial growth factor (VEGF), angiopoietins (Ang 1,2,3,4), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factor-p (TGFP), tumor necrosis factor-alpha (TNF-α);
- On the second or third day, after preliminary removal of the main pericardial and retrosternal drainage tubes, the aspirate (80–100 mL) is injected through the pericardial thin drainage tube, which is then removed and the hole is sealed (Figure 4);

Patients underwent ^{99m}Tc single-photon emission computed tomography (SPECT) of the myocardium synchronized with electrocardiography; echocardiography, and chest computed tomography. Two hundred and two patients (150 patients from group I and 52 patients from group II) underwent bypass graft angiography in the postoperative period at different time points (1 month to 5 years postoperatively). The SF-36 questionnaire was used to evaluate their quality of life. The normality of data was tested using the Shapiro–Wilk test and Kolmogorov–Smirnov test. Descriptive statistics included the number of cases (n), mean (M), standard deviation (SD), median (Me), and lower and upper quartiles [Q1 – Q3]. To compare normally distributed variables (and variables close to it), we used Student's t-test. To compare non-normally distributed variables, we used Wilcoxon test for paired samples and Mann–Whitney U-test for independent samples. The direction and strength of correlation between two quantitative variables were evaluated using the Spearman rank correlation test for non-normally distributed variables and Pearson's correlation test for normally distributed variables. Differences were considered significant at $p < 0.05$.

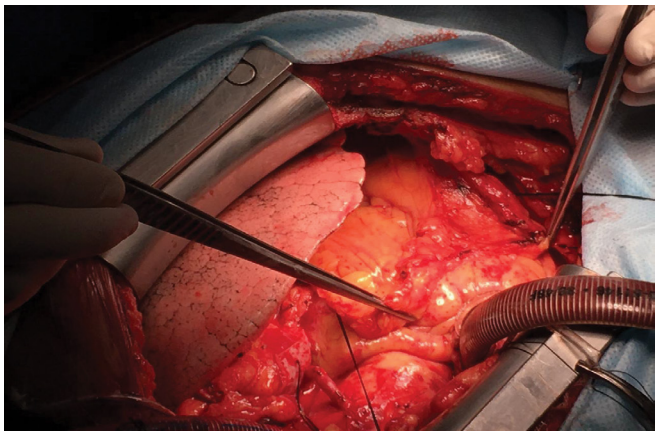

Figure 3: Wrapping of the heart with mediastinal fat.

Figure 4: Injection of aspirate (fluid containing vascular growth factors) into the residual pericardial cavity (2 days postoperatively).

Results

None of the patients from group II had intraoperative complications associated with the YurLeon technique. There were no significant differences in the incidence of early (within 10 days) postoperative complications (such as hemorrhagic, cardiac, neurological, and respiratory) between groups I and II. In group I, the FC of angina decreased from 3 [3-4] to 2 [2-2] 3 months postoperatively ($p = 0.017$) and to 2 [1-2] 12 months postoperatively ($p > 0.05$). In group II, the FC of angina changed from 3 [3-4] (before revascularization) to 2 [2-2] 3 months after revascularization and to 1 [1-2] 12 months after revascularization ($p = 0.013$). There was a significant difference between the two groups at the time-point 12 months postoperatively (Table 1).

Next, we assessed changes in the LV ejection fraction (EF) in these patients. In group I, LV EF increased from 48.69 ± 10.12% to 53.15 ± 7.98% after 3 months ($p = 0.021$). In Group II, LV EF increased from 49.61 ± 10.55% to 54.27 ± 8.52% after 3 months ($p = 0.0021$). However, 12 months postoperatively, there was a significant difference in LV EF between group I and group II (50.12 ± 6.20% vs 56.10 ± 5.81%, respectively; $p = 0.001$) (Table 2; Figure 5).

Table 1: Changes in the FC of angina (Me[Q1-Q3]).

Groups / Time-point	Group I (n = 586)	Group II (n = 494)	Difference between groups I and II (p)
Before revascularization	3[3-4]	3[3-4]	>0.05
Three months after revascularization	2[2-2]	2[2-2]	>0.05
Twelve months after revascularization	2[1-2]	1[1-2]	<0.05

Table 2: Changes in LV EF, % (M±SD).

Groups / Time-point	Group I (n = 586)	Group II (n = 494)	Difference between groups I and II (p)
Before revascularization	48.69±10.12%	49.61±10.55%	>0.05
Three months after revascularization	53.15±7.98%	54.27±8.52%	>0.05
Twelve months after revascularization	50.12±6.20%	56.10±5.81%	<0.05

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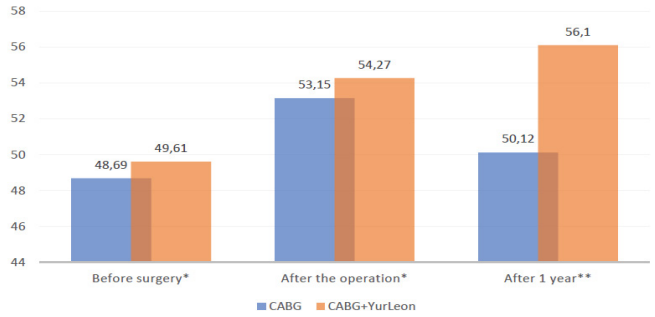

Figure 5: Chart demonstrating changes in EF (%) after CABG or CABG + YurLeon (*significant differences, Wilcoxon test; $p < 0.05$; **significant differences, Mann-Whitney U test; $p < 0.05$).

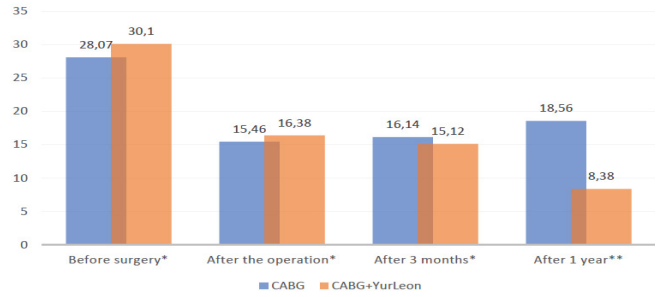

Figure 6: Chart demonstrating changes in rest extent (%) (*significant differences, Wilcoxon test; $p < 0.05$; **significant differences, Mann-Whitney U test; $p < 0.05$).

Table 3: Changes in rest extent, % (M±SD).

Groups / Time-point	Group I (n = 586)	Group II (n = 494)	Difference between groups I and II (p)
Before revascularization	28,07±6,11%	30,1±7,32%	>0.05
Seven days after revascularization	15,46±7,8%	16,38±7,5%	>0.05
Three months after revascularization	16,14±4,2%	15,12±5,1%	>0.05
Twelve months after revascularization	15,56±9,56%	8,38±5,79%	<0.05

Similar dynamics was observed when we measured the dynamics of rest extent using SPECT. There was a significant difference in the rest extent between the two groups 12 months postoperatively: 18.56 ± 9.56% in group I and 8.38 ± 5.79% in group II ($p = 0.003$) (Table 3; Figure 6,7).

CT scans of patients who had undergone CABG + YurLeon demonstrated that none of them had displacement of pericardial fat (Figure 8).

We also assessed patients' quality of life using the SF-36 questionnaire before the surgery and then 2.5–3 months and 12 months postoperatively. We observed a significant improvement of the quality of life 2.5–3 months following revascularization. The following parameters demonstrated the most significant changes: Physical functioning (PF): from 28 ± 10.15 to 60 ± 12.41 points (group I), ($p = 0.012$); from 25 ± 9.24 to 57 ± 11.58 points (group II) ($p = 0.011$).

Role physical (RP): from 15 ± 7.12 to 37 ± 10.11 points (group I), ($p = 0.007$); from 14 ± 8.33 to 42.01 ± 10.60 points (group II) ($p = 0.005$). Bodily pain (BP) (the score increases as the pain decreases): from 24 ± 10.10 to 45 ± 9.21 points (group I), ($p = 0.004$); from 21 ± 9.74 to 45.21 ± 9.67 points (group II) ($p = 0.0032$). Twelve months postoperatively, the quality of life improved in both groups compared to baseline. Physical functioning (PF): increase from 28 ± 10.15 to 75 ± 14.15 points (group I), ($p = 0.002$); from 25 ± 9.24 to 87 ± 10.32 points (group II) ($p = 0.001$).

Role physical (RP): increased from 15 ± 7.12 to 79 ±

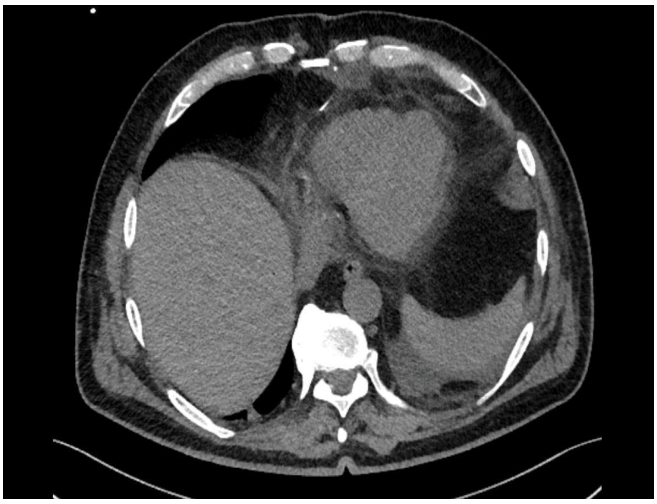

Figure 8: Chest computed tomography scan of a 67-year-old male patient after CABG + YurLeon; arrows indicate pericardial fat attached to the heart.

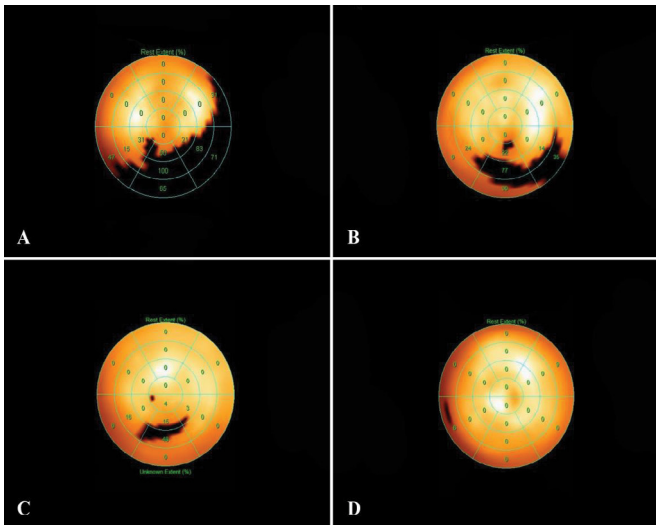

Figure 7: Myocardial scintigraphy of a 71-year-old male patient after CABG + YurLeon before surgery (A), seven days after revascularization (B), three months after revascularization (C), twelve months after revascularization (D).

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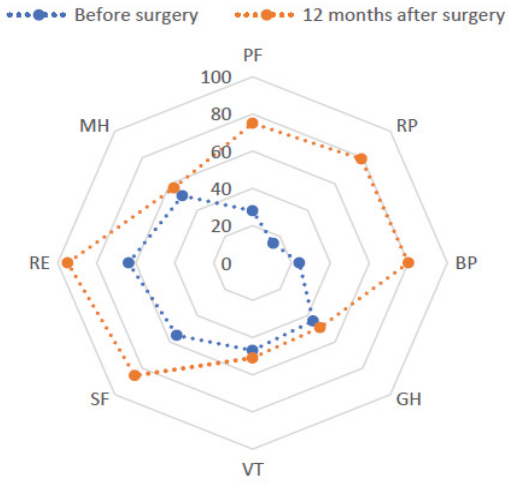

Figure 9: Quality of life before surgery and 12 months after conventional CABG. PF–Physical Functioning; RP–Role Physical; BP–Bodily Pain; GH–General Health; VT–Vitality; SF–Social Functioning; RE–Role Emotional; MH–Mental Health.

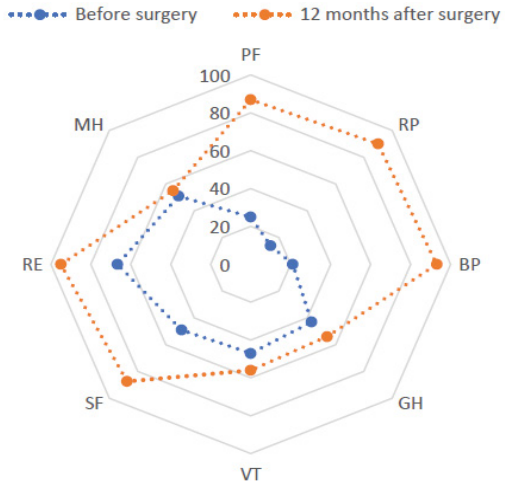

Figure 10: Quality of life before surgery and 12 months after CABG + YurLeon. PF–Physical Functioning; RP–Role Physical; BP–Bodily Pain; GH–General Health; VT–Vitality; SF–Social Functioning; RE–Role Emotional; MH–Mental Health.

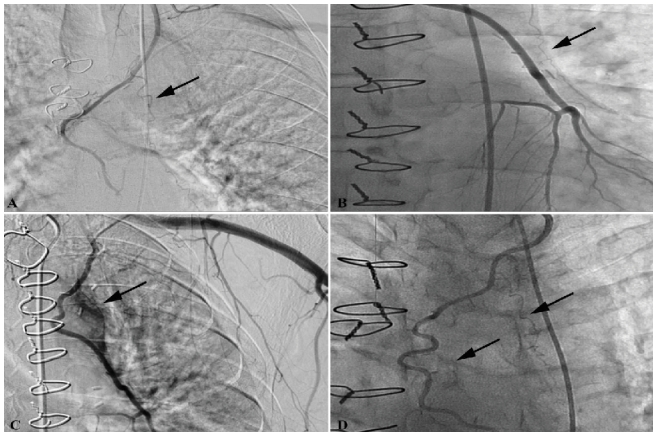

Figure 11: A-D. Angiography of patients after CABG + YurLeon; 6-12 months after surgery (arrows indicate the branches from LITA).

7.01 points (group I), (p = 0.03); from 14 ± 8.33 to 90.01 ± 10.50 points (group II) (p = 0.001). Bodily pain (BP) (the score increases as the pain decreases): from 24 ± 10.10 to 80 ± 5.21 points (group I), (p = 0.012); from 21 ± 9.74 to 93.10 ± 6.37 points (group II) (p = 0.001). Patients from the CABG + YurLeon group demonstrated more significant improvement of the quality of life than patients from the CABG group (Figure 9,10). The other parameters did not change significantly after the time-point of 3 months.

Bypass graft angiography performed in 202 patients (150 patients from group I and 52 patients from group II) in the postoperative period demonstrated that additional extracardial blood supply of the myocardium is formed no earlier than 3 months postoperatively. It was more frequently detected in patients from group II; however, given the absence of objective criteria to measure vascularization, no statistical analysis was performed (Figure 11). Seventeen out of 150 patients from group II (11.3%) and 2 out of 52 patients from group II (3.8%) had myocardial infarction associated with graft occlusion in the late postoperative period (p = 0.001).

Discussion

The advances in pharmacotherapy and endovascular techniques used for CAD led to an increased proportion of elderly patients with diffuse coronary lesions [1,11,12]. Treatment of such patients remains challenging; therefore, methods aimed to promote extracardial neoangiogenesis are increasingly popular [13]. The YurLeon technique developed by us is based on our idea of indirect myocardial revascularization described earlier [14,15]. Triggering of aseptic pericarditis via mechanical intraoperative treatment of the epicardium and pericardium with abrasive material, subtotal pericardectomy, lipocardiopexy, and intrapericardial injection of a sterile exudate collected from the drainage tube during the first 24 h postoperatively (containing vascular growth factors) stimulate neoangiogenesis and formation of the capillary network between the heart and mediastinal tissues. This article details some clinical aspects of the treatment for patients with diffuse coronary lesions, who undergo CABG plus stimulation of extracardial neoangiogenesis [16]. Patients in both groups demonstrated increased LV EF immediately after surgery and 3 months postoperatively. In the late postoperative period, we observed significant differences in LV EF between groups I and II (50.12 ± 6.20% *vs* 56.10 ± 5.81%, respectively; p = 0.001). The increase in myocardial contractility registered 3 months postoperatively is ensured by direct improvement of myocardial perfusion. Further changes in EF after CABG + YurLeon result from stimulation of extracardial neoangiogenesis, which provides additional blood supply to myocardial areas where bypass surgery was impossible for various reasons (diffuse coronary artery lesions, distal occlusion, small diameter of the coronary vessels). Patients after CABG demonstrated gradual improvement of perfusion, which started immediately after surgery and continued during

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the next 3 months. Early postoperative changes are associated with the area of the grafted arteries. Changes during the first 3 months were ensured by opening of previously existing but non-functioning collaterals. Afterwards, there was no dynamics of myocardial perfusion. However, patients from the CABG + YurLeon group demonstrated changes in both early and late (after 12 months) postoperative period. This suggests the importance of extracardial revascularization for further myocardial recovery, especially in patients with diffuse coronary artery lesions. Improved quality of life was reported by patients in both groups, without a significant difference between them in the early postoperative period. However, patients from the CABG + YurLeon group presented with an improved quality of life (physical functioning, role physical, and social functioning) 12 months postoperatively, whereas patients from CABG group had no significant improvement by this time. Identification of the bypass blood supply using bypass graft angiography is technically challenging. It requires selective contrasting of many small arteries with preferable application of the Rentrop technique (contrasting of the bypass artery when the main artery supplying the myocardium is blocked by a balloon). Such manipulations are associated with an extremely high risk. Graft angiography was conducted in either early or late postoperative period in patients who had strict medical indications. Our findings suggest that complex revascularization CABG + YurLeon reduced the number of repeated cardiac events due to coronary graft occlusion, which was ensured by additional blood supply to the myocardium from extracardial sources.

Conclusion

The application of the new technique that includes intraoperative scarification, desquamation of the epicardium and pericardium, subtotal pericardectomy, and lipoepicardiopexy did not lead to bleeding, hemodynamically significant cardiac arrhythmias, conduction disorders, or ischemic changes. Moreover, it allowed us to improve treatment outcomes in the late postoperative period in patients with diffuse coronary lesions. Stimulation of extracardial neoangiogenesis increases myocardial perfusion and contractility, improves clinical condition of patients and their quality of life. CABG + YurLeon is a safe and effective surgical technique for CAD patients with diffuse coronary lesions, which ensures additional blood supply for the myocardium in the late postoperative period.

Funding

The study had no sponsorship.

Conflict of Interest

The authors declare no conflict of interest.

Highlights

The stimulation of indirect revascularization improves perfusion and myocardial function; The YurLeon is a safe and effective method of treating patients with coronary artery disease; The positive effect of the method is manifested 2.5 – 3 months after surgery, followed by progressive improvement of heart function.

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