INTRACORONARY USE OF LEVOCARNITINE FOR CORONARY ARTERY STENT INSERTION IN HIGH-RISK PATIENTS

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The main causes of postoperative mortality associated with percutaneous coronary interventions involving the coronary artery stent insertion are perioperative myocardial infarction and acute heart failure due to inadequate protection of the myocardium against ischemia/reperfusion. The standard therapy includes beta blockers, anticoagulants, antiplatelet drugs. Two clinical cases of successful use of intravenous levocarnitine for cardioprotection in senile patients with acute forms of coronary heart disease with multivessel lesions are reported. The postoperative period went well, smooth dynamics of biomarker levels (troponin I, creatine phosphokinase, MB fraction of creatine phosphokinase) was observed, and ischemic ECG changes were relatively small. The expected results of the technique application include reduction of intraoperative and postoperative complications of ischemia/reperfusion and the increase in effectiveness of the stent insertion clinical outcomes in high-risk patients.

Keywords: coronary heart disease, acute coronary syndrome, myocardial infarction, ischemia/reperfusion, percutaneous coronary interventions, levocarnitine, intracoronary administration

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ИНТРАКОРОНАРНОЕ ПРИМЕНЕНИЕ ЛЕВОКАРНИТИНА ПРИ СТЕНТИРОВАНИИ КОРОНАРНЫХ АРТЕРИЙ У ПАЦИЕНТОВ ВЫСОКОГО РИСКА

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Основные причины послеоперационной летальности при выполнении чрескожных коронарных вмешательств со стентированием коронарных артерий — периоперационный инфаркт миокарда, аритмии и острая сердечная недостаточность вследствие неадекватной защиты миокарда от ишемии/реперфузии. Стандартная терапия включает бета-адреноблокаторы, антикоагулянты, дезагреганты. Описаны два клинических случая успешного внутривенного применения левокарнитина с целью кардиопротекции у пациентов старческого возраста с острыми формами ишемической болезни сердца при многососудистом поражении. Послеоперационный период протекал гладко, отмечалась сглаженность динамики биомаркеров (тропонин I, креатинфосфокиназа, МВ-фракция креатинфосфокиназы), ишемические сдвиги ЭКГ были мало выражены. Ожидаемые результаты применения методики — снижение интраоперационных и послеоперационных осложнений ишемии/реперфузии и повышение эффективности клинических результатов стентирования у пациентов высокого риска.

Ключевые слова: ишемическая болезнь сердца, острый коронарный синдром, острый инфаркт миокарда, ишемия/реперфузия, чрескожные коронарные вмешательства, левокарнитин, внутрикоронарное введение

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Today, percutaneous coronary interventions (PCI) are performed annually in at least 5,000,000 patients with coronary heart disease (CHD) all over the world [1], among them more than 200,000 are performed annually in Russia [2]. The major causes of postoperative mortality associated with such interventions include perioperative myocardial infarction (MI), arrhythmia,

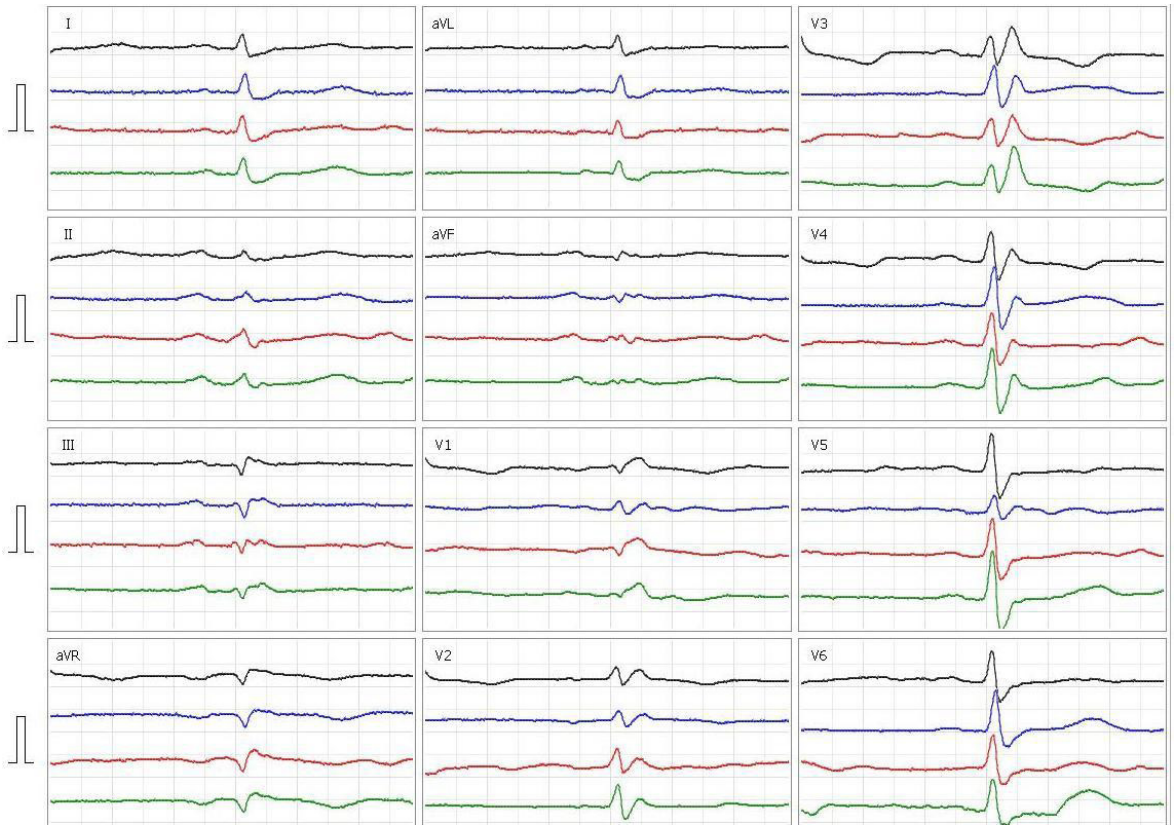

Fig. 1. Dynamic changes in ECG of patient H. aged 76: ECG recorded on 20.09.2023 (before LC administration) is highlighted in *green*; ECG recorded on 21.09.2023 is highlighted in *red*, ECG recorded on 25.09.2023 is highlighted in *blue*; ECG recorded on 26.09.2023 (after LC administration) is highlighted in *black*

and acute heart failure due to inadequate protection of the myocardium against ischemia/reperfusion under conditions of ballooning and stent insertion into the affected coronary arteries.

The recent clinical guidelines of the European Society of Cardiology (ESC) on treatment of acute coronary syndrome (ACS) issued in 2023 [3] specify that various strategies to protect the myocardium during PCI are studied in preclinical and clinical trials: coronary postconditioning, remote ischemic conditioning, early intravenous administration of metoprolol, glycoprotein IIb/IIIa inhibitors, drugs designed to preserve integrity of mitochondria, nitric oxide production. Adenosine, glucose modulators, hypothermia and other techniques are considered as cardioprotectors. Thus, additional cardioprotection means are nowadays in high demand, while the strategies to reduce ischemia/reperfusion damage generally remain an unfulfilled clinical need.

We believe that levocarnitine (L-carnitine, γ-trimethylamino-β-hydroxybutyrate, LC), the natural endogenous component of mammalian tissues, is a very promising agent in terms of myocardial protection. The LC antioxidant effect in ischemia/reperfusion can be associated with the free fatty acid metabolism optimization and attenuation of the inhibiting effect of reactive oxygen species on the aerobic metabolism [4]. It has been confirmed that the levels of LC drop sharply in the ischemic myocardium of individuals with acute MI, cardiomyopathy, and heart failure of various origin [5, 6].

Practically the first Russian study that revealed beneficial effects of LC on the myocardium in acute MI [7] was represented by the study focused on assessing the protective effects of intravenous LC in ACS, where the left ventricular ejection fraction (LVEF) reduction to less than 40% was the inclusion criterion [8].

The LC beneficial effects on the course of ACS were also confirmed by other authors. Thus, intravenous LC therapy reduced the corrected QT dispersion, the NO bioavailability was enhanced [9, 10]. Beneficial effects of using LC in patients with ACS were reported within the early period, along with good tolerability of the drug [11]. In individuals with acute MI, there was a significant decrease in the average peak levels of myocardial necrosis markers in blood (CPK-MB and troponin) [12]. Intravenous administration of LC turned out to be effective in myocardial ischemia/reperfusion injury, ventricular dysfunction, heart arrhythmia, and toxic myocardial damage. The LC beneficial effects were reported in infants, adolescents, young adults, adults, and elderly patients with acute and chronic heart failure (CHF) [13–15].

In the past, trimetazidine [16] and phosphocreatine (Neoton) [17] were used for adjuvant cardioprotection during percutaneous interventions, which was not very successful and did not become a common myocardial protection method.

Clinical cases

We have earlier provided the results of the first clinical use of intracoronary levocarnitine in patients with acute MI [18]. Here we provide another two cases of using the method during emergency PCI in senile patients.

Observation 1

Patient H. aged 76 underwent inpatient treatment in the cardiology unit of the Saint Petersburg Clinical Hospital of the Russian Academy of Sciences between 20.09.2023 and 26.09.2023. According to the medical history, H. had been suffering from moderate hypertension for a couple of years. He insisted he had no acute MI or acute cerebrovascular accident (CVA). In 2018, sigmoid cancer was detected, surgery was performed, and the patient received the course of chemotherapy.

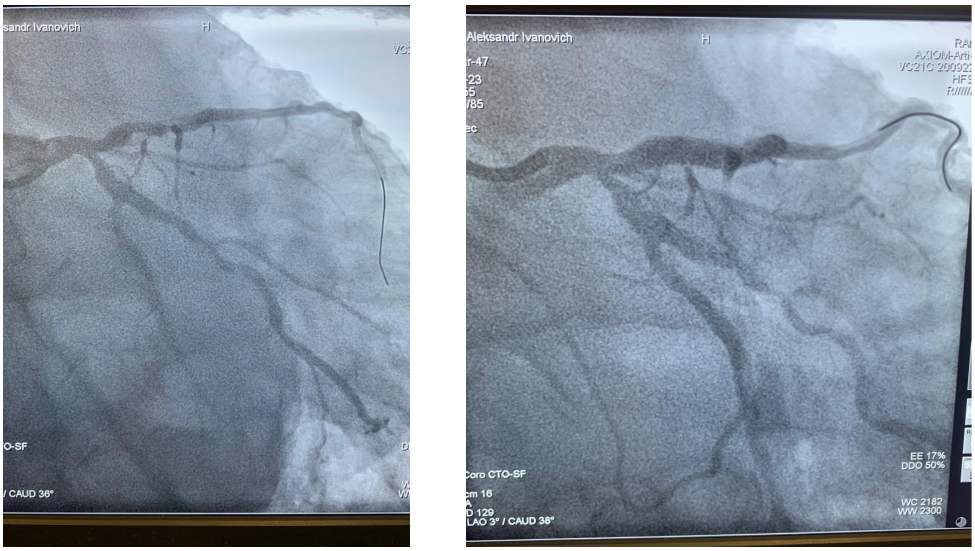

Fig. 2. Angiography of the affected coronary artery of patient H. performed before (*on the left*) and after (*on the right*) the stent insertion

In 2019, prostate cancer was revealed, due to which the patient received endocrine therapy every 3 months. Since 2017 he was followed up by angiosurgeons due to infrarenal aortic aneurysm. Previously, stent insertion into the anterior interventricular artery was performed. Starting from the night of 20.09.2023, the recurrent attacks of anginal pain emerged, due to which the patient used nitrospray three times with a positive effect. In the morning of 20.09.2023, the emergency hospitalization took place, followed by diagnostic coronary angiography with immediate stent insertion into the RCA (three BioMatrix Flex stents; Singapore). To reduce the extent of ischemic damage, intracoronary administration of the 1000 mg LC solution (Elcar) was performed. The patient received Elcar in a dose of 500 mg per day (No. 7) between 20.09.2023 and 26.09.2023. According to the echocardiography (ECHO) data, LVEF was 53% on 20.09.2023 and 56% on 22.09.2023. The dynamic changes in echocardiography (ECG) data are provided in Fig. 1, angiography data are presented in Fig. 2, and the dynamic changes in biomarkers of myocardial ischemia/necrosis are provided in Table 1.

Observation 2

Female patient L. aged 78 underwent inpatient treatment at the Saint Petersburg Clinical Hospital of the Russian Academy of Sciences between 25.09.2023 and 30.09.2023. Medical history: essential hypertension for many years, type 2 diabetes mellitus diagnosed in 2006. The CHD onset occurred in 2017, stent insertion into the circumflex branch (CB) of the left coronary artery (LCA) (two stents) was performed. Aggravation of symptoms started from March 2023: shortness of breath and chest pain during exercise emerged. Standard therapy was supplemented by prescription of the course of meldonium in outpatient settings, diuretic therapy was added. However, progressive worsening was observed. Echocardiography performed in August 2023 revealed LVEF reduction to 30%. On the night of 25.09.2023 the patient noted a burning sensation around her heart at rest. She was diagnosed with ACS without ST segment elevation on ECG and underwent emergency diagnostic coronary angiography (LMCA stenosis 90%, CB outflow subocclusion) followed by angioplasty with stent insertion into the CB. To reduce the extent of ischemic damage, intracoronary administration of the 1000 mg LC (Elcar) solution was performed.

The patient received intravenous infusions of Elcar in a dose of 500 mg per day (No. 5) between 26.09.2023 and 30.09.2023. According to the echocardiography (ECHO) data, LVEF was 36% on 25.09.2023 and 39% on 27.09.2023. The dynamic changes in ECG are provided in Fig. 3, angiography is presented in Fig. 4.

The dynamic changes in biomarkers of myocardial ischemia/necrosis in patient L. are provided in Table 2.

Clinical case discussion

The literature data on the successful use of intravenous LC medication aimed to ensure cardioprotection in patients with CHD substantiate the research focused on assessing the intracoronary drug administration route, since this substance exerts pronounced protective effects confirmed both *in vivo* and *in vitro* (antioxidant, anti-ischemic and metabolic, i.e. related to the cell energy supply). It is PCI in high-risk patients (elderly and senile patients with multivessel coronary lesions), during which it would be possible to assess the efficacy, response time, safety, and probable dose dependence of such protection.

The fact that the tissue levels of LC decrease with age in individuals with chronic and especially acute CHD is one more

Table 1. Dynamic changes in the levels of myocardial ischemia/necrosis biomarkers in patient H.

	Reference values	20.09.2023	21.09.2023	22.09.2023	25.09.2023
High-sensitivity troponin I (hsTnI)	0–39,2 pg/mL	5	2371	1684	555
ALT	10–40 U/L	16	19	18	19
AST	10–40 U/L	17	25	18	18
CPK	0–190 U/L	81	228	90	
CPK-MB	0–24 U/L	9	20	8	10

Note: ALT — alanine aminotransferase, AST — aspartate aminotransferase, CPK — creatine phosphokinase, CPK-MB — creatine phosphokinase-MB.

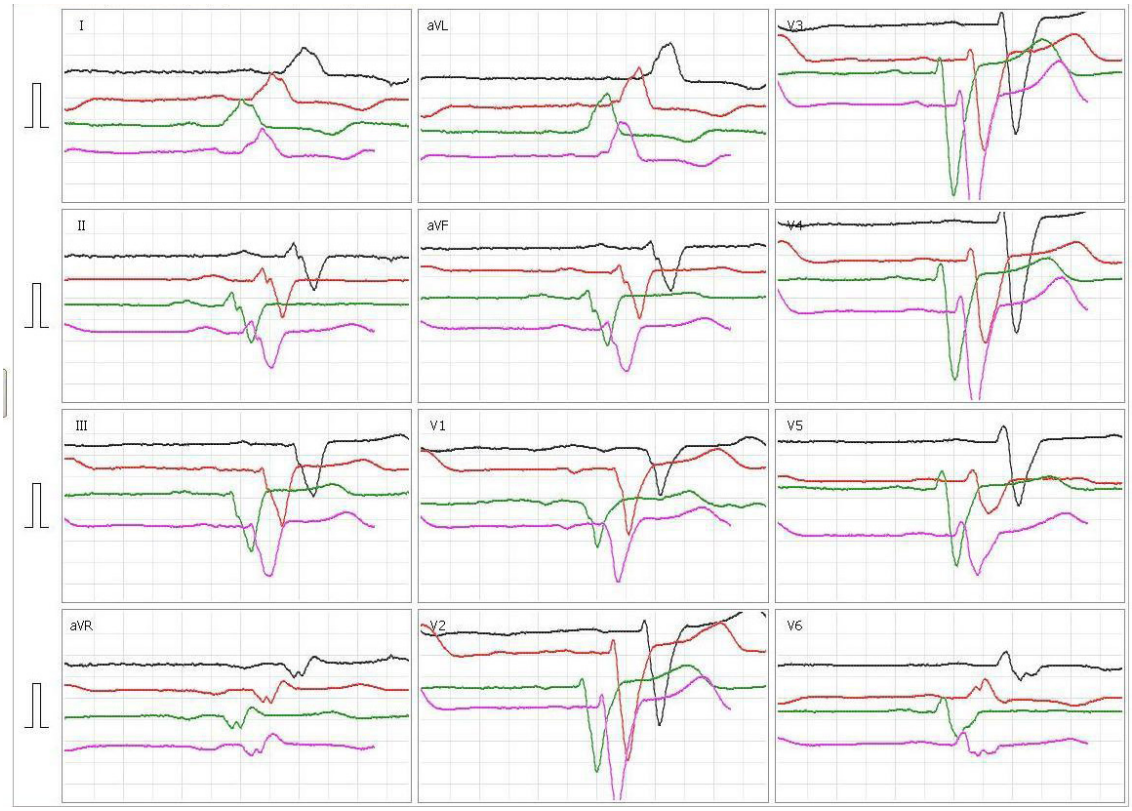

Fig. 3. Dynamic changes in ECG of patient L. aged 76: ECG recorded on 25.09.2023 at 10:32, before LC (Elcar) administration, is highlighted in *black*; ECG recorded on 25.09.2023 at 18:52, after LC (Elcar) administration, is highlighted in *red*; ECG recorded on 26.09.2023 is highlighted in *green*; ECG recorded on 29.09.2023 is highlighted in *pink*

reason to study the LC efficacy in the high-risk elderly patients with CHD [19]. It is also important that LC used as part of the combination drug therapy demonstrates an improved safety profile in patients with comorbidities, exerting no effect on P450 cytochrome [20, 21].

Given the data of the large-scale meta-analysis of 13 randomized controlled trials (RCTs) focused on the secondary prevention of cardiovascular disorders (comparison of LC and placebo), we can expect the decrease in the rate of ventricular arrhythmias and angina attacks in patients having a history of MI [22]. It seems quite likely that manifestations of heart failure will decrease when using the described technique, since, according to meta-analysis of 17 RCTs focused on using LC in patients with CHF [23], the increase in LVEF, optimization of the LV end-diastolic and end-systolic volume, significant decrease in blood levels of brain natriuretic peptide (BNP) and N-terminal pro b-type natriuretic peptide (NT-proBNP) after administration of the drug have been reported [24].

Apparently, the postoperative period went relatively well in both reported cases; smooth dynamics of biomarker levels (troponin I, creatine phosphokinase, MB fraction of creatine phosphokinase, transaminases) and the systolic function stability were observed; the ischemic ECG changes were relatively small.

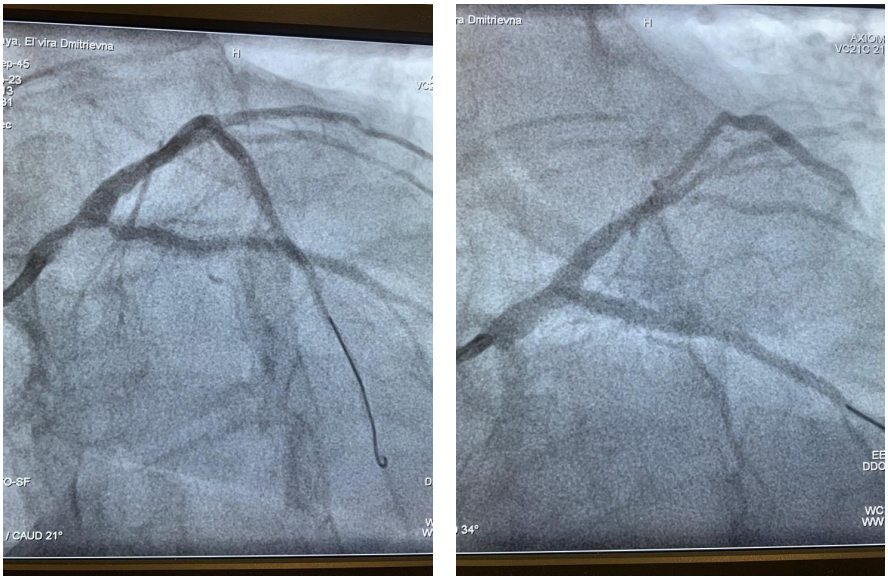

Fig. 4. Angiography of the affected coronary artery of patient L. performed before (*on the left*) and after (*on the right*) the stent insertion

Table 2. Dynamic changes in the levels of myocardial ischemia/necrosis biomarkers in patient L.

	Reference values	25.09.2023	27.09.2023	28.09.2023
High-sensitivity troponin I (hsTnI)	0–39,2 pg/mL	12.1	132.2	73.9
ALT	10–40 U/L	20	39	15
AST	10–40 U/L	18	28	17
CPK	0–190 U/L			83
CPK-MB	0–24 U/L	7	9	8

Note: ALT — alanine aminotransferase, AST — aspartate aminotransferase, CPK — creatine phosphokinase, CPK-MB — creatine phosphokinase-MB.

CONCLUSION

Thus, the proposed technique involving intracoronary LC administration during PCI in high-risk patients can become effective for protection of myocardium against the ischemia/reperfusion complications, which will improve the outcomes of revascularization and reduce the rate of complications. Strong conclusions can be drawn only after accumulation and analysis of sufficient data within the framework of the expected future research due to the paucity of available observations.

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