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Türk Hijyen ve Deneysel Biyoloji Dergisi

The role of endothelium and calcium and large conductance calcium-activated potassium channels in the effect of fospropofol on vascular smooth muscles

Fospropofolün vasküler düz kaslar üzerindeki etkisinde endotel, kalsiyum ve büyük iletkenli kalsiyumla aktive olan potasyum kanallarının rolü

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ABSTRACT

Objective: Regarding the unfavorable properties of propofol we investigated the effects of fospropofol, a water-soluble prodrug of propofol, on human internal mammary artery (IMA) rings, as an alternative. Since desired vascular tonus is crucial during cardiac surgery the effect of agents used for induction and/or sedation is important. To clarify the endothelium dependent and calcium and potassium channel modulated mechanism of action of these drugs will enable us to control the patients during and after surgery in intensive care period.

Methods: The arterial rings obtained from the remenants of the IMA used in 19 patients underwent coronary artery bypass grafting were mounted in the organ baths and stabilized under resting tension of 0.5-1 g in physiological Krebs solution at 37°C (gassed with 95%O_2 and 5% CO_2, pH=7.4). The basal and KCl (120mM)-stimulated vascular tonus and the effect

ÖZET

Amaç: Propofolün tolere edilmesi zor olan yan etkileri nedeni ile, alternatif molekül olarak bir propofol öncül molekülü olan ve suda çözünebilen fospropofolün insan internal meme arteri (İMA) halkaları üzerindeki etkilerini araştırmayı amaçladık. Kalp ve damar cerrahisi sırasında istenen damar tonusunun sağlanması kritik öneme sahip olduğu için anestezi indüksiyonu ve/veya sedasyon için kullanılan ajanların etkisi de dikkate alınmalıdır. Bu ilaçların endotel bağımlı, kalsiyum ve potasyum kanalıyla modüle edilen etki mekanizmalarının aydınlatılması, hastaların ameliyat sırasında ve sonrasında yoğun bakım döneminde kontrol altında tutulmasını sağlayacaktır.

Yöntem: Koroner arter bypass ameliyatı yapılan 19 hastadan elde edilen IMA parçalarının kullanılmayan bölümlerinden arter halkaları elde edildi ve organ banyolarına asıldı. Fizyolojik Krebs solüsyonunda (%95 O_2 ve %5 CO_2 ile gazlandırılan, pH=7,4, 37°C) 0,5-1 g gerim altında dengeye gelmeleri sağlandı. Bazal ve KCl

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of cumulative propofol (n=8) and fospropofol (n=11) (10^{-7}-10^{-5} M) was recorded. In another group of IMA segments same protocol of fospropofol was applied to endothel-intact and denuded vessels to investigate the role of endothelium. Then to understand the involvement of L-type Ca^{+2} and BKCa K^{+} channels, the vessels were preincubated by nifedipine (n=8) or iberiotoxin (n=7) followed by the KCl stimulation and fospropofol doses. All the arterial responses were recorded real-time by Biopac data acquisition and analysis system. The results were normalized by tissue weight and given as the percentage of KCl-induced contraction.

Results: Fospropofol caused less and later vasodilation compared to propofol ($p<0.05$). The role of endothelial layer in the vasodilatory role of fospropofol was shown by attenuated effect in endothel-denuded rings. Blocking BKCa potassium channels with iberiotoxin increased contraction and blunted the vasodilatory effect of fospropofol.

Conclusion: In conclusion, fospropofol appears to be a better alternative to propofol with potentially reduced risk of vasodilation-induced hypotension and maintaining vascular tone. further studies are required to validate these findings and to better understand its underlying mechanisms.

Key Words: Vascular tonus, smooth muscle, endotelium, fospropofol

(120 mM) ile uyarılan vasküler tonus ve propofol (n=8) ve fospropofol (n=11) (10^{-7}-10^{-5} M)'ün kümülatif olarak etkileri kaydedildi. Deney protokolünün diğer serisinde, endotel tabakasının rolünü araştırmak için endoteli sağlam ve haraplanmış damarlara yukarıdaki fospropofol protokolü uygulandı. Daha sonra L tipi Ca^{+2} ve BKCa K^{+} kanallarının etkisini göstermek için damarlar nifedipin (n=8) veya iberiotoksin (n=7) ile inkübe edildikten sonra KCl ile uyarıldı e fospropofol dozları uygulandı. Tüm kayıtlar Biopac veri toplama ve analiz sistemi ile gerçek zamanlı yapıldı. Damar cevapları, doku ağırlığına göre düzeltildi ve KCl uyarısı ile elde edilen kasılma cevabının yüzdesi olarak verildi.

Bulgular: Fospropofol, propofole göre daha az ve daha geç vazodilatasyona neden oldu ($p<0.05$). Fospropofolün vazodilatör etkisinde endotel tabakasının rolü endolteli haraplanmış dokulardaki azalmış gevşetici etki ile gösterildi. BKCa potasyum kanallarının iberiotoksin ile bloke edilmesi kasılmayı arttırdı ve fospropofolün vazodilatör etkisini azalttı.

Sonuç: Sonuç olarak, fospropofol, potansiyel olarak vazodilatasyona bağlı hipotansiyon riskini azaltıp vasküler tonusu korunması nedeniyle propofole için iyi bir alternatif gibi görünmektedir. Ancak bu bulguların doğrulanması ve altta yatan mekanizmaların daha iyi anlaşılması için ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Damar tonusu, düz kas, endotel, fospropofol

INTRODUCTION

Propofol is widely used as an intravenous general anesthetic and/or sedative-hypnotic agent. The main reasons for the widespread use of propofol are its rapid onset of action, short half-life and high clearance rate (1, 2). However, it contains serious side effects such as pain at the injection site, thrombophlebitis, hyperlipidemia, allergic reactions, infections and propofol infusion syndrome, which are thought to be related to the oil-in-water emulsion formulation of propofol (3). Fospropofol ($C_{13}H_{19}O_5PNa_2$; 2, 6-diisopropylphenoxymethyl phosphate disodium) is a recently developed water-soluble prodrug that is hydrolyzed by endothelial cell surface alkaline phosphatases to yield propofol, phosphate, and formaldehyde. It was approved by the FDA in 2008 for use in monitored anesthesia care sedation (1, 4, 5). The efficacy of fospropofol in the sedation has been investigated in patients undergoing

colonoscopy (6, 7), flexible bronchoscopy (8), minor surgical procedures and in ventilated ICU patients (5, 9). These trials have proven that fospropofol may be used safely in outpatient settings and offers the targeted level of sedation for brief diagnostic and therapeutic procedures. Furthermore, because fospropofol does not contain any lipid solvents, it may have additional advantages over propofol, such as a lower risk of infection or contamination, no risk of allergic reaction to the solvents in lipid-formulated propofol, and unfavorable plasma lipid profile when infused for a long time (1, 4). Moreover, propofol has been shown in several studies to promote vasodilation through various pathways (1, 10-12). Propofol induced hypotension is a common adverse effect, particularly noticeable in elderly and/or the individuals with high blood pressure. Although fospropofol is a prodrug and its side effects are widely known, there is no evidence in the literature that it causes hypotension by reducing vascular tone similar to propofol (13). Clinical studies have reported the incidence of hypotension with fospropofol use in humans to be approximately 4-6% (5). As, there is no report regarding the effects and possible mechanisms of action of fospropofol on human vascular smooth muscle (VSM), we aimed to demonstrate the *in vitro* effects of fospropofol on human internal mammary artery (IMA) rings, compare with propofol and investigate its mechanism of action.

MATERIAL and METHOD

The protocol was explained to the patients who are scheduled for coronary artery bypass graft (CABG) surgery. The patients, who agreed to participate and gave informed consent (n=19), were included to the study. The discarded parts of the IMA that were not used for grafting and considered as medical waste were used in the *in vitro* experiments conducted in Hacettepe University Medical Faculty Physiology Laboratory.

Tissue Preparation

The redundant distal end of the IMA was clipped off and immediately placed in cold- oxygenated Krebs-Henseleit (118.4 mM NaCl, 4.7 mM KCl, 1.2 mM KH_2PO_4, 1.2 mM $MgSO_4$, 25.0 mM $NaHCO_3$, 2.5 mM $CaCl_2$, 12.2 mM glucose; pH: 7.35-7.40) solution, maintained at +4°C, until it was delivered to the laboratory. The arterial segments were dissected gently from adhering fat and connective tissue and 3-4 mm long full thickness endothelium-intact and mechanically destructed endothel-denuded vascular rings were prepared (14, 15). The rings were mounted in a 10 mL double layered water bath filled with Krebs-Henseleit solution and gassed with 95% O_2 and 5% CO_2 at 37°C and attached to isometric force displacement transducer (MAY FDT 05, Commat, Ankara, Turkey). Contraction force of the arterial rings was recorded real time by data acquisition/analysis system (BIOPAC MP35, BIOPAC Systems Inc., Golenta, CA, USA). The rings were allowed to equilibrate under final resting tension of 0.5 g for at least one hour with washouts every 15 minutes. The ring in one of the baths was spared as the time control (TC). After equilibration all the rings were challenged with 80 mM KCl both to test their viability and to obtain the reference for maximum contraction (Figure 1).

Effect of Fospropofol or Propofol on KCl-Induced Contraction and Effect of Endothelial Layer

10 minutes after KCl stimulation fospropofol (n/N=11/11/group) or propofol (n/N=8/8) was applied to the bath fluids of endothelium-intact and endothelium-denuded rings cumulatively at 10^{-7}-10^{-5} M doses (16, 17) in 5 min intervals in different sets of experiments (Figure 1a).

Contribution of L type Ca+2 or Large Conductance Calcium-Activated Potassium (BKCa) Channel Inhibitors in the effect of Fospropofol on the Basal and KCl -Induced Contractions in the Endothel-intact and denuded arterial rings

To investigate the possible mechanism of action and the role of calcium and potassium channels in the effect of fospropofol on VSM, equilibrated IMA rings were either pre-incubated with Ca^{+2} channel blocker

nifedipine (10^{-5} M; n=8) (18-20) or K^+ channel blocker iberiotoxin (10^{-5} M, n=7) (21, 22) for 20 minutes. The rings were stimulated by KCl (80 mM) for 10 minutes, followed by the cumulative fospropofol (10^{-7}-10^{-5} M) application as described above. The consecutive fospropofol doses were applied in 5 min intervals. After completion of the protocols, 120 mM KCl was added to all of the baths and tissue viability is assured (Figure 1b).

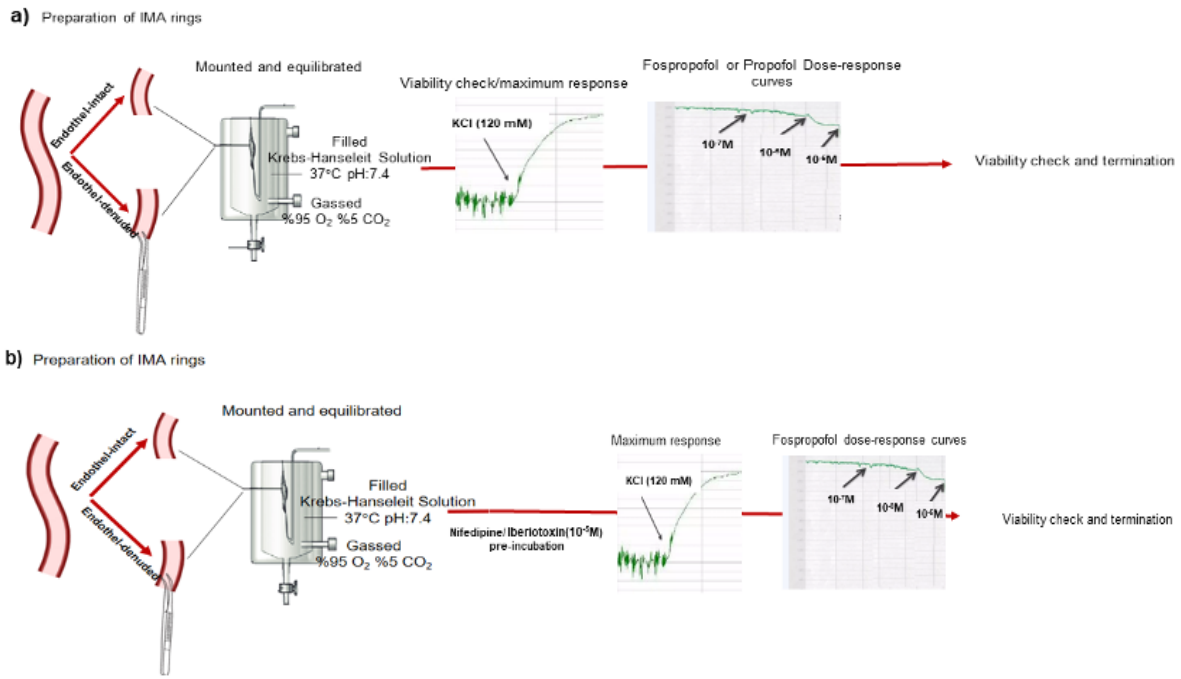

Figure 1. Summary of experimental protocol
a) Effect of propofol or fospropofol on endothel intact or denuded IMA rings
b) Effect of fospropofol on nifedipine or iberiotoxin exposed endothel intact or denuded IMA rings.

Chemicals

Drugs and carriers were freshly prepared and added directly into the bath in order not to exceed the volume more than 10%.

The chemicals used for Krebs Henseleit solution was purchased from Merck Co. Nifedipine (N7634 - Sigma), iberiotoxin (14008- Cayman), fospropofol (CS-O-01559 - Clearsynth) and propofol (A735445 – Toronto Research Chemicals) was generously gifted by Prof. Vedat Yıldırım MD.

Calculations and Statistics

The basal and stimulated contractions as well as the response to propofol or fospropofol was extracted from experimental records as maximum contraction and area under curve (AUC).

Both results of the tonus of the rings were first normalized for tissue weight (gram per 100 milligram of tissue: g/100 mg) and the effects of the drugs on contractions were evaluated as a percentage of maximum response to KCl-induced contraction.

Analysis was performed using Biopac MP36 BSL Pro 3.6.7 software and SPSS 23.0 statistical package for Mac OS. Data was first tested for normal distribution by Shaphiro-Wilk test and as parametric criteria has not been met, Related-Samples Friedman's Two-Way Analysis of Variance by Ranks was employed to compare different measurement points of the same ring. Independent-Samples Kruskal-Wallis Test was used to compare different protocols, followed by Mann-Whitney U test for pair-wise comparison when required. Bonferoni correction for *p* value was applied.

The results are presented as mean ± standard errors of mean (SEM). $p<0.05$ was considered to be statistically significant. The number of rings and patients were designated as "n" and "N", respectively.

The study was approved by the Health Sciences University, Gülhane Scientific Research Ethics Committee (Date: 08.04.2021 and Number: 2021/158).

RESULTS

The general characteristics of the patients whose arterial segments were analyzed in this study are presented in Table 1. The patients were comparable in terms of age and plasma lipid profiles; however, the only variable that differed significantly was smoking status, as all male patients had a history of smoking.

Table 1. The general properties of the participated patients

Patients	Age	Smoking (%)	Cholesterol (mg/dl)	Triglyceride (mg/dl)	HDL (mg/dl)	LDL (mg/dl)
Women (n=7)	67.6±8.9	15%	223.6±50.8	128.3±32.2	48.1±5.6	140.5±43.6
Men (n=12)	64.3±12.3	100%	203.1±48.9	117.7±55.8	36.9±5.3	105.6±33.1

HDL: High density lipoprotein, LDL: Low density lipoprotein

The first series of experiments aimed to compare the effects of fospropofol in contraction response of IMA rings with propofol. The cumulative dose (10^{-7}-10^{-5} M)-contraction-curves of propofol and fospropofol is given in figure 2. The basal tonus and maximum force of contraction when stimulated by KCl was similar for all of the rings. The propofol-treated rings dilated significantly more compared to fospropofol-applied IMA segments in each of the doses tried ($p<0.05$). On the other hand, both drugs caused attenuated tonus when compared to TC rings where no drug was applied after KCl stimulation, but this effect was only significant at the highest dose of fospropofol (Figure 2).

The timeline evaluation of the vasodilatory effect of fospropofol and propofol revealed significant difference, so that the main decrease in force of contraction occurred at the period between 3rd to 4th minute (8.68±0.76%) in fospropofol applied rings in contrast to the major observable effect recorded between first and second minutes of propofol application (11.26±3.95%). This finding indicated a faster vasodilatory response of propofol in comparison to fospropofol.

The second part of the protocol was designed to investigate the role of endothelial layer in fospropofol-induced relaxation. The cumulative dose-response curves were obtained in endothelium-intact and -denuded rings. The results revealed lack of vasorelaxant effect in endothelium-denuded samples (Figure 3) even at the highest dose applied and significant difference between endothel-intact and denuded rings' response.

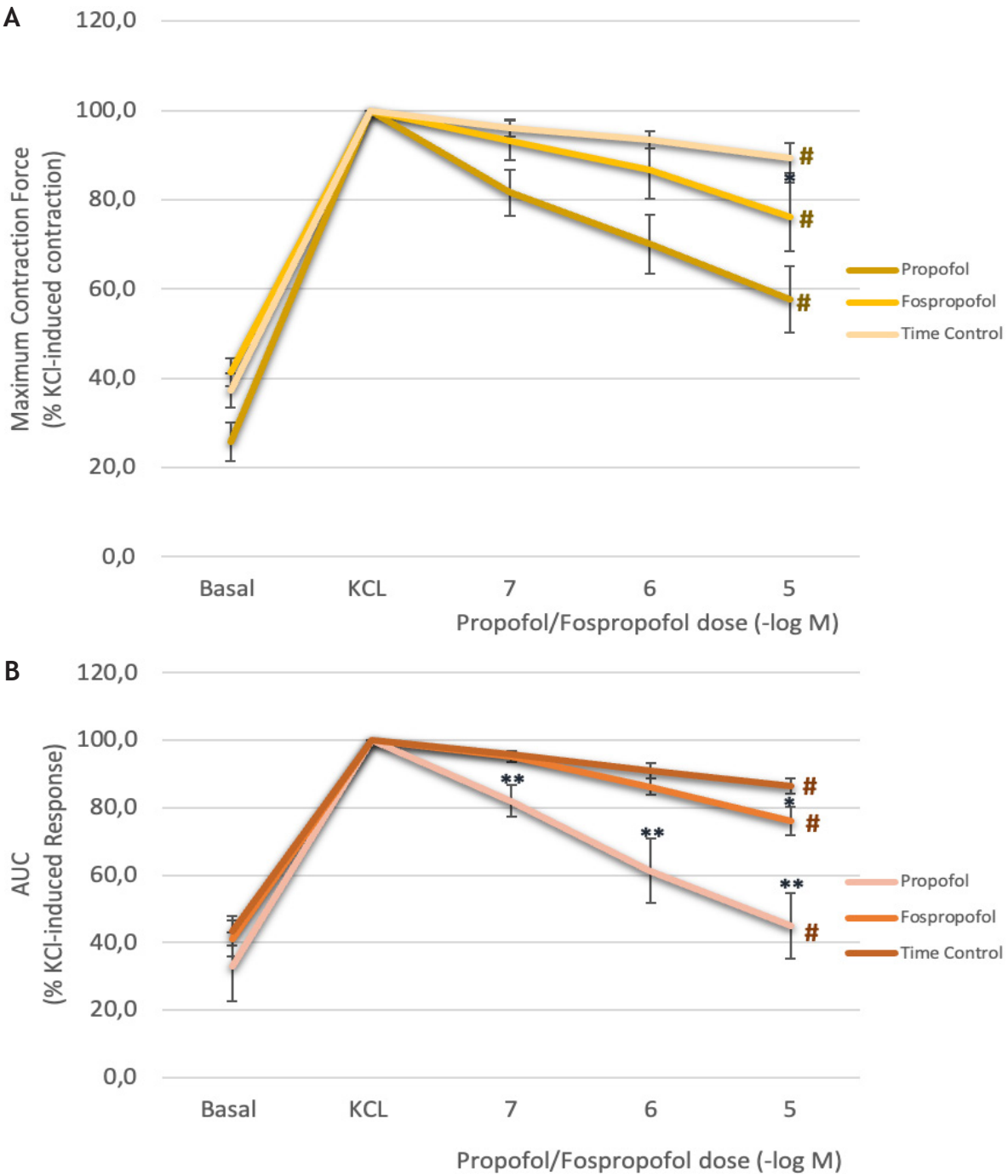

Figure 2. The response of the internal mammary artery rings under basal, KCl-stimulated (80 mM) and fospropofol or propofol (10^{-7} - 10^{-5} M) treated conditions

A) Maximum force of contraction B) Area under curve for 10 min. intervals.

Data (Mean ±SD) is given as the percent of KCl-stimulated response. *p<0.05 vs time control, **p<0.05 vs time control and fospropofol, # p<0.05 within group between consecutive doses

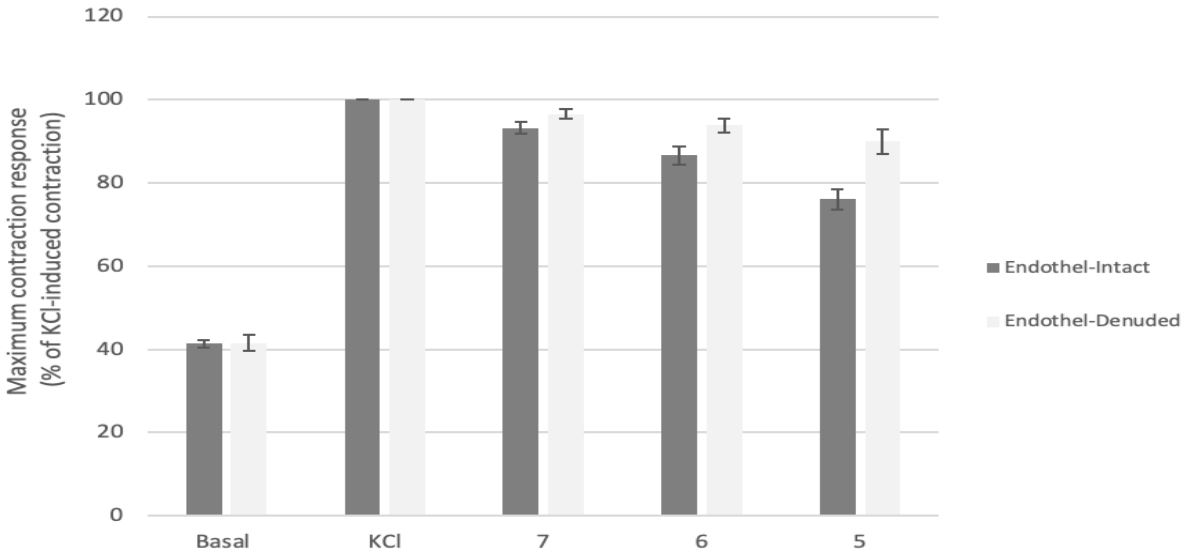

Figure 3. The maximum force of contraction of the endothel-intact and denuded internal mammary artery rings under basal, KCl-stimulated (80 mM) and fospropofol (10^{-7}-10^{-5} M) treated conditions. Data (Mean ±SD) is given as the percent of KCl-stimulated response. *p<0.05 vs endothel-intact, **p<0.05 vs KCl-stimulation.

Further we investigated the role of L type Ca^{+2} and Ca^{+2} activated large conductance BKCa channels in the effect of fospropofol (Figure 4). The application of Ca^{+2} channel blocker decreased vascular tonus both under basal and stimulated conditions and in response to fospropofol treatment (p<0.05 vs control and iberiotoxin pre-incubated rings). In contrary iberiotoxin application by blocking BK_{Ca} channels, slightly strengthen basal and KCl-stimulated contraction response and attenuated the vasodilatory effect of fospropofol (p<0.05 vs control). The results were similar for AUC (Figure 4 B). The evaluation of groups for cumulative effect of fospropofol revealed significantly increasing inhibition with each consecutive dose in control and nifedipine applied rings (p<0.05) whereas the force of contraction was comparable between fospropofol doses and to the maximum response in iberiotoxin exposed arterial rings (Table 2, Figure 4).

Table 2. The vasorelaxation response to fospropofol presented as percent inhibition of the KCl-stimulated contraction in the control rings

	Inhibition percentage of KCl- stimulated contraction (%)			
Fospropofol (M)	Control	Nifedipine	Iberiotoxin	***p****
10^{-7}	4.65	2.82	2.48	NS
10^{-6}	$13.58^{a,b}$	5.97^{d}	3.98^{d}	<0.05
10^{-5}	$23.91^{a,b,c}$	$9.18^{a,b,d}$	5.27^{d}	<0.05
p**	<0.005	<0.005	NS	

*Between-group comparison, **Within-group comparison
a) ***p***<0.05 vs Maximum contraction in the same group, b) ***p***<0.05 vs 10-7 M in the same group c) ***p***<0.05 vs 10-6 M in the same group d) ***p***<0.05 vs TC at the same concentration of fospropofol
Ca+2 channel blocker; nifedipine and K+ channel blocker; iberiotoxin preincubated IMA rings. The cumulative fospropofol application significantly increased inhibition in control and nifedipine applied rings.

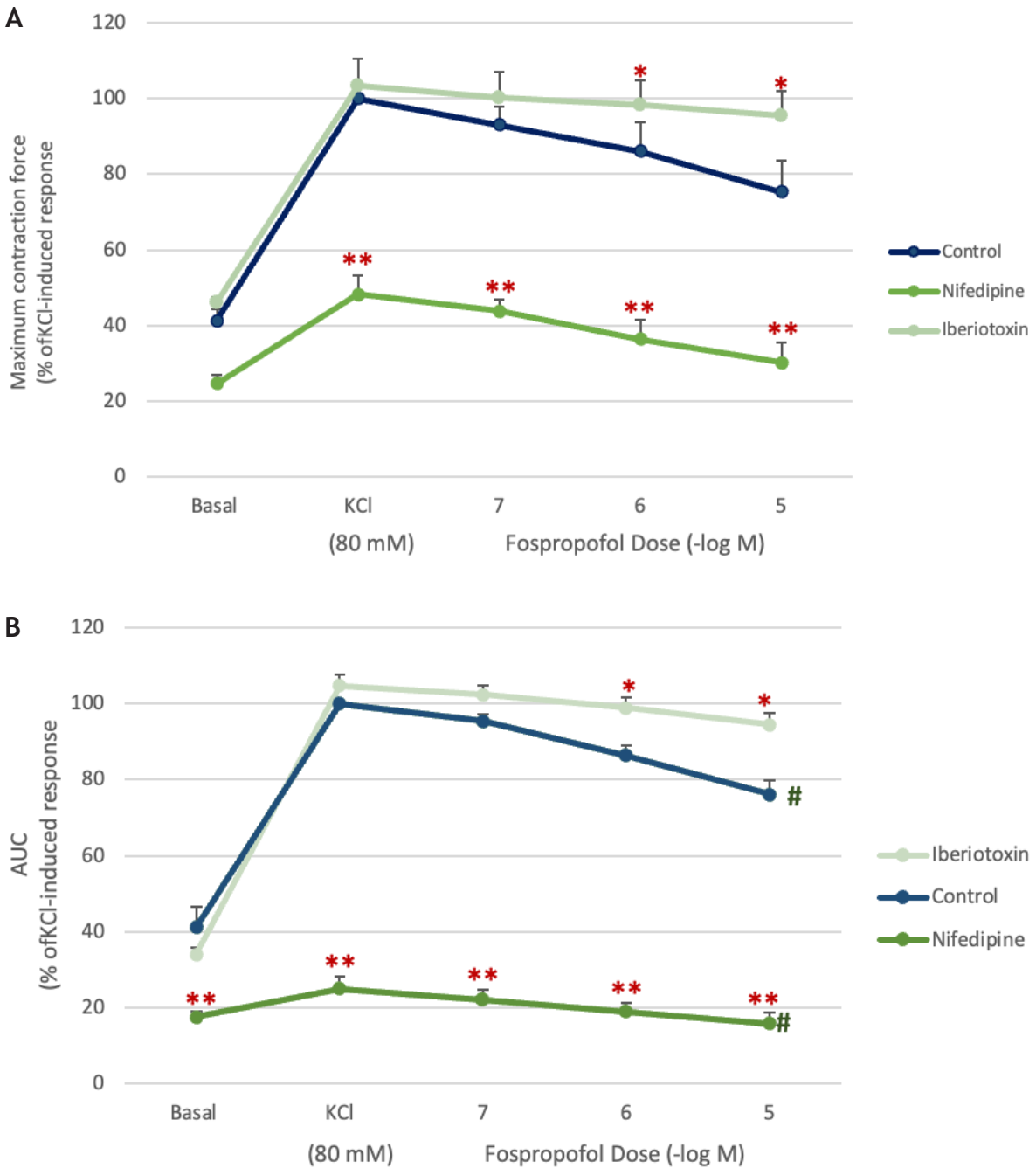

Figure 4. The response of the internal mammary artery rings under basal, KCl-stimulated (80 mM) and fospropofol (10^{-7} -10^{-5} M) treated conditions in control, iberiotoxin or nifedipine pre-incubated rings

A) Maximum force of contraction

B) Area under curve for 10min. intervals.

Data (Mean ±SD) is given as the percent of KCl-stimulated response. *p<0.05 vs Time-control, **p<0.05 vs control and iberiotoxin, # p<0.05 within group between consecutive doses.

DISCUSSION

In this study we investigated the comparative effect of fospropofol and propofol on basal and potassium-induced vascular tonus of IMA, and the role of endothelial layer. Our results indicated significantly lower vasorelaxant effect of fospropofol when compared to propofol, in addition to the involvement of endothelium in mediation of vascular tonus for fospropofol similar to propofol. Despite the various pharmacokinetic advantageous of propofol resulting in widespread use all over the world as an induction anesthetic and sedative-hypnotic (1), due to a wide range of side effects the search for an alternative molecule is on. As we showed significantly less impact of fospropofol on VSM; we examined the contribution of L-type Ca^{+2} and BK_{Ca} channels which are likely to be involved in the mechanism of action of fospropofol. Nifedipine almost nearly abolished the KCl-induced contractions, whereas iberiotoxin slightly enhanced vascular response and blunted fospropofol effect.

Fospropofol is the water-soluble phosphate ester of propofol and documented to act via metabolization to propofol (5). However, recent data attracts attention to mechanisms of action for fospropofol other than its metabolic conversion to propofol. The most likely mechanism is the metabolic side product, formate (23), which is a substrate for chloride-formate exchanger, which will end up with increased chloride efflux in exchange of increased extracellular formate (24) and result in increased depolarization in VSM i.e. increased tonus. On these bases to overcome the main obstacle in the use of propofol; vasorelaxation and associated hypotensive effect, fospropofol can be the best candidate for an alternative. The significantly less vasorelaxant effect for fospropofol in comparison to propofol in the present study, not only adds to the previously reported favorable profile for this molecule but also supports the ones suggesting other mechanisms besides its metabolization to propofol. Our results analyzed for the first time the timeline of the propofol and fospropofol effect, where the vasorelaxant effect of fospropofol was significantly later then its application in comparison to propofol. This finding adds to the favorable profile of fospropofol, so that management of the patients and the artery to be grafted is easier. This first study of fospropofol on human arterial VSM response suggests a safer profile in regard of hypotension risk.

As we have also shown, the endothelial layer of the vessels is crucial in vascular tone (14, 15) the role of endothelium in the action of propofol is controversial; there are reports indicating no endothelium involvement (1) as well as the ones pointing out its importance (25). In support of the latter one, we documented higher contractile response in endothelium-denuded IMA rings and less vasorelaxant effect.

Moreover, the results of various studies in various species reported endothelium-independent or dependent mechanisms or different ion channels in mechanism of action. That's why, we tested the *in vitro* effect of fospropofol on human arteries in Ca^{+2} channel and K^{+} channel blocked conditions. The need for calcium for any contractile mechanism is very well documented, and regarding the basic knowledge that high intracytoplasmic calcium concentration is achieved by the ion provided from extracellular fluid, the attenuated response to stimulation in nifedipine exposed IMA rings is expected (26, 27). The vascular contraction was already very low in amplitude, however, the vasorelaxant effect of fospropofol followed the same pattern as it was in control rings. This fact should bring another fact to our attention that in patients using calcium channel blockers the response of VSM will be very low.

In contrast to calcium channel blockage the rings exposed to BK_{Ca} inhibitor iberiotoxin exhibited higher contraction response and almost totally abolished relaxant effect of fospropol. The BK_{Ca} channels when activated results in hyperpolarization of VSM cell membrane due to increased K^{+} efflux and subsequent vasorelaxation. This mechanism was previously shown to be effective in the vasorelaxant response

of propofol (1). As a prodrug it is also involved in the mechanism of action of fospropofol on VSM.

The major limitation of this study is that the experiments were conducted on arterial segments obtained from patients who underwent coronary artery bypass grafting (CABG), who likely had varying degrees of changes. Therefore, the findings should be interpreted with caution and ideally repeated using healthy vascular tissues.

Considering the overall results, fospropofol appears to be a promising candidate due to its favorable pharmacological profile, controlled onset of action, and ability to maintain vascular tone—potentially minimizing both cardiovascular and other side effects associated with propofol. However, given that fospropofol, like propofol, exhibits endothelium-dependent effects, both agents should be used with caution in patients with suspected or known endothelial dysfunction. Similarly, their use should be carefully monitored in patients receiving calcium channel blockers.

ETHICS COMMITTEE APPROVAL

* The study was approved by the Health Sciences University, Gülhane Scientific Research Ethics Committee (Date: 08.04.2021 and Number: 2021/158).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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