## Project summary

Revascularization strategies including percutaneous coronary intervention (PCI) and coronary artery bypass grafting surgery (CABG) are commonly used to treat coronary artery disease (CAD). Postoperative outcomes of revascularization are critically determined by the patency of coronary artery or CABG grafts, which is compromised by vascular spasm and/or atherosclerotic plaque formation. Grafts spasm is still a clinical problem. The mechanism of spasm may involve many pathways, particularly those that affect the intracellular calcium concentration related to calcium and potassium channels.

During CABG, adequate pharmacologic vasodilators are a necessary part of the anti-spastic protocol. All vasodilator drugs relax the vessel by a specific mechanism(s), and therefore, there is no “perfect” single vasodilator as the “best” vasodilator to prevent or treat spasm of the grafts against all mechanisms of contraction.

Also, because the functional states of endothelial and smooth muscle cells significantly affect postoperative patency of vessels, a large group of phytochemicals, polyphenolic flavonoids, with their various beneficial health effects, like improved endothelial function, antitrombotic, antiatherogenic, vasorelaxant and antihypertensive effects, represents the promising agents for protection against cardiovascular diseases. Flavanols, such as epicatechin and catechin, and their oligomers, the procyanidins, represent a major class of secondary, polyphenolic plant metabolites. Flavanols are commonly present in higher plants, and their high content in certain food plants, such as *Vitis vinifera* (grape wine), *Camellia sinensis* (tea), and *Theobroma cacao* (cocoa) are especially noteworthy in the context of human nutrition. The mechanism of cardiovascular benefits probably includes vasodilatory effect of flavonoids. The mechanisms by which flavonoids cause vasodilation are uncertain. Since no data on the effects of flavonoids on human blood vessels, testing vasodilatory effect and mechanism of action of flavonoids on the human bypass grafts is a very topical.

For this reason, the main objectives of the research under this project were:

1. Studies of the effect of clinically used anti-spasm agents and those with potential for clinical use on the vessels;
2. Studies of the effect and mechanism of action of polyphenolic flavonoids as potential cardioprotective agents.

Keywords**:** bypass graft, vasodilation, nicorandil, flavonoids.

## Sažetak projekta OI 175088

Revaskularizacione strategije koje uključuju perkutanu koronarnu intervenciju (PCI) i aortokoronarnu bajpas operaciju (CABG) se obično koriste za lečenje koronarne arterijske bolesti (CAD). Postoperativni ishodi revaskularizacije primarno zavise od prohodnosti koronarnih arterija ili bajpas graftova, a koja može biti značajno redukovana vaskularnim spazmom i/ili stvaranjem aterosklerotskog plaka. Spazam graftova još uvek predstavlja značajan klinički problem. Mehanizam nastanka spazma uključuje različite puteve, posebno one koje utiču na intracelularnu koncentraciju kalcijuma koja je u vezi sa aktivnošću kalcijumovih i kalijumovih kanala.

Tokom CABG, u cilju prevencije i reverzije spazma, neophodna je primena odgovarajućih farmakoloških vazodilatatora. Svi vazodilatatorni lekovi relaksiraju krvni sud svojim specifičnim mehanizmom(ima), tako da ne postoji "idealan" pojedinačni vazodilator za prevenciju ili terapiju spazma bajpas graftova različitog mehanizma nastanka.

Takođe, s obzirom da funkcionalno stanje endotela i glatkih mišićnih ćelija značajno utiče na postoperativnu prohodnost krvnih sudova, primena velike grupe fitoagenasa, polifenolnih flavonoida, čije kardioprotektivno dejstvo uključuje poboljšanje endotelne funkcije, antiagregacijsko, antiaterogeno, vazodilatatorno i antihipertenzivno dejstvo, može imati veoma značajnu ulogu u prevenciji kardiovaskularnih oboljenja. Flavanoli, kao što su epikatehin i katehin, i njihovi oligomeri, procijanidini, predstavljaju glavnu klasu sekundarnih, polifenolnih metabolita biljaka. Flavanoli su uobičajeno prisutni kod viših biljaka, i njihov visok sadržaj u određenim jestivim biljkama, kao što su *Vitis vinifera* (vinova loza), *Camellia sinensis* (čaj) i *Theobroma cacao* (kakao), je posebno vredan pažnje u kontekstu ljudske ishrane. Mehanizam vazodilatacije prouzrokovane flavonoidima još uvek nije potpuno jasan. S obzirom da nema puno podataka o vazodilatatornom efektu flavonoida na izolovanim humanim krvnim sudovima, ispitivanje vazodilatatornog efekta i mehanizma delovanja flavonoida na humanim bajpas graftovima je veoma aktuelno.

Zbog svega navedenog, osnovni ciljevi istraživanja u okviru ovog projekta, su:

1. Ispitivanje efekta lekova u prevenciji i terapiji spazma i njhovog potencijala za kliničku primenu;
2. Ispitivanje efekta i mehanizma delovanja polifenolnih flavonoida kao potencijalnih kardioprotektivnih agenasa.

Ključne reči: bajpas graftovi, lekovi u terapiji spazma, polifenolni flavanoidi

## Selected results/Odabrani rezultati

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