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

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Running title: Sugammadex and vascular reactivity

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

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

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

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

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

22 These results further demonstrate that sugammadex does not exert direct contractile or relaxation
23 effects on human internal mammary artery and saphenous vein rings. Additionally, sugammadex does
24 not have a direct effect on contractions induced by voltage-operated calcium channels in isolated

1 human arteries. In pharmacokinetic studies of volunteers administered clinically relevant doses of
2 sugammadex (4–16 mg/kg), the plasma concentration was approximately 10^{-6} – 10^{-5} M [4]. The
3 concentration range used in our study (10^{-6} – 10^{-4} M) includes the range used in clinical practice. Even
4 at concentrations exceeding the clinical dose, sugammadex had no effect on the isolated human
5 arteries.

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

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

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

21 In conclusion, sugammadex did not directly affect vascular contractility in isolated human internal
22 mammary artery or saphenous vein rings. Therefore, the observed vasospasm reported in the above

- 1 cases was not likely a direct effect of sugammadex on vascular tone. Instead, it may be attributed to
- 2 hypersensitivity reactions or changes in different mediators induced by sugammadex administration.

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Figure legends

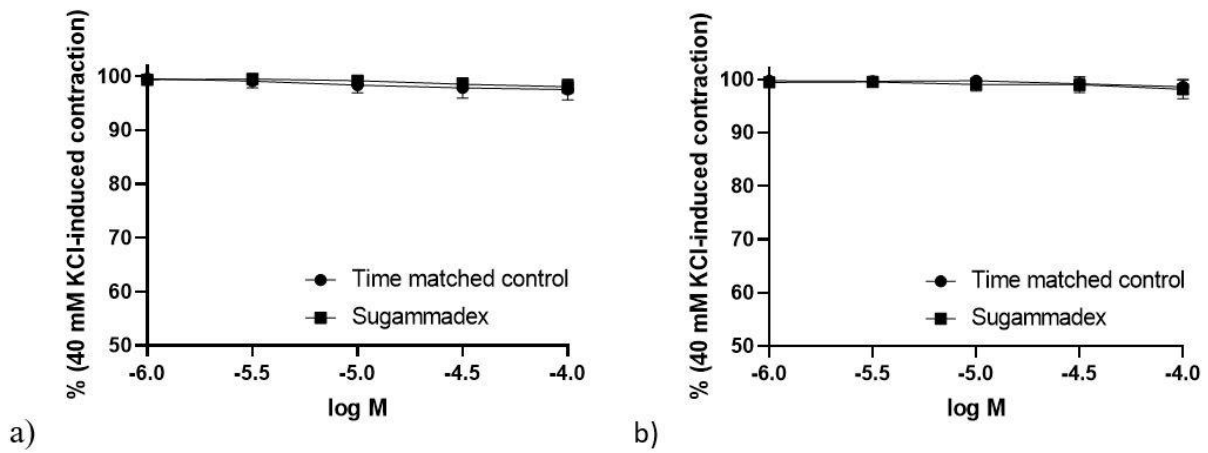


Figure 1. Effect of sugammadex on KCl-induced contractions in A) isolated human internal mammary artery rings ($n = 6^*$, $P = 0.632$) and B) isolated human saphenous vein rings ($n = 6^*$, $P = 0.958$). Data are presented as the mean \pm SD.

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