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Intracoronary nitroglycerin for ischemia reperfusion injury in elderly patients with acute coronary syndrome undergoing urgent endovascular revascularization

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Background: Endovascular coronary revascularization is a golden standard of first aid in patients with acute coronary syndrome. Myocardial ischemia-reperfusion injury is a major complication of coronary stenting, with the elderly patients forming a high-risk group. Nitroglycerin is known to exhibit cardioprotective effects, however studies have displayed controversial results concerning effectiveness of the drug. Therefore, we aimed to investigate cardioprotective effect of nitroglycerin during urgent coronary revascularization procedure in elderly patients and evaluated our results.

Methods: Patients aged 60 years and older who underwent emergent coronary revascularization for acute coronary syndrome at our institution between 11/18 and 02/19, were managed and studied prospectively. All patients received standard perioperative pharmacotherapy. After adding intracoronary nitroglycerin bolus to our anesthetic procedure, we evaluated the ST segment elevation regression rate, incidence of hemodynamic changes and rate of arrhythmias.

Results: Thirty patients received standard perioperative pharmacotherapy (CG). Another 30 patients additionally received nitroglycerin intracoronary prior to reperfusion (SG). In the nitroglycerin group a reduced frequency of no- and slow-reflow phenomena (6,7% vs 26,7%; p = 0,04), faster rate of ST segment elevation regression in the first hour post reperfusion (42.4 ± 17.6% vs 34.5 ± 9.7%; p = 0.036), lower rate of bradycardia (10% vs 33,3%; p = 0,03) and hypotension (13,3 vs 40%; p = 0,02) were observed. Arrhythmia incidence did not differ between the groups (p = 0,365).

Conclusions: Nitroglycerin is a widespread drug with cardioprotective capabilities. As our study shows, intracoronary administration of nitroglycerin reduces the incidence of no- and slow-reflow phenomena and hastens the rate of ST segment elevation regression 60 minutes' post reperfusion.

Key words: Acute coronary syndrome, endovascular coronary revascularization, no-reflow phenomenon, nitroglycerin, reperfusion injury, cardioprotection.

Intrakoronares Nitroglycerin bei Ischämie-Reperfusionsverletzung bei älteren Patienten mit akutem Koronarsyndrom nach endovaskulärer Notfallrevaskularisation. *Hintergrund:* Endovaskuläre Revaskularisation ist der Goldstandard bei der Ersten Hilfe für Patienten mit akutem Koronarsyndrom. Die Ischämie-Reperfusionsverletzung des Myokards ist eine schwerwiegende Komplikation des koronaren Stentings und ältere Patienten sind dabei einem hohen Risiko ausgesetzt. Es ist bekannt, dass Nitroglycerin eine kardioprotektive Wirkung hat, doch zeigen Studien widersprüchliche Ergebnisse hinsichtlich der Wirksamkeit des Arzneimittels. Daher war es unser Ziel, die kardioprotektive Wirkung von Nitroglycerin während der koronaren Notfallrevaskularisation bei älteren Patienten zu untersuchen und die Ergebnisse zu bewerten.

Methoden: Patienten ab 60 Jahren, die sich im Zeitraum November 2018 bis Februar 2019 einer koronaren Notfallrevaskularisation wegen eines akuten Koronarsyndroms in unserer Einrichtung unterzogen hatten, wurden behandelt und nahmen an einer prospektiven Studie teil. Alle Patienten erhielten eine perioperative Standardpharmakotherapie. Nachdem wir unserem Anästhesieverfahren einen intrakoronaren Nitroglycerinbolus hinzugefügt hatten, bewerteten wir die Regressionsrate der ST-Segmenterhöhung, die Häufigkeit hämodynamischer Veränderungen und die Häufigkeit von Arrhythmien.

Ergebnisse: Dreißig Patienten erhielten eine standardmäßige perioperative Pharmakotherapie (KG [Kontrollgruppe]). Weitere 30 Patienten erhielten vor der Reperfusion zusätzlich intrakoronares Nitroglycerin (EG [Behandlungsgruppe]). In der Gruppe, die Nitroglycerin erhalten hatte, gab es eine Abnahme der Häufigkeit von Ereignissen wie Abwesenheit und Verzögerung des Flusses (6,7 % gegenüber 26,7 %; p = 0,04) und eine höhere Regressionsrate des Anstiegs des ST-Segments in der ersten Stunde nach der Reperfusion (42, 4 ± 17,6 % vs. 34,5 ± 9,7 %; p = 0,036). Es wurden eine geringere Inzidenz von Bradykardie (10 % vs. 33,3 %; p = 0,03) und Hypotonie (13, 3) vs. 40 %; p = 0,02) festgestellt. Die Häufigkeit von Arrhythmien in den Gruppen differierte nicht (p = 0,365).

Zusammenfassung: Nitroglycerin ist ein weit verbreitetes Medikament mit kardioprotektiven Eigenschaften. Wie unsere Studie zeigt, verringert die intrakoronare Nitroglycerin-Gabe das Auftreten von Blutflussmangel und Verlangsamung des Blutflusses und verbessert die Regression der Anstiegsrate vom ST-Segment 60 Minuten nach der Reperfusion. **Z Gefäßmed 2021; 18 (1): 17–22.**

Schlüsselwörter: akutes Koronarsyndrom, endovaskuläre koronare Revaskularisation, Blutflussmangels, Nitroglycerin, Reperfusionsverletzung, kardioprotektive Wirkung

Background

Ischemic heart disease (IHD) takes a leading part in the structure of mortality from cardiovascular pathology in the USA [1]. Acute myocardial infarction (AMI) plays a significant role in the structure of morbidity of IHD: out of 17,6 million people suffering from IHD 8,5 million have also had an AMI [2]. In Ukraine, the proportion of IHD is nearly 34% in the structure of cardiovascular pathology, with the pathology causing around 68% of deaths among all cardiovascular patients [3]. Patients at the age of 60 years and above remain at a higher risk of complications when it comes to the treatment of ACS. In a report of the American Heart Association for the year 2017 the incidence of AMI in patients of 75 y.o and above was 17,5% in men and 11% in women [4]. Age is an independent risk factor for postoperational stent thrombosis and bleeding [5–7], elderly patients, as depicted in studies, tend to have a relatively higher number of co-morbidities, worse cognitive status, and often more complex coronary artery lesions [8, 9]. Another curious find is a significantly larger time gap between the onset of symptoms and the beginning of coronary revascularizaion procedure in elderly [10, 11].

Coronary artery (CA) stenting is currently a renowned "gold standard" approach in the urgent revascularization of AMI and had been remaining one of the leading recommendations in the European Society of Cardiology guidelines for the management of patients presenting with ST-elevation AMI (STEMI) [12]. In patients presenting with non-ST elevation AMI (NSTEMI) and unstable angina pectoris, percutaneous coronary interventions (PCI) are also able to provide adequate

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myocardial revascularization [13] and significantly decrease the frequency of resorting to coronary artery bypass graft (CABG) surgery [14], being the full-fledged alternative of the latter. However, any revascularization is prone to the phenomenon of ischemia-reperfusion injury (IRI). Myocardial IRI is a set of pathological processes occurring in cardiomyocytes after restoration of blood flow in the previously occluded vessel and leading to a wide array of intra- and postoperative complications such as reperfusion arrhythmias, myocardial stunning, microvascular obstruction and lethal myocardial IRI [15].

Nitroglycerin (NG) as well as other nitrates are being actively utilized as the means of pharmacologic prophylactic of IRI and are especially effective through intracoronary administration directly before the recanalization of the infarct related artery [16, 17]. According to some researchers, IRI gets more threatening with age: age has a positive correlation with the severity of reperfusion necrosis and apoptosis of cardiomyocytes in rat and human models alike [18].

NACIAM randomized trial indicates that an infusion of N-acetyl cysteine (NAC) paired with low doses of NG over the span of 48 hours resulted in reduction of the infarction are both immediately after and 3 months' post revascularization [19]. A study, conducted by Gori T. et al. concluded that NG administration, compared to placebo, reduced ischemia-reperfusion manifestations in the vessel endothelium [17]. In another research Yui H et al. concluded that NG, compared to placebo, reduces infarct size/area at risk of the left ventricle as well as the incidence of reperfusion arrhythmias [20]. However, a study conducted by Sun L. et al. in animal models, proved that prolonged therapy with NG in rats resulted in inactivation of an enzyme aldehyde dehydrogenase-2 (ALDH2), and in an increase of infarct area almost by 200% [21]. A study by Lisi M. et al. has shown that NG had had less effect on the value of FMD after ischemia-reperfusion, compared to pentaerythrityl tetranitrate (PETN) another drug from the nitrate group. Additionally, PETN, unlike NG, possesses the capability to release nitric oxide without ALDH2, thus solving the issue of tolerance to NG [22].

Considering the contradictions emerging from the abovementioned studies and the complexity of diagnostic and treatment process of the elderly, our study aimed to research the extent of cardioprotective effect of nitroglycerin in elderly patients presenting with acute coronary syndrome and undergoing urgent percutaneous endovascular revascularization.

Methods

Study design and data collection

This observational analytic prospective single-center study was carried out in accordance with the Declaration of Helsinki. Ethical approval was provided by the Shupyk National Academy of Postgraduate Education Bioethics committee. All patients of this study gave their written informed consent to the analysis of their clinical data.

Our study examined patients 60 years of age or above diagnosed with ACS and hospitalized for urgent coronary artery stenting at "Kyiv Heart Institute" of Ministry of Health of Ukraine between November 5th, 2018 and February 11th, 2019. A group of patients receiving standard therapy adopted by the Kyiv Heart Institute formed the Control group (CG). Patients, that had an intracoronary administration of 200 mg of nitroglycerin to the infarct-related artery (IRA) prior to reperfusion in addition to the standard pharmacotherapy are referred to as a Study group (SG). All patients were managed during the whole length of perioperative period, additional clinical data was extracted from patient's medical histories and surgical reports. Part of the data concerning pharmacotherapy prior to hospitalization and comorbidities has been acquired by direct patient questioning. Percutaneous coronary intervention (PCI) was performed according to generally accepted methods. Technical aspects of the procedure such as stent and balloon choice, time of inflation and the amount of pressure applied have been individually determined by each operator.

Anesthetic management for the urgent coronary revascularization

Upon admission to the ICU all patients had respective necessary diagnostic procedures performed (ECG, echo, troponin test, etc.,). ECG was recorded at a paper speed of 25mm/s and an amplification of 10 mm/mV. Hypotensive (mean arterial pressure < 70 mm Hg), patients had a continuous intravenous (IV) infusion of either isotonic sodium chloride solution or Gelofusine. All emergency patients were provided with IV infusions of heparin (12,5 units/kg/hr) and a small dosage of NG (1,5 ± 0,3 mcg/kg/min).

In the catheter lab, standard noninvasive monitoring was established for all patients (arterial blood pressure, pulseoximetry and ECG). All patients received standard premedication consisting of fentanyl (1 ml) and diazepam (1 ml), administered IV. Directly before stent implantation patients received additional heparin bolus (100 units/kg). After the stent implantation patients received 600 mg of aspirin and 300 mg of ticagrelor or clopidogrel orally.

Evaluation of results

Stenosis of coronary artery by more than 50% was considered hemodynamically significant. Infarct-related artery (IRA) was determined as an artery, severe occlusion or subocclusion of which by either thrombus or vessel dissection led to the appearance of acute myocardial infarction (AMI). IRA was identified by the endovascular surgeon. The incidence of no- and slow-reflow phenomena has been evaluated using the TIMI flow grade [23] with slow-reflow corresponding to Grade 2, no-reflow corresponding to Grades 1 and 0; Grade 3 corresponded to normal vessel flow.

ST segment elevation was measured 80 ms after the J point and considered present if the deviation was ≥ 0.2 mV (2 mm) in men and ≥ 0.15 mV (1.5 mm) in women in V2–V3 leads (≥ 0.1 mV [1 mm] in other leads), it was evaluated only in patients with STEMI. Regression of the ST segment elevation was characterized in percentage of total elevation and measured 60 minutes' post reperfusion and 24 hours post reperfusion.

Reperfusion arrhythmias were identified as a recurring disruption of cardiac rhythm (excluding bradycardia), that was registered after the restoration of blood flow in the IRA and had a

persisting character. Bradycardia after reperfusion was defined as a decrease in heart rate (HR) below 60 or a sudden decrease of HR by more than 10 beats/minute directly following reperfusion; reperfusion hypotension was defined as the rapid decrease in the systolic blood pressure lower than 90 mmHg, or by at least 20 mmHg following the restoration of blood flow in the IRA. Incidence of bradycardia and hypotension were evaluated together as components of Bezold-Jarisch reflex often following the recanalization of right coronary artery (RCA).

Statistical analysis

All statistical analysis was performed in STATISTICA 10 (TIBCO Software Inc., California, USA). The normality of distribution of analyzed data was determined with Kolmogorov-Smirnov and Shapiro-Wilk test. Normally distributed data was expressed as mean value ± standard deviation (SD). Data that was not normally distributed, was expressed as median and interquartile range (IQR). To assess the study groups for statistical difference following criteria have been used: Student's t-test for normally distributed data and Mann-Whitney's U test for the data that was not normally distributed. Categorical data was compared using Pearson's chi-squared test and Fisher's exact test. Significance level was set to $p < 0.05$.

Results

A total of 67 patients aged 60 years or older underwent emergent coronary stenting for ACS between November 5th, 2018 and February 11th, 2019 at our department of endovascular diagnostics and treatment. 7 patients were excluded from the study due to various reasons. The resulting number of patients was 60. 30 patients received standard pharmacotherapy (CG), afterwards, the pharmacotherapy was altered by adding the NG bolus to the IRA, and another 30 patients were managed (SG). The baseline characteristics and comorbidities upon admission did not statistically differ between groups (Tab. 1).

Lesion and procedural characteristics

Only the surgical and lesion characteristics related and able to influence the study endpoints were included in Table 2. The prevalence of different culprit lesion localizations was compared between the groups; analysis did not show statisti-

Table 1. Baseline characteristics and comorbidities

Factor	Total (n = 60)	SG (n = 30)	CG (n = 30)	P-value
Age (y)	67.23 ± 5.25	67.43 ± 5.41	67.03 ± 5.16	0.77[1]
Male, n (%)	43 (71.7)	19 (63.3)	24 (80)	0.12[2]
Female, n (%)	17 (28.3)	11(36.7)	6 (20)	0.126[2]
Hospitalization, d	2 (2)	2 (2)	2(2,75)	0.326[3]
STEMI, n (%)	37 (61.7)	18 (60)	19 (63.3)	1[2]
NSTEMI, n (%)	18 (30)	10 (33.3)	8 (26.7)	0.778[2]
Unstable angina, n (%)	5 (8.3)	2 (6.7)	3 (10)	1[2]
BMI (kg/m^2)	29,06 ± 4,34	28.92 ± 4.64	29.19 ± 4.09	0.812[1]
DM II, n (%)	10 (16.7)	4 (13.3)	6 (20)	0.365[2]
Smokers, n (%)	22 (36.7)	13 (43.3)	7 (20)	0.17[2]
Hypertension, n (%)	46 (76.7)	25 (83.3)	21 (70)	0.18[2]
Arrhythmias, n (%)	12 (20)	4 (13.3)	8 (26.7)	0.167[2]
LVEF (%)	50.47 ± 6.32	50.2 ± 6.93	50.73 ± 5.72	0.747[1]
History of AMI, n (%)	7 (23.3)	5 (16.7)	2 (6.7)	0.423[2]
History of CABG, n (%)	1 (1.67)	–	1 (3.3)	–
History of stroke, n (%)	2 (3.3)	–	2 (6.7)	–
Renal failure*, n (%)	1 (1.67)	1 (3.3)	–	–

SG: study group, CG: control group, BMI: body mass index, DM II: diabetes mellitus type II, LVEF: left ventricular ejection fraction, AMI: acute myocardial infarction, CABG: coronary artery bypass grafting, *base creatinine clearance < 90 ml/min. Values are presented as mean ± SD, median (IQR) or count/percentage. [1]using Students t-test, [2]Fisher's exact test, [3]Man-Whitney U test.

Table 2. Coronary lesion and procedural characteristics.

Factor	Total (n = 60)	SG (n = 30)	CG (n = 30)	P-value
Infarct-related artery				
LAD, n (%)	30 (50)	17 (56.7)	13 (43.3)	0.439[1]
LCX, n (%)	12 (20)	5 (16.7)	7 (23.3)	0.748[1]
RCA, n (%)	18 (30)	8 (26.7)	10 (33.3)	0.779[1]
Number of stents implanted				
1 stent, n (%)	43	23 (76.7)	20 (66.7)	0.567[1]
2 stents, n (%)	10	4 (13.3)	6 (20)	0.73[1]
3 stents, n (%)	4	1 (3.3)	3 (10)	0.612[1]
4 stents, n (%)	3	2 (6.7)	1 (3.3)	1[1]

SG: study group, CG: control group, LAD: left anterior descending artery, LCX: left circumflex artery, RCA: right coronary artery. Values are presented as count (percentage). [1]Fisher's exact test.

Table 3. ST-segment elevation and regression

Factor	Total (n = 37)	SG (n = 18)	CG (n = 19)	P-value
ST Elevation, mV	0.68 ± 0.2	0.64 ± 0.19	0.72 ± 0.2	0.212[1]
ST Regression in 60 min, (%)	38.5 ± 13.7	42.4 ± 17.6	34.5 ± 9.7	0.036[1]
ST Regression in 24 hrs, %	55.3 ± 18.2	53 ± 17.4	57.5 ± 19.1	0.345[1]

SG: study group, CG: control group. Values are presented as mean ± SD. [1]calculated using Students t-test.

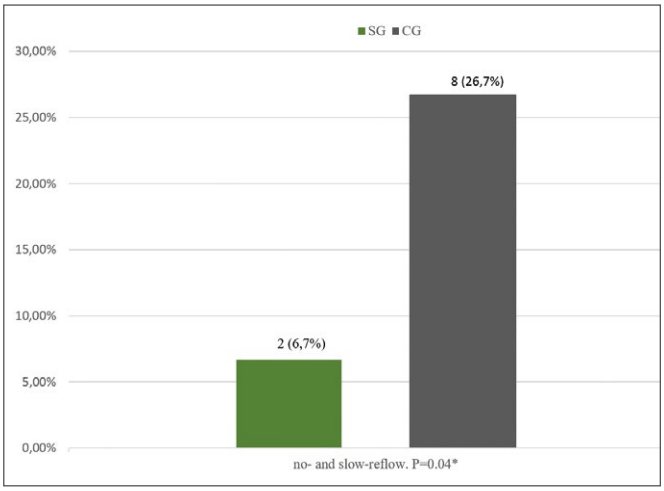

Figure 1. Appearance of no- and slow-reflow phenomena
SG: study group, CG: control group. Values are presented as count (percentage). *Fisher's exact test.

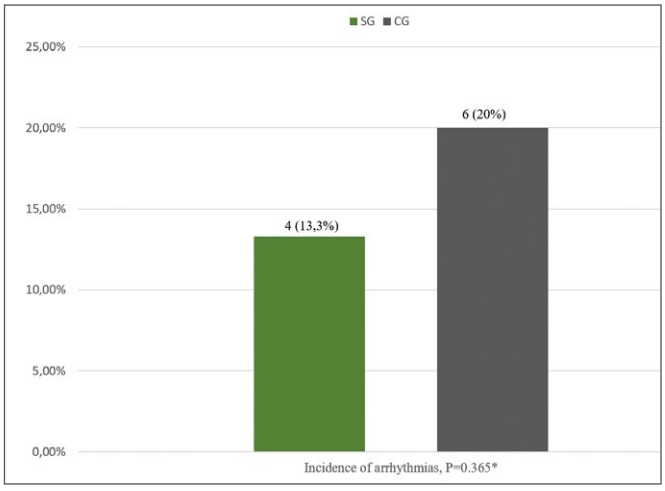

Figure 2. Incidence of arrhythmias
SG: study group, CG: control group. Values are presented as count (percentage). *Fisher's exact test.

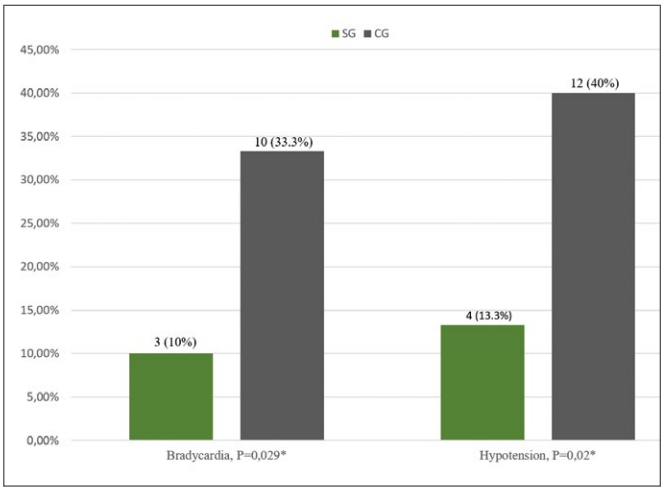

Figure 3. Bradycardia and hypotension
SG: study group, CG: control group. Values are presented as count (percentage). *Fisher's exact test.

cally significant difference (p > 0.05) (Tab. 2). The number of implanted stents per patient in SG and CG was not normally distributed, and the median (IQR) representation of the values was not representative. Therefore, the number of patients who had one, two, three and four stents implanted respectively had been evaluated and compared. The groups did not statistically differ by these parameters (p > 0.05) (Tab. 2).

No- and slow-reflow after revascularization

The frequencies of registration of no- and slow-reflow phenomena have been assessed during the study with results displayed in Figure 1. The evaluation showed a significantly lower incidence of these pathological conditions in SG (p = 0.04) .

ST-segment elevation and regression

ST-segment elevation upon admission and its regression in 60 minutes and 24 hours post reperfusion are presented in Table 3. The number of patients with STEMI did not statistically differ between the groups (Table 1; p = 1) so the comparison was accurate. ST deviation on admission did not significantly differ between SG and CG (p = 0.212), whereas the difference in the mean values of ST regression measured 24 hours after reperfusion was significant (p = 0.036). However, this difference was smoothed out when the ST elevation was measured and regression was calculated 24 hours post reperfusion (p = 0.345) (Tab. 3).

Reperfusion arrhythmias

In the conducted study reperfusion arrhythmias have been presented with the episodes of ventricular extrasystolia and sinus tachycardia directly after reperfusion, some of which appeared to be prone to antiarrhythmic therapy. The incidence of arrhythmias did not statistically differ between the groups (p = 0.365) (Fig. 2).

Hemodynamic changes after reperfusion

The incidence of bradycardia and hypotension are presented in Figure 3. SG and CG did significantly differ by the number of cases of bradycardia (p = 0.028), and hypotension (p = 0.02) (Fig. 3). Other hemodynamic changes occurring after reperfusion were insignificant and did not statistically differ in groups (p > 0.05).

Discussion

Results of the conducted study prove the effectiveness of NG for the prophylactic of certain reperfusion complications, with

the drug owing to either its cardioprotective effects or to the vasodilation of coronary bed. However, NG also possesses dose-related hypotensive capabilities, limiting its use in already severely hypotensive patients [20]. The continuous administration of small doses of NG from admission, in our case, did not result in significant inhibition of ALDH-2 and development of nitrate tolerance before the administration of the intracoronary bolus to patients of SG. This, however, does not contradict the findings of corresponding studies [17, 19, 21], and may still be an issue with higher doses of NG of a lengthier infusion period.

ST-segment regression after the recanalization of coronary artery is a significant ECG sign of a successfully restored blood flow and, according to certain studies, does correlate with the extent of postoperative angina and TIMI grade flow perfusion level [23] – this was confirmed by our findings: the number of patients with TIMI flow Grades 0–2 was lower in SG (Fig. 1), correspondingly, SG showed significantly higher rate of ST-segment elevation resolution in 60 minutes after reperfusion (Tab. 3). Studies prove NG administration has a positive effect on the incidence of and duration of reperfusion arrhythmias [20], though, our research did not find statistical difference in the occurrence of this complication (Fig. 2), possibly, due to the study groups not being large enough. In order to demonstrate a more detailed clinical image, present study analyzed the incidence of bradycardia and hypotension separately- and not as elements of Bezold-Jarisch reflex. Our study demonstrated a significantly lower incidence of both bradycardia and hypotension in SG, meaning the combined rate of these complications was also statistically lower in the study group (Fig. 3).

Cardioprotection in elderly and choosing the right drug

The elderly, especially, very elderly (> 90 years) are severely underrepresented in clinical trials, often falling under the exclusion criteria [5]. A focus on preventive cardioprotection in the group is explained by the worse outcomes of coronary revascularization in elderly [5, 6, 7] and the worse toleration of reperfusion by the aged myocardium: aging was shown to augment reactive oxygen species formation [24] and increase ischemia-induced apoptosis [25] thus aggravating the IRI. A wide variety of pharmacological agents have been demonstrated to exert cardioprotective capabilities. According to a study comparing the cardioprotective effects of verapamil, nicardipine and NG, verapamil, and NG, rather than nicardipine, were nearly equally good at preventing arrhythmias and decreasing infarct area in rabbits [20]. Calcium channel blockers, however, exert better cardioprotective capabilities when administered prior to ischemia and not prior to reperfusion [26]. Non-selective (isoproterenol) and selective agonists of β1-adrenoreceptors (AR) (denopamine), β2-AR (formoterol and clenbuterol) reduced both the incidence of ventricular arrhythmias and infarct size/area at risk in animal models [27]. However, β-agonists should be used very cautiously, or better, avoided in elderly with ACS since they may aggravate the symptoms of ACS in patients already belonging to a high risk group; moreover, the cardioprotective effects of these drugs were shown to be totally eliminated by pretreatment with beta-blockers [28] often used for treatment of ACS. Adenosine A2a and A2b receptors were demonstrated to participate in the cardioprotection process with adenosine receptor agonists possessing cardioprotective capabilities [29]. A randomized clinical trial, however, concludes there is no significant improvement in myocardial perfusion after intra-coronary adenosine administration [30].

Limitations

The main limitation of the study was its focus on immediate cardioprotective benefits of NG for there was no possibility to assess incidence of delayed manifestations of IRI and the delayed cardioprotective capabilities of NG. Additionally, due to the patients being in a high-risk group when it comes to MACCE and intraoperative complications [5, 6, 7], and having multiple comorbidities, heterogeneity in anesthesiologic management in perioperative period was present. Overall, nitroglycerin causes relatively little complications during intracoronary administration, while being a widespread medication exerting cardioprotective effects. However, the extent of postponed cardioprotective effects of nitrates remains largely unresearched and a randomized trial, studying the delayed cardioprotective effects of nitrates is required.

Conclusions

Elderly patients with ACS fall into a high-risk group, when it comes to periprocedural complications of PCI and aged myocardium is proven to suffer more from the IRI. NG is a drug with cardioprotective capabilities, combining high clinical accessibility with a relative safety. Our study has demonstrated that NG, when administered intracoronary to culprit vessel prior to reperfusion, reduced the incidence of no- and slow-reflow phenomena post reperfusion, increased the rate of ST-segment elevation resolution in 60 minutes post PCI for patients with STEMI, and led to a decrease in the incidence of severe bradycardia and hypotension after recanalization, resulting in better tolerance of PCI.

Conflict of Interest

The authors declare that there is no conflict of interest.

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