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Vasorelaxing effect of levosimendan against 5-hydroxytryptamine-induced contractions in isolated human conduit bypass grafts

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Abstract

Levosimendan is a novel inodilator drug developed for the treatment of heart failure. The possible vasodilating property of the drug in human coronary artery bypass grafts was investigated. Isometric tensions of the left internal thoracic artery (LITA, n = 8) as well as the proximal and distal segments of the radial artery (RA, n = 8 and 8) were measured in isolated organ baths. Concentration–relaxation curves for levosimendan (0.009–1.14 μmol L^{-1}) were obtained against 5-hydroxytryptamine (5-HT; serotonin, 0.002–9.3 μmol L^{-1})-induced contractions. 5-HT-induced contraction of LITA was considerably smaller than that of the proximal and distal RAs. Levosimendan relaxed the grafts in the following order of calculated maximum efficacies (E_{max}): LITA > proximal RA > distal RA (LITA 100.3 ± 16.2% of 5-HT-induced maximum tension, proximal RA 86.9 ± 8.6%, distal RA 59.4 ± 17.5%, $P < 0.05$ LITA vs distal RA). The potency values of levosimendan, expressed as the negative logarithm of 50% effective concentrations (pD_2), were comparable in the three bypass grafts (LITA -6.52 ± 0.44 log mol L^{-1}, proximal RA -6.60 ± 0.49 log mol L^{-1}, distal RA -6.85 ± 0.45 log mol L^{-1}). The results suggest that levosimendan is an effective vasorelaxant of conduit bypass grafts and may serve as a new therapeutic tool, especially in the case of LITA and proximal RA grafts, for relieving perioperative spasm and subsequent graft failure.

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Introduction

Conduit arteries are being used for coronary artery bypass grafting (CABG) with increased frequency because of their association with improved graft patency and long-term survival in coronary artery disease. A major problem with the extensive use of these conduits is spasm leading to acute ischemia, which may contribute to graft failure (Barner 1973; Curtis et al 1975; Sarabu et al 1987). Recent improvements in the early and mid-term patency rates of internal thoracic arteries (ITAs) and radial arteries (RAs) may be attributed to the less traumatic harvesting technique and the use of vasodilators in the peri- and postoperative periods. Vasodilator therapy includes drugs with different mechanisms of action, including calcium channel blockers (Acar et al 1992; Borger et al 1998), papaverine (Acar et al 1992), milrinone (Tatoulis et al 1998), nitroglycerin (Zabeeda et al 2001), nicorandil (Sadaba et al 2000) and adrenergic receptor blockers (Taggart et al 2000; Mussa et al 2003). Nitroglycerin and diltiazem are the preferred drugs for relieving or preventing graft spasm (Shapira et al 1999; Tabel et al 2004). However, most of these drugs are devoid of inotropic action and may even deteriorate cardiac contractility, for example the calcium antagonists, or decrease or increase heart rates, effects that may be harmful in the peri-CABG setting. Inotropic dopamine caused a variable effect in ITAs and contracts RAs (Katai et al 2004). It is therefore reasonable to assume that an inodilator drug may be superior over the currently used vasorelaxing drugs for relieving graft spasm, especially in patients with left ventricular dysfunction.

Levosimendan is a novel inodilator drug that, in addition to its inotropic action, decreases the cardiac preload of the heart by relaxing capacitive veins (Haikala et al

1995; Udvary et al 1995; Hőhn et al 2004). The inodilator also dilates the conduit type of coronary arteries (Gruhn et al 1998; Patericza et al 2003). Although the preoperative administration of levosimendan improved the cardiac haemodynamic conditions in patients undergoing CABG surgery (Barisin et al 2004), a direct effect of the drug on human bypass graft arteries has not yet been demonstrated.

The present investigation was devoted to study of the vasodilating capacity of levosimendan in conduit bypass grafts precontracted with 5-hydroxytryptamine. The isometric tensions of the isolated left internal thoracic artery (LITA) and RA were studied. The proximal and distal parts of the RA were separately studied in order to explore possible differences in their contractile and/or relaxing capacities.

Materials and Methods

Materials

The drugs used and their sources were as follows: serotonin (5-hydroxytryptamine creatinine sulfate, Sigma, St Louis, MO, USA) and levosimendan (Orion-Pharma, Espoo, Finland). Levosimendan was dissolved in 70% ethanol and further diluted in Krebs–Henseleit solution. Serotonin was dissolved in double-distilled water. Nifedipine (Adalat) was purchased from Bayer (Bayer Health Care AG Leverkusen, Germany).

Methods

Characteristics of patients

Sixteen patients undergoing elective coronary bypass surgery (CABG) were involved in the present study. LITA was obtained from eight patients (age 65.7 ± 2.9 years), proximal and distal parts of the RA were obtained also from eight patients (age 65.4 ± 3.2 years). Three patients suffered from diabetes and only one female patient was included in each group. Conservative treatment included statins, aspirin, nitrates, ACE-inhibitors, calcium channel blockers, beta blockers, diuretics and antidiabetic drugs. None of the patients had suffered from severe chronic heart failure and all patients in the two groups received a beta-receptor blocking drug. Despite the conservative medications 100% of the patients were hypertensive and two-thirds of them were hypercholesterolaemic. Approval to use discarded arterial tissues was given by the Human Investigation Review Board, University of Szeged, Hungary (No.164/2002 and No.161/2004).

Harvesting technique

We obtained 5–6-mm long segments of LITA and RA. Arterial samples were prepared atraumatically with the Ultracision Harmonic Scalpel (Ethicon Endo-Surgery, USA). This technique allows cutting, coagulation and dissection of tissue at lower temperatures than in the case of the electrosurgical method, thus minimizing thermal damage to the tissue. Once harvesting of the arterial samples had been started, low-dose nifedipine (0.2–$0.4\,\mathrm{mg\,h^{-1}}$) was given in intravenous infusion to prevent early vasospasm. The LITA or RA was then carefully dissected with the accompanying veins. We used an in-situ LITA graft during CABG and prepared 1 cm above the bifurcation for the in-vitro study. Samples of RA were obtained at the origin of the brachial artery (proximal part) and at the level of the wrist (distal part). Arterial tissues were then placed into ice-cold Krebs–Henseleit solution and immediately transported to the laboratory. The composition of the Krebs–Henseleit solution was (in $\mathrm{mmol\,L^{-1}}$): NaCl 120, KCl 4.2, $CaCl_2$ 1.5, $NaHCO_3$ 20, $MgCl_2$ 1.2, KH_2PO_4 1.1, glucose 11 and EGTA $0.27\,\mu\mathrm{mol\,L^{-1}}$. In the laboratory, the arteries were dissected free from the surrounding connective tissue and cut into rings of 3 mm long.

Isometric tension measurements

Closed-ring segments of LITA as well as the proximal and distal ones of RA were mounted on stainless-steel hooks and placed into water-thermostated (at 37 °C) organ chambers containing 2 mL of Krebs–Henseleit solution. The solution was continuously bubbled with a gas mixture of 95% O_2 and 5% CO_2 at pH 7.4. One of the hooks was anchored inside the organ chamber and the other one was connected to a force-displacement transducer (Hugo Sachs Elektronic, Type F30, Germany) to measure changes in isometric tension as previously described by Patericza and colleagues (Patericza et al 2003). In each isolated type of graft we optimized the resting (basal) tension during a preliminary series of experiments. The tension to which the vessels were subjected was increased manually in increments of 5 mN (milliNewtons) over 30 min to achieve maximum active tension for the minimum resting tension using $10\,\mu\mathrm{mol\,L^{-1}}$ serotonin. The optimum values were found to be 20 mN for all three grafts. In this series of experiments the rings were stretched up to 20 mN and equilibrated for 60 min. During this period tension was continuously readjusted to the above value of stretch and the medium was changed in every 15 min.

Protocol

RA ring segments cut from the proximal and distal parts of the same artery were mounted in parallel in separate organ chambers (LITA samples from different individuals were studied independently) and equilibrated for 60 min. Following the equilibration period the rings were contracted with 0.002–$9.3\,\mu\mathrm{mol\,L^{-1}}$ serotonin. When the contraction reached a stable plateau levosimendan was administered cumulatively (0.009–$1.14\,\mu\mathrm{mol\,L^{-1}}$) into the organ baths.

Data analysis

Contractions induced by 0.002–$9.3\,\mu\mathrm{mol\,L^{-1}}$ serotonin were expressed in milliNewtons. Relaxations induced by levosimendan were expressed as a percentage of serotonin-induced steady-state contraction amplitude. The equation $y = a^*x/(x+b)$ was fitted to the individual dose–response curves for levosimendan and efficacy/E_{max} (a) and 50% effective concentration ($b = \mathrm{EC50}$) values were calculated. EC50 values were converted to pD_2 and expressed in $-\log\mathrm{mol\,L^{-1}}$ concentrations.

Statistical analysis

All data are expressed as mean ± standard error of the mean (mean ± s.e.m.). Statistical significance was tested with one-way analysis of variance followed by the Newman–Keuls multiple comparison test. E_{max} and pD_2 values were compared with Students' *t*-test and *P* values less than 0.05 were considered statistically significant.

Results

Contractile effect of 5-hydroxytryptamine on the proximal and distal RAs as well as on the LITA

5-hydroxytryptamine (5-HT, 0.002–9.3 μmol L^{-1}) enhanced the tone of the LITA and that of the proximal and distal parts of RA concentration dependently (Figure 1). The contractile effect of 5-HT was more pronounced in the radial arteries than in the thoracic artery. The proximal RA responded with a significantly larger contraction than LITA at and above 0.31 μmol L^{-1} of 5-HT (at 0.31 μmol L^{-1} 5-HT: proximal RA = 13.0 ± 4.9 mN vs LITA 3.6 ± 1.6 mN, n = 8 and 8, $P < 0.05$). The distal RA also developed higher active tension than the LITA but the difference in effect was not statistically significant. The developed maximum tension (E_{max}) calculated by fitting a logistic curve showed similar results (E_{max}: LITA = 11.0 ± 1.9 mN, proximal RA = 27.0 ± 4.5 mN and distal RA = 18.5 ± 6.8 mN, $P < 0.01$ LITA vs proximal RA). The sensitivity of the grafts to the contractile agent, expressed as pD_2 values, did not differ significantly in the case of the three conduit blood vessels (pD_2 values: LITA = −6.04 ± 0.51 log mol L^{-1}, proximal RA = −6.52 ± 0.40 log mol L^{-1}, distal RA = −6.57 ± 0.25 −log mol L^{-1}).

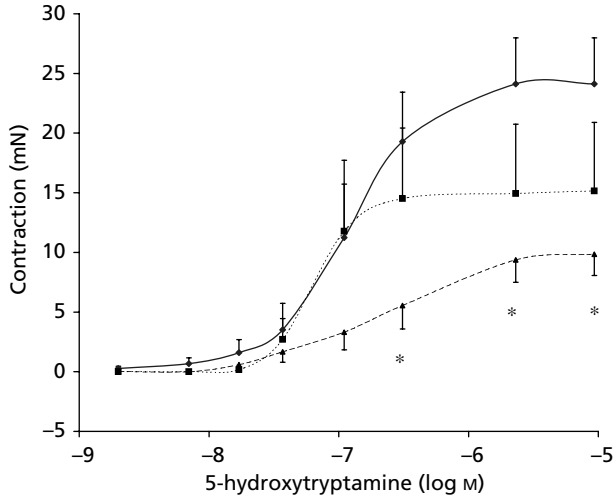

Figure 1 Effect of 5-HT (0.002–9.3 μmol L^{-1}) on the tone of the proximal and distal parts of the RA as well as on that of the LITA. Values are expressed as mean ± s.e.m. (◆ = proximal segment of RA, n = 8; ■ = distal segment of RA, n = 8; ▲ = segment of LITA, n = 8). Asterisk denotes significant differences ($P < 0.01$) between the corresponding values of the proximal part of the RA and the LITA.

Vasorelaxation by levosimendan in proximal and distal RAs as well as in LITA

Figure 2 demonstrates that levosimendan concentration dependently (0.009–1.14 μmol L^{-1}) relaxed the three conduit bypass grafts precontracted with 5-HT. Relaxations of the three grafts were evident at even submicromolar concentrations of the inodilator drug. The maximal relaxing responses to the inodilator were similar in the case of LITA and proximal RA, and the calculated efficacy values also showed no statistically significant differences between the two grafts (E_{max}: LITA = 100.3 ± 16.2% of 5-HT-induced maximum tension, proximal RA = 86.9 ± 8.6%). Levosimendan partially relaxed the distal RA = 59.4 ± 17.5%, $P < 0.05$ vs LITA). The sensitivity of LITA as well as of the proximal and distal RA samples to the vasodilating effect of the drug were calculated to possess comparable pD_2 values (LITA −6.52 ± 0.44 log mol L^{-1}, proximal RA −6.60 ± 0.49 log mol L^{-1}, distal RA −6.85 ± 0.45 log mol L^{-1}).

Discussion

In the present study we have demonstrated the vasodilating efficiency of the novel inodilator levosimendan in the two main conduit arteries, the LITA and the RA, that are used frequently for CABG surgery. In isolated organ baths, the inodilator drug relaxed the 5-HT (serotonin)-evoked active contractions of both LITA and RA in

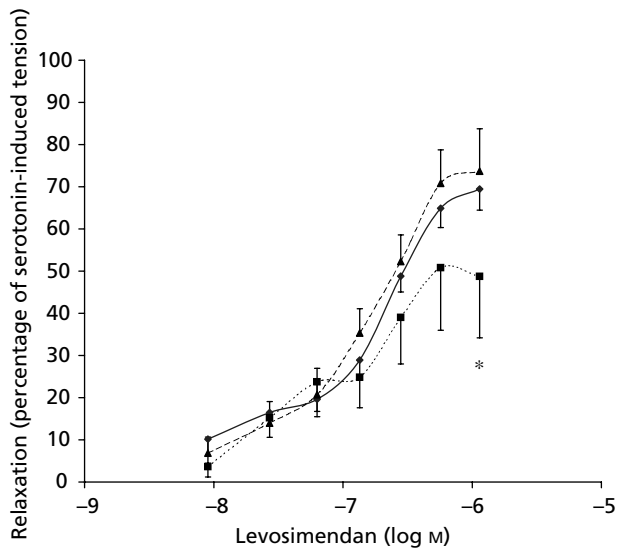

Figure 2 Vasorelaxing effect of levosimendan (0.009–1.14 μmol L^{-1}) in the proximal and distal RAs as well as in the LITA. The rings were contracted with 5-HT, added cumulatively (0.002–9.3 μmol L^{-1}). The relaxation of the tissue by levosimendan was expressed as a percentage of the contraction induced by 5-HT. Values are expressed as mean ± s.e.m. (◆ = proximal segment of RA, n = 8; ■ = distal segment of RA, n = 8; ▲ = segment of LITA, n = 8). Asterisk denotes significant difference ($P < 0.05$) between the corresponding values of the distal part of RA and LITA.

those submicromolar concentrations that were proved to have therapeutic efficiency in patients with heart failure (Sandell et al 1995). Levosimendan completely or almost completely relaxed the LITA and proximal RA, respectively. Distal RA revealed 50–60% maximum relaxation to the inodilator drug. The response of LITA to the constrictor effect of serotonin was less than that of the proximal part of the RA whereas the distal RA developed tension in magnitude between LITA and the proximal segment of RA.

Both the thoracic and radial arteries are middle-sized musculoskeletal arteries and may develop vasoconstriction (Chardigny et al 1993). A 6-year follow-up study explored a higher occlusion rate of RA grafts (33.7%) compared with left internal mammary/thoracic arteries (4.8%) (Khot et al 2004). Indeed, the contractile response elicited on RA rings by a variety of vasoconstricting stimuli, including serotonin, is markedly superior to that exhibited by the internal thoracic artery or gastroepiploic artery (Chardigny et al 1993; Manasse et al 1996; He & Yang 1997; Sperti et al 1999; Daneshmand et al 2004). Our present observations support these findings in that the calculated maximum developed tension induced by 5-HT was larger in RAs than in LITA. Furthermore, noradrenaline (norepinephrine) and adrenaline (epinephrine) contracted both parts of the RA more than that of the ITA (Chardigny et al 1993; Chester et al 1998). Taken together, RAs appear to develop higher tension than LITA both on the locally released serotonin during blood clotting and following sympathetic activation.

Active contraction induced by 5-HT is considered to be an important pathological mechanism for inducing arterial spasm and may cause perioperative and late failure of bypass conduits (Sperti et al 1999). 5-HT (serotonin) is a diagnostic tool for angiographic testing of graft patency in the postoperative period (Gaudino et al 2005). Although, in contrast to the early perioperative period, late postoperative graft failure is not exclusively due to spasm but involves additional intimal hyperplasy, for both periods new types of vasodilators have been considered necessary, especially in patients carrying RA grafts (Gaudino et al 2005). Calcium channel antagonists as vasodilators are the standard therapy for relieving CABG vasospasm, and diltiazem, verapamil, amplodipine and nifedipine have been proved to be partially effective against several different pathological contractions produced, for example, by endothelin and noradrenaline (Bond et al 2000). However, 5-HT-induced contraction, mostly due to local activation of the circulating platelets, was found to be less susceptible to the vasodilating effect of diltiazem (Sperti et al 1999). In a follow-up study, oral calcium antagonist therapy was unable to attenuate the immediate spastic reaction of RA following endovascular infusion of serotonin (Gaudino et al 2005). On the basis of these findings, 5-HT-induced tension in-vitro appeared to represent a type of resistant spasm that may be susceptible for a new vasodilator.

The inodilator, levosimendan, dilates human saphenous veins and also conduit blood vessels by activating ATP-sensitive and other types of hyperpolarizing potassium channels (Pataricza et al 2003; Hőhn et al 2004). Activation of potassium channels exerts receptor-independent relaxation of the arterial smooth muscles, including the conduit type of coronary arterial samples isolated from animals (Pataricza et al 2004). Levosimendan was found to be an effective antagonist against contractions induced by prostaglandin $F_{2\alpha}$, endothelin, potassium and noradrenaline (Gruhn et al 1998; Krassói et al 2000; Pataricza et al 2000). Moreover, activation of ATP-sensitive potassium channels induced by this drug may protect the heart against myocardial ischaemia through activation of sarcolemmal and mitochondrial potassium ion channels (Papp et al 2005). In the present study we did not demonstrate a mechanism underlying the effect of levosimendan in conduit grafts, but in human saphenous veins we have demonstrated the role of K_{ATP} channels in the vasodilating mechanism of levosimendan (Hőhn et al 2004). The mechanism by which the inodilator, levosimendan, relaxes the conduit grafts is presently unknown. Activation of ATP-sensitive potassium channels by levosimendan (K_{ATP}, Yildiz et al, personal communication) and, at micromolar concentrations, a possible inhibition of cAMP-phosphodiesterase enzyme (cAMP-PDE) might play a role. Novakovic et al (2003) demonstrated that one of the most specific K_{ATP} activator substances, levcromakalim, is an efficient vasodilator of the ITA, suggesting that hyperpolarization of the smooth muscle cells might be a mechanism of levosimendan-induced vasodilation. Milrinone, known to be an inhibitor of cAMP-PDE, has recently been shown to possess lower potency in RA than in ITA (Wei et al 2005), suggesting a minor role of cAMP in regulating the tone of RA in contrast to that of ITA. This observation excludes the role of cAMP, at least up to 1.14 μM of levosimendan, since the proximal RAs and ITAs revealed similar concentration–response curves for the inodilator in our present study. Thus the mechanism of action of levosimendan in the conduit grafts requires further investigation. Levosimendan-induced relaxation and contraction to 5-HT showed the largest variability in the distal RA. This finding is in agreement with those obtained by Chester et al (1998), which also demonstrated the largest individual variability of the distal RA among the same three conduit grafts used in our study. They did not find statistically significant differences between the distal and proximal parts of RA samples as far as the contractile responses to adrenaline and noradrenaline are concerned. These findings suggest that the contractile machinery of the two parts of the RA graft did not considerably differ from each other, although the distal part shows interindividual differences.

Levosimendan appears to have two advantages over other drugs. In contrast to papaverine it does not deteriorate the endothelial function (He 1998; Gruhn et al 1998) and it may cause a long-lasting vasodilation (Harrison et al 2001; Luther et al 2004). Levosimendan may also be more effective than calcium antagonists against endothelin-induced vasocontriction (Gruhn et al 1998; Bond et al 2000). We did not confirm the integrity of the conduit grafts morphologically or functionally by using endothelium-dependent relaxants, and

this renders a limitation of our method. Furthermore, it should be stated that the effectiveness of levosimendan alone does not represent an overall improvement in the 'vasodilating reserve' of the grafts. It is important to note, however, that the vasoactivity of levosimendan does not require an intact endothelium, at least under in-vitro conditions (Gruhn et al 1998), suggesting an efficient vasodilation of the grafts by the inodilator in the presence of damaged vascular endothelium.

Conclusions

The present results reveal that levosimendan efficiently relaxes the LITA and the proximal RA. Although the maximum vasodilation was less marked in distal RA than in the LITA, levosimendan was also highly effective at submicromolar concentrations in this segment of RA. In addition to the vascular effects, the inodilator improves myocardial efficiency without increasing the oxygen consumption of the heart (Michaels et al 2005). The beneficial effect on stunned myocardium following coronary angioplasty also offers the use of levosimendan in CABG patients (Sonntag et al 2004).

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