The effects of sugammadex on isolated human internal mammary artery and saphenous vein rings

Mert C. Ongun, M.D.¹, Bahar Oc, M.D.², Mehmet Oc, M.D.³, Hulagu Bariskaner, M.D. PhD.¹

¹ Department of Medical Pharmacology, Faculty of Medicine, Selcuk University, Konya, Turkey
² Department of Anesthesiology and Reanimation, Faculty of Medicine, Selcuk University, Konya, Turkey
³ Department of Cardiovascular Surgery, Faculty of Medicine, Selcuk University, Konya, Turkey

Running title: Sugammadex and vascular reactivity

*Corresponding author:
Mert C. Ongun, M.D.
Department of Medical Pharmacology, Selcuk University Faculty of Medicine, Selcuklu, Konya, 42131, Turkey
Phone: +90 332 224 3855
E-mail: mertcanongun55@gmail.com

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Sugammadex (γ-cyclodextrin) is a synthetic molecule that reverses the neuromuscular blockade caused by nondepolarizing agents such as rocuronium. It promotes the rapid elimination of these drugs through the urine by encapsulation [1]. The potential benefits of sugammadex include reduced postoperative residual curarization, shorter anesthesia time, and increased patient turnover in the operating room, with fewer side effects than alternative drugs such as neostigmine and antimuscarinic drugs [2].

Although sugammadex is generally considered safer than neostigmine, reports on serious cardiovascular adverse events associated with its use have increased. Rare cases of hypotension, bradycardia, bronchospasm, cardiac arrest, and coronary vasospasm following intravenous administration of sugammadex have been reported [2,3]. These rare yet serious cardiovascular events have raised concerns that the observed vasospasm or vasodilation in these patients may be a direct effect of sugammadex. Thus, studies on the direct functional effects of sugammadex on cardiovascular tissues are warranted.

However, limited research has been conducted on the direct cardiovascular effects of sugammadex. One study investigated the effect of sugammadex on the vascular tone of isolated rat aortas and found no direct effect on vasoreactivity [1]. To date, no studies have examined the functional effects of sugammadex on human arteries in vitro. Therefore, we aimed to investigate the effects of sugammadex on the human internal mammary artery and saphenous vein.

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This study was approved by the Selcuk University Ethics Committee (Protocol Number: 2023/353). All procedures in this study were done in accordance with the ethical principles of Helsinki Declaration. Informed consent was obtained from all participants included in the study. Patients aged 18 to 75 undergoing coronary artery bypass surgery between July 2023 and December 2023 were included in the study. Participants who had concomitant illnesses such as diabetes mellitus, chronic cardiovascular diseases, vasculitis, liver, or kidney failure were excluded from the study. Samples from the internal mammary artery and saphenous vein were collected during the surgery. Vascular samples were immediately transferred to the laboratory in a cold Krebs–Henseleit solution. Excess fat and connective tissue were removed from the vessels, which were then cut into 2–4-mm rings. Internal mammary artery and saphenous vein rings were mounted and allowed to equilibrate for 60 min under resting tensions of 14.7 mN and 19.6 mN, respectively. Maximum contraction responses were obtained with 40 mM high K+ Krebs to verify the viability of the tissue and to use as a control. After the tissues were washed and rested for 60 min, concentration-response curves were obtained with sugammadex \( (10^{-6} - 10^{-4} \text{ M}) \) cumulatively added to the bath following repeated 40 mM high K+ Krebs pre-contraction. Sugammadex responses were compared with time-matched controls. Two-way ANOVA was used as the statistical analysis method for comparison. Data are presented as means ± standard deviation (SD). The threshold for statistical significance was set at \( P < 0.05 \).

When comparing the time-matched controls with cumulative sugammadex responses, no statistically significant difference was observed. Our findings indicate that sugammadex \( (10^{-6} - 10^{-4} \text{ M}) \) has no effect on KCL-induced contractions in isolated human internal mammary artery and saphenous vein rings (Fig. 1).

These results further demonstrate that sugammadex does not exert direct contractile or relaxation effects on human internal mammary artery and saphenous vein rings. Additionally, sugammadex does not have a direct effect on contractions induced by voltage-operated calcium channels in isolated
human arteries. In pharmacokinetic studies of volunteers administered clinically relevant doses of sugammadex (4–16 mg/kg), the plasma concentration was approximately $10^{-6}–10^{-5}$ M [4]. The concentration range used in our study ($10^{-6}–10^{-4}$ M) includes the range used in clinical practice. Even at concentrations exceeding the clinical dose, sugammadex had no effect on the isolated human arteries.

Sugammadex-induced hypotension and bradycardia have been reported in a case report and literature review [2]. Some of the suspected cases were thought to be linked to sugammadex hypersensitivity, as suggested by elevated serum tryptase levels and/or positive skin prick test results [2,5]. Our results showed that sugammadex has no direct relaxing effect on pre-contracted internal mammary artery and saphenous vein rings.

Furthermore, in a recent case report, coronary vasospasm and cardiac arrest occurred after sugammadex use in cardiac radiofrequency catheter ablation without signs of hypersensitivity [3]. The authors observed cardiac arrest in a patient with sudden ST elevation, confirmed by urgent coronary angiography showing total right coronary artery collapse. They concluded that the absence of hypersensitivity reactions suggested a direct effect of sugammadex on coronary vasospasm.

Another case report described anaphylactic-shock-induced coronary vasospasm resulting from the rocuronium-sugammadex complex [5]. Kounis syndrome is an uncommon acute coronary syndrome associated with allergic reactions. This syndrome results from inflammatory mediators, such as arachidonic acid metabolites, platelet-activating factors, and various cytokines, that are released from mast cells in hypersensitivity reactions.

In conclusion, sugammadex did not directly affect vascular contractility in isolated human internal mammary artery or saphenous vein rings. Therefore, the observed vasospasm reported in the above
cases was not likely a direct effect of sugammadex on vascular tone. Instead, it may be attributed to hypersensitivity reactions or changes in different mediators induced by sugammadex administration.
References


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Figure legends

**Figure 1.** Effect of sugammadex on KCl-induced contractions in A) isolated human internal mammary artery rings (n = 6*, P = 0.632) and B) isolated human saphenous vein rings (n = 6*, P = 0.958). Data are presented as the mean ± SD.

*The number of internal mammary artery or saphenous vein rings.