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Total Knee Replacement Surgery is Followed by Transitory Endothelial Dysfunction

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A B S T R A C T

Acute coronary syndrome (ACS) presents today the leading group of post-operative cardiovascular complications, while endothelial dysfunction (ED) is one of the key elements in its development. The chronic ED represents thus the basis for the gradual development of atherosclerotic changes, while its sudden aggravation leads to ACS. The persistent ED occurs due to the effects of chronic cardiovascular risk factors, while according to the available studies it can also develop or aggravate under the impact of different acute events. We have directed this study to the investigation of the dynamic of endothelial function before and after a major orthopaedic surgical intervention. This randomised prospective study included 19 patients that underwent the intervention of total knee replacement and 20 healthy examinees of the adequate age and gender. High-resolution ultrasound test based on the flow mediated dilatation of the brachial artery is what at we carried out at the beginning of the research, respectively 12, 24 48 and 72 hours, as well as 7 days after the surgical intervention. The starting values of the FMD test were within the normal range in both groups, although the ability of dilatation upon stimulus was significantly lower in the investigated group. The FMD percentage change in the total sample was negatively connected with the body weight, not having shown additional connections with other cardiovascular risk factors. During the early post-operative period, a significant transitory lowering of the FMD percentage change was recorded, having reached the lowest value 24 hours after the surgery. During the seven-day prospective surveillance, no significant cardiovascular complications were recorded. Further research is necessary in order to confirm these results as well as the testing of the possible connection of the described post-operative transitory endothelial dysfunction with the development of cardiovascular complications and the adverse event.

Key words: *endothelial dysfunction, flow mediated dilatation, acute coronary syndrome, total knee replacement, postoperative complications*

Introduction

The increase in life expectancy, present in developed countries in the last decades, has a significant impact on the overall health issue and the priorities of public health, but also on the interests of science.

The trend of rise in prevalence of degenerative diseases of the locomotor system and the accompanying rise in the number of orthopaedic surgical interventions are in direct connection with the aging of population. Thus, the number of interventions relating to the total knee replacement in the USA from the year 1976 to 2008 has increased seven times[1], while this number has tripled in the Netherlands in the period from the year 1996 to

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2005[2]. At the same time, increased average age also means having a higher prevalence of cardiovascular diseases, which have remained among the leading medical problems in general in spite of the modern methods of treatment[3]. Nowadays, cardiovascular diseases also have significant impact on the progression and outcome of major orthopaedic surgical interventions. The routine use of low molecular weight heparin in orthopaedic surgery has almost eradicated the occurrence of pulmonary thromboembolism, which earlier used to be the most common non-surgical complication[4]. Its place has been taken by the acute coronary syndrome (ACS)[5], which involves unstable angina pectoris, ST-elevation myocardial infarction and non ST-elevation myocardial infarction[6]. The basis of ACS is regularly manifested by the chronic atherosclerosis of coronary arteries with the occurrence of acute changes. Although the said relationship is universal and often does not offer a possibility to identify the actual trigger for the acutisation of atherosclerotic event, inflammatory transformation and destabilisation of atherosclerotic plaque is the basis of ACS[7–9]. Nowadays, we know that the development of endothelial dysfunction (ED) has a key role in the progression of chronic atherosclerotic disease, but also in the development of the acute atherosclerotic plaque. In this process, its insofar hard and stable capsule becomes soft, unstable and prone to disruption[10]. The rupture of destablised atherosclerotic plaque leads into the development of acute thrombosis of the affected coronary artery, which presents the anatomic basis for the clinical picture of ACS[11]. The generalised neurohumoral reaction of the body to different events, thus also to surgery as a major stressful event, can present one of the incentives for the development of ED that then leads to ACS[12]. The basic characteristics of endothelins are their generalising quality and functional unity. The normal function of endothelins confirmed at the peripheral artery indicates thus the normal global endothelic as well as coronary function, while the establishment of an individual function of the endothelin (vasoreactivity, coagulational, inflammatory or proliferatic status) speaks of its general functional status, which, as it is the case with the light bulb switch, can only be twofold, namely, normal or pathological[13,14]. Although we still do not have the method of evaluating endothelial function that would be fully applicable for a routine clinical practice[15], the most widely used method today is the indirect evaluation of availability of nitric oxide (NO), as the most important endothelial mediator, by the flow mediated dilatation test of the brachial artery[16].

The risk of ACS in the early post-operative period is estimated in major prospective studies to around 6%[17,18], however, its incidence is significantly different depending on the applied diagnostic criteria and the examined group of patients[19]. Today we know that diagnosing ACS in the early period after the surgical intervention bears certain specific features and limitations with regard to the general population. Only 16% of patients that develop myocardial infarction (MI) during or after the surgery complain of pains in the chest, while only a half mentions another symptom[16]. The said is explained by the specific conditions in the period around major surgical interventions, standard application of analgesics and sedatives as well as the lowered ability of the patient to notice and indicate symptoms.

The modern definition of MI points out that it is the clinical event that occurs as a consequence of ischemia induced necrosis of cardiomyocytes that has to be proved by a combination of diagnostic criteria, the presence of subjective disturbances, electrocardiographic changes and the establishment of specific biochemical markers[20]. As the greatest part of data on perioperational incidence of MI results from the period preceding the routine application of sensitive troponin tests, its development is probably more frequent than the data indicated by the available studies, while the exact incidence still needs to be investigated.

The determination of the hazard of development of cardiovascular complications in each of the most frequent surgical interventions is necessary for today's clinical practice[21,22]. Besides major prospective studies that are needed for this, the above said also involves a better acquaintance with the actual mechanisms of occurrence of acute vascular events in the early period after the surgical interventions[23].

According to the available data, the ACS development in the early post-operative period today has a significant impact on the long-term outcome of surgical treatment[24], the length of hospital stay and total costs of the health care system. In up-to-date surgery, the post-operative ACS has thus imposed itself as a new priority in diagnostics, treatment and prevention, so that a great interest directed to the research of mechanisms of its development is not surprising[25,26]. Although ED is the key event in the development of ACS, its dynamics in the period following surgical interventions has so far been poorly studied, while in the field of major surgical interventions that present the ever greater part of elective surgical interventions, it has hardly been investigated at all.

Material and Methods

Patients

A total of 39 patients took part in the study, out which there were 26 women. In the experimental group there were 19 patients (15 women), while in the control 20 (11 women, $p=0.213$). Groups of patients did not vary according to the age, height, weight and values of measured blood pressure, but cholesterol levels were statistically significantly higher in the studied group (Table 1). The representation of permanent medicament therapy (beta-blockers, statins and ACE-inhibitors) did also not vary between groups (all $p>0.05$).

Nonselected patients were included in the study, who, according to the clinical presentation order, underwent the total knee replacement surgery at the Orthopedic Clinic Hospital Lovran during the month of October in the year 2010, as well as a group of healthy examinees of

TABLE 1
PATIENTS' CHARACTERISTICS

	$\bar{X}$±SD		p
	Experimental N=19	Control N=20	
Age (y)	71±6	69±5	0.143
Height (cm)	168±8	172±10	0.229
Weight (kg)	84±11	81±11	0.330
Cholesterol (mmol/L)	5.2±1.0	4.2±0.6	0.001
RRd*	82±9	77±11	0.110
RRs**	146±10	134±16	0.006

*RRd – diastolic blood pressure; **RRs – systolic blood pressure

the adequate age and gender who responded to the public call for a check-up. All surgical interventions were made with the use of tourniquet, according to the standard protocols of the Good Clinical Practice.

The study did not include patients with the unstable angina pectoris or suspicion of acute coronary syndrome, cardiac decompensation, uncontrolled (acute diabetic complications, uncorrected diseases of the thyroid gland), manifest peripheral vascular disease, active infectious or other inflammatory diseases including inflammatory diseases of connective tissue, unregulated diabetics (glycolised haemoglobin ≥7.0 %), smokers, women in the generative age and patients above the age of 80. During the study time, all patients were clinically followed at a permanent basis, with electrocardiograph analysis made and troponin I in plasma measured on the daily basis.

Ethical principles

All those involved in the study gave their written permission for participation in this research programme, previously approved by the ethics committee of the Lovran Clinic for Orthopaedic Surgery and the School of Medicine of the University of Rijeka.

FMD test

Before the surgical intervention and 1, 24, 48 and 72 hours and 7 days after the intervention, the assessment of endothelial function was made by high-resolution ultrasound flow mediated brachial artery dilatation measurement according to the leading guidelines for its performing and interpretation[16]. The examination was performed on the ultrasound apparatus SonoSite NanoMaxx multifrequent (6–13 MHz) with a linear probe at the frequency of 11 MHz, with the simultaneous electrocardiograph recording, in a quiet and dark space.

Prior to each examination, a prescribed preparation of the patient was performed, while measurements were made on the brachial artery of the dominant arm, in B mode during the diastole. First, we measured the initial diameter of the brachial artery, and then had the sphyngomanometer cuff inflated on the brachium of the tested arm up to the value of pressure that was 50 mmHg higher than the systolic blood pressure. The compression was maintained for 5 minutes, after which the change in the diameter of the tested artery was measured in longitudinal view for 2 minutes after deflation. The difference of maximal and initial diameter was expressed in the FMD percentage change. Upon the completion of the FMD test, with a minimally ten-minute long pause, we investigated nitroglycerin mediated dilatation on the application of glycerol nitrate in the dose of 400 μg sublingually by measuring the diameter of the same artery for four minutes upon the application. All examinees whose NMD test results were below the referent values were excluded from further research due to the supposed non-endothelial impact on the FMD test.

Statistical analysis

Categorical variables are presented with absolute and relative frequency and distribution compared with Chi-square test. Continuous variables are expressed as mean ±standard deviation because the distribution was normal ($p>0.05$; Kolmogorov-Smirnov test). Differences between groups were examined with independent t-tests. Repeated measures ANOVA models were used to assess within-group differences in FMD percentage change for the experimental group. The association of variables was calculated with Pearson's correlation coefficient.

The level of significance for which conclusions were considered statistically significant was $p<0.05$. The analyses were performed with MedCalc 11.2.0.0. (Medcalc Inc, Mariakerke, Belgium) and Statistica 9.1 (Statsoft Inc, Tulsa, USA).

Results

Prior to the total knee replacement patients had a significantly lower FMD percentage change than healthy examinees, although absolute values of the test were within the normal range (Figure 1) in both groups. In all patients the initial FMD percentage change was negatively connected with the body weight ($r=-0.43$; $p=0.006$), however, it did not show a significant connection with the values of blood pressure, cholesterol and glycolised hemoglobin, or with the taking of beta-blockers, statins or ACE-inhibitors (all $p>0.05$). None of these cardiovascular risk factors was connected with with the changes of FMD percentage during the research. The values of NMD test did not vary between groups ($p=0.430$; 13.8±9.1 *vs*. 15.1±5.3), while pathological values of this measurement were not recorded in any single examinee included in the research. During the study, we did not record clinical, electrocardiograph or laboratory (increase in troponin I) elements for the development of acute cardiovascular complications.

The post-operative serial FMD testings showed a significant transitory damage of the endothelial function in the first week after the surgical intervention. The post-operative dynamic of the FMD percentage change showed »U-shape« dynamics, values were progressively lowered during the first 24 hours after the surgery, after

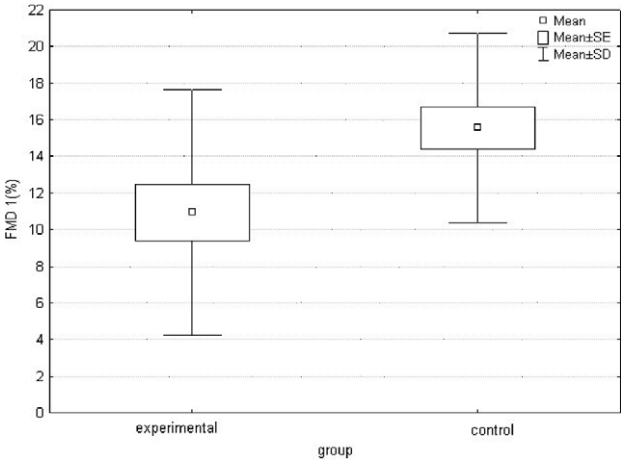

Fig. 1. Differences in FMD percentage change between experimental and control group (p=0.02; 11±6.7 vs. 15.7±5.3)

which they began to increase gradually until the seventh day when (FMD 1 *vs.* FMD 6; p>0.05) they reached the initial values (Figure 2).

With the pairwise comparison analysis we obtained significant differences between FMD 3 and FMD 6 (6.6±3.4 *vs.* 10.4±2.3; p=0.022).

Discussion and Conclusion

The decreased ability of the brachial artery in FMD test to dilate upon the controlled outside stimulus in the early period after the major orthopaedic surgery indicates the decrease in the capacity for endogenous NO production. The decreased availability of this most significant intermediary and marker of endothelial function indicates the development of ED, which is transitory according to our results, becoming worse during the first post-operative day, reaching its peak 24 hours after the operation, after that regressing in the first week, all until the seventh day when it normalises spontaneously. Although the FMD test quantifies the vasodilatation capability of the periferial artery, the known body unity of endothelial function tells us that this examination perfectly correlates with the endothelial function of coronary arteries[25,27]. The FMD test has a predictive power of 95% for the detection of the pathologic coronary angiogram (14), as well as a better specific quality in the detection of myocardial ischemia than the classic ergometric test[28], while it is also significant that this method of assessing endothelial function proves to have an obvious capability to predict acute vascular events[29]. Thus the transitory ED described in our research can present one of the important mechanisms of the development of post-operative ACS as the most significant cardiovascular complication in orthopaedic surgery today, having a significant impact on the overall outcome of the treatment[24].

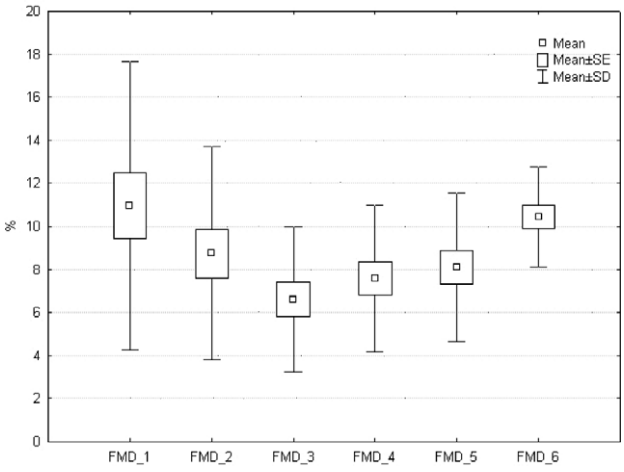

Fig. 2. Differences in FMD percentage change in patients that underwent major orthopaedic surgery with regard to post-operative course (p=0. 008).

It is from the continuation of this subject matter research that we expect to have the confirmation for this hypothesis based on the before-mentioned facts. Although it is indisputable that additional investigation is needed for the confirmation of results that we have presented, it is also necessary for them to be examined in other types of surgical interventions, accompanied by a long-term prospective surveillance in order to have a precise assessment of the predictive capability of FMD test in different phases before and after the surgical intervention. Further studies will have to raise the issue of examining the possibility of therapy modification of the post-operative ED that we have described. The testing of medication which we know to be efficient in the therapy of chronic ED (beta-blockers, statins, ACE-inhibitors) regarding the perioperative dynamics of the endothelial function and the long-term outcome, appears to be a challenging field whose research is of a primary necessity[21].

Although our results suggest the existence of differences in initial FMD test between patients that have to undergo the total knee replacement and healthy examinees of the adequate age and gender, there are some limitations in the interpretation that have to be discussed and taken into account in further research. Even though the established total cholesterol levels are not of clinical significance, the examined group has statistically significantly higher values. Prior to the surgical intervention, the group of patients also showed higher absolute values of body weight and systolic and diastolic blood pressure, although these differences do not express a statistical significance. Knowing specific lifestyles and total health status of patients with severe arthrosis of the knee who are candidates for the total knee replacement surgery, we could connect these differences with their significantly reduced physical activities and a strictly sedentary lifestyle[31,32]. Furthermore, but also very important is the issue of direct connection between limited physical activity with endothelial function and/or its direct connection based on the adverse profile of classic cardiovascular risk factors in orthopaedic patients. Although the eventual testing of these impacts will require great efforts in re-

search studies that follow, their results could provide significant data to our knowledge of endothelial function. The confirmation of connectedness between the functional status of endothelial and the functional status of the locomotor system is a challenging idea with a clear basis in literature[30], definitely asking for a thorough research.

Soon after the discovery of ED as a key pathological mechanism in vascular biology, we had the description of the clear connection of persistent ED with almost all classic cardiovascular risk factors as its long-term causes[11]. However, of a more recent date, acute instigators of the occurrence or aggravation of ED have been described. Thus, nowadays we know that a psychological or physical stress, acute infection or another newly occurred inflamed state, smoking, even an inappropriate meal, can bring about the development of a sudden, generalised and non-selective endothelial dysfunction, the complications of which depend on the intensity, length and degree of existing atherosclerotic changes[33,34]. Although surgical interventions, including orthopaedic ones, undoubtedly present a major stressful event and a powerful pro-inflammatory stimulus[26], data on the dynamics of perioperational endothelial function remain scarce. Its changes in the period following the orthopaedic interventions have not been investigated at all, just as is the case with investigations of possible connectedness with the development of perioperational cardiovascular events. It is the major orthopaedic interventions that are an ideal model for further trials to investigate the perioperative endothelial function. We are talking about major surgical interventions performed on the massive scale, the elective character of which enables optimal planning and execution of prospective clinical studies. Besides their contribution to the knowledge of general vascular biology, the obtained results could probably be directly applicable in the investigated group of patients, this being of great public health significance. The early detection of endothelial dysfunction as a risk factor and the correlated possibility of decreasing post-operative complications in major orthopaedic interventions that nowadays present the greatest part of elective surgical interventions is a challenging idea for the testing of which further trials are necessary.

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UGRADNJA TOTALNE ENDOPROTEZE KOLJENA PRAĆENA JE TRANZITORNOM ENDOTELNOM DISFUNKCIJOM

S A Ž E T A K

Akutni koronarni sindrom (AKS) danas predstavlja vodeće postoperativne kardiovaskularne komplikacije, dok je endotelna disfunkcija (ED) jedan od najvažnijih čimbenika njegovog razvoja. Kronična ED osnova je postupnog razvoja i progresije aterosklerotskih lezija, dok njeno akutno pogoršanje vodi razvoju akutnih komplikacija ateroskleroze – razvoju AKS. Perzistentna ED nastaje pod djelovanjem različitih kroničnih kardiovaskularnih rizičnih čimbenicima, ali se prema ograničenim dostupnim izvorima može naglo razviti ili akutno pogoršati pod djelovanjem različitih akutnih događaja. U skladu s navedenim, predmetno je istraživanje usmjereno utvrđivanju endotelnog funkcionalnog statusa prije velike ortopedske kirurške operacije i njegove dinamike u ranom razdoblju nakon zahvata. Randomizirana prospektivna studija uključila je 19 bolesnika koji su podvrgnuti zahvatu ugradnje totalne koljenske endoproteze i 20 zdravih ispitanika odgovarajuće dobi i spola. Visokorezolucijski ultrazvučni test procjene endotelne funkcije temeljen koji koristi protokom posredovanu dilataciju brahijalne arterije (FMD) izvodio se na početku ispitivanja, te 12, 24, 48 i 72 sata, kao i 7 dana nakon operativnog zahvata. Početne vrijednosti FMD-a bile su unutar referentnih raspona u obje grupe, iako je sposobnost spontane dilatacije nakon naglog povećanja protoka testiranom arterijom bila značajno niža u ispitivanoj skupini. Razina promjene FMD-indeksa u ukupnom je uzorku iskazala negativnu korelaciju s tjelesnom težinom, dok nije bila značajno povezana s bilo kojim drugim klasičnim kardiovaskularnim rizičnim čimbenikom. Tijekom ranog postoperativnog razdoblja, zabilježeno je značajno, ali prolazno smanjenje FMD-indeksa koji je najniže razine dosegao 24 sata nakon operacije. Tijekom sedmodnevnog postoperativnog praćenja u ispitivanoj skupini nismo zabilježili razvoj značajnih kardiovaskularnih komplikacija. Potrebna su daljnja istraživanja kako bi se potvrdili ovi rezultati i istražila moguća povezanost opisane reaktivne postoperativne endotelne disfunkcije s razvojem kardiovaskularnih komplikacija i drugih neželjenih događaja.