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Original Article

# Taurine relaxes human radial artery through potassium channel opening action

Kemal Gokhan Ulusoy[1], Erkan Kaya[5], Kubilay Karabacak[2], Melik Seyrek[1], İbrahim Duvan[4], Vedat Yildirim[3], and Oguzhan Yildiz[1,*]

*Departments of [1]Medical Pharmacology, [2]Cardiovascular Surgery, [3]Anesthesiology, Gulhane Faculty of Medicine, University of Health Sciences, Ankara 06018, [4]Department of Cardiovascular Surgery, Guven Hospital, Ankara 06540, [5]Department of Cardiovascular Surgery, Gaziantep Faculty of Medicine, Gaziantep University, Gaziantep 27310, Turkey*

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***Correspondence**
Oguzhan Yildiz
E-mail: oguzhany01@gmail.com

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**ABSTRACT** The vascular actions and mechanisms of taurine were investigated in the isolated human radial artery (RA). RA rings were suspended in isolated organ baths and tension was recorded isometrically. First, a precontraction was achieved by adding potassium chloride (KCl, 45 mM) or serotonin (5-hydroxytryptamine, 5-HT, 30 μM) to organ baths. When the precontractions were stable, taurine (20, 40, 80 mM) was added cumulatively. Antagonistic effect of taurine on calcium chloride (10 μM to 10 mM) -induced contractions was investigated. Taurine-induced relaxations were also tested in the presence of the $K^+$ channel inhibitors tetraethylammonium (1 mM), glibenclamide (10 μM) and 4-aminopyridine (1 mM). Taurine did not affect the basal tone but inhibited the contraction induced by 5-HT and KCl. Calcium chloride–induced contractions were significantly inhibited in the presence of taurine (20, 40, 80 mM) ($p<0.05$). The relaxation to taurine was inhibited by tetraethylammonium ($p<0.05$). However, glibenclamide and 4-aminopyridine did not affect taurine -induced relaxations. Present experiments show that taurine inhibits 5-HT and KCl -induced contractions in RA, and suggest that large conductance $Ca^{2+}$-activated $K^+$ channels may be involved in taurine –induced relaxation of RA.

## INTRODUCTION

Taurine is a sulfur-derived conditional essential amino acid which is found in substantial amounts in many human and animal tissues. It is almost ubiquitous in distribution, with high concentration in electrically excitable tissues (heart and brain), retina, platelets and secretary structures [1]. It is suggested that taurine exerts a great variety of biological actions such as osmoregulation, membrane stabilization, conjugation of bile acids, neuromodulation, thermoregulation, detoxification, regulation of calcium homeostasis, antioxidation, and modulation of vascular function [1,2].

Several pharmacodynamics studies have shown that taurine induces hypotensive effects in human and animals [3]. Moreover, oral administration of taurine in hypertensive patients relieves hypertensive symptoms, and it also reduces brachial artery reactivity and arterial stiffness [4]. It has been suggested that both central and peripheral actions of taurine may be involved in its hypotensive effects [5].

In isolated animal arteries, taurine exerts vasodilation through endothelium-dependent and independent mechanisms [5]. Previous studies showed that taurine relaxed precontracted rabbit ear artery (REA), rat thoracic aorta (RTA), and rat mesenteric artery (RMA), *in vitro* [6-8]. Additionaly, Niu et al. [9] reported that taurine relaxed RTA, and rat renal artery (RRA) and RMA arterial rings trough large conductance $Ca^{2+}$-activated $K^+$ channel ($BK_{Ca}$) opening action. On the other hand, Liu et al. [10] reported that some potassium channels were involved in taurine-induced



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relaxation of the contractions in porcine coronary artery (PCA). However, they did not identify the type of potassium channel involved. We have recently shown that taurine relaxes human internal mammary artery (IMA), the graft of choice in coronary artery bypass grafting (CABG), through the activation of $BK_{Ca}$ [11].

Human radial artery (RA) is the frequently used arterial graft after IMA in both low- and high-risk patients undergoing CABG. However, because of its muscular structure, RA is susceptible to early spasm. Vasospastic tendency of RA grafts is usually countered in the operating room (immediately after harvest) by treating the artery with papaverine or milrinone, or both, and placing it in a bath of heparinized saline containing nitroglycerine (NTG) or a combination of NTG and a calcium channel blocker, such as Hong Kong Solution, to prevent spasms [12]. However, there is still a debate about which vasodilator solution is superior to other. This situation has been rationale to several studies. Nisanoglu et al. [13] compared 4 different agents (saline, nitroglycerin, diltiazem, papaverine) in order to evaluate pre- and postoperative flow rates and hemodynamic parameters. There was only mean flow rate increase in nitroglycerin group when compared to other groups [13]. Likewise, the use of intravenous or oral combinations of previously mentioned vasodilator drugs are recommended to avoid from immediate postoperative and post discharge vasospasm [14].

The long-term outcome after CABG depends on graft patency. RA grafts have 84~96% long-terms patency rates when used either aortocoronary bypass or as a composite graft [15,16]. Protective effects of some vasodilatory drugs were assessed in several studies [14,17]. However, data provided by these studies did not give enough opinion about expected protection from postoperative vasospasm of RA grafts with the study drugs.

Taurine may induce vasodilation through vascular smooth muscle or endothelial mechanisms. To our knowledge, the effects of taurine in human vascular beds and the underlying mechanism(s) are not well documented yet. The present experiments were designed to observe the effects of taurine on RA, and to explore its vasodilator mechanism(s) by studying the effects of different specific inhibitors of well-known mechanism(s) and endothelial denudation on the action of taurine.

# METHODS

## Tissue preparation

Approval to use discarded RA tissue was granted by the ethics committee of Gulhane Faculty of Medicine, and this investigation conforms to the principles outlined in the Declaration of Helsinki (2013). RA segments were obtained from patients undergoing CABG an immersed immediately in cold (4°C) Krebs-Henseleit solution (NaCl, 118 mM; KCl, 4.7 mM; $CaCl_2$, 2.5 mM; $KH_2PO_4$, 1.2 mM; $MgSO_4$, 1.2 mM; glucose, 10 mM; and $NaHCO_3$, 25 mM; pH 7.4). RA preparations were then transferred immediately to the laboratory where the adhering fat and connective tissue were removed, and they were cut into 3- to 4-mm length rings. The rings were suspended on L-shaped braces in 10 ml organ baths containing Krebs-Henseleit solution for tension measurement along the former circumferential axis. The solution within the bath was aerated with a mixture of 95% $O_2$ and 5% $CO_2$ at 37°C, pH 7.35~7.45 throughout the experiment. The upper hooks were connected to force-displacement transducers (model FT03, Grass Instruments, Astro-Med Inc, West Warwick, RI, USA). The changes in isometric force were recorded continuously with a multichannel recorder polygraph (model P122, Grass Instruments, Astro-Med Inc, West Warwick, RI, USA) by using computer software (Polyview, version 2.0, Grass Instruments, Astro-Med Inc, West Warwick, RI, USA). Passive resting tension was adjusted to 2.0 g and all consecutive measurements represented force generated upon this baseline. A 2 h equilibration period was allowed before the following four protocols being undertaken, and the rings were washed every 30 min during this time course. For testing the viability, RA rings were activated with 45 mM KCl after the equilibration period. The preparations that were contracted more than 2 g were included in the experiments. The tissues were washed every 10 min during 30 min until baseline was reached.

## Effects of taurine on basal tone

In some experiments, cumulative concentrations (20, 40, 80 mM) of taurine were added to organ bath to test its effect on basal resting tone, and changes in tension were recorded.

## Effects of taurine on RA rings precontracted with KCl and serotonin (5-hydroxytryptamine, 5-HT)

In some experiments, each adjacent RA ring was incubated with one of the taurine concentrations (20, 40 or 80 mM), in separate organ baths, 20 min before contraction either with KCl (45 mM). In another set of experiments, 5-HT (30 μM) precontraction was used instead of KCl precontraction for the same experimental procedure mentioned above. In other experiments, the RA preparations were incubated with taurine (80 mM) for 20 min and then the contractions to KCl (11, 22, 45, 68 mM) were tested in the absence and presence of taurine.

## Effects of taurine on $CaCl_2$-induced contractions in RA rings

In another set of experiments, to investigate the $Ca^{2+}$-channel antagonistic of taurine, concentration-response curves to $CaCl_2$ (10 μM to 10 mM) were obtained in the absence and presence of taurine (20, 40, 80 mM) as described previously [11,18,19]. In this protocol, following the equilibration, RA rings were first

challenged with 45 mM KCl to test tissue viability, and then the rings were washed three times at 15-min intervals with $Ca^{2+}$-free Krebs solution containing 1 mM ethylenediaminetetraacetic acid (EDTA, disodium salt). Then, the rings were incubated with $Ca^{2+}$-free (containing 1 mM EDTA) high KCl (45 mM) Krebs solution with or without taurine (20, 40, 80 mM) for 20 min. Then, cumulative concentration-response curves to $CaCl_2$ (10 μM to 10 mM) were constructed.

### Influence of endothelium on taurine responses

To investigate the effect of endothelial denudation, the endothelial layer of some RA segments were removed by mechanical rubbing with a wire. The arterial rings were first precontracted with 45 mM KCl, then the relaxation to acetylcholine (ACh, 1 μM) was tested to evaluate the success of endothelial denudation. In endothelium-denuded and -intact preparations, taurine (20, 40, 80 mM) was added to organ bath after precontraction with KCl (45 mM), and the relaxations to taurine were compared with control taurine responses.

In additional set of experiments, effects of nitric oxide synthase (NOS) and cyclooxygenase (COX) inhibitors on taurine responses were tested. After the equilibration period, arterial rings were challenged with 45 mM KCl to test their viability. Then, the tissues were washed out every 10 min for three times in waiting period. Before precontraction with the depolarizing agent KCl (45 mM), the rings were incubated with COX inhibitor indomethacin (10 μM) and NOS inhibitor L-NAME (100 μM).

### Experiments with selective $K^+$ channel inhibitors

In these experiments, after the equilibrium and challenge with KCl (45 mM), the rings were incubated with either $BK_{Ca}$ and voltage-sensitive $K^+$ channel ($K_v$) inhibitor TEA (1 mM), ATP-sensitive $K^+$ channel ($K_{ATP}$) inhibitor glibenclamide (10 μM), $K_v$ inhibitor 4-AP (1 mM) or inward rectifier $K^+$ channel ($K_{IR}$) inhibitor $BaCl_2$ (30 μM) for 30 min, and relaxations to taurine (20, 40, 80 mM) were recorded.

### Chemicals

Taurine, glibenclamide, indomethacin, Nω–nitro-L-arginine methyl ester (L-NAME), and $BaCl_2$ were purchased from Sigma Chemical (St Louis, MO, USA). KCl and TEA were obtained from Merck (Darmstadt, Hessen, Germany). 4-Aminopyridine (4-AP) was purchased from Acros Organics (Thermo Fischer Scientific, New Jersey, NJ, USA).

### Statistical methods

The KCl, 5-HT and $CaCl_2$ responses in presence and absence of taurine were expressed as % of maximum KCl contraction as arithmetic mean±SEM in each corresponding tissue. Comparison among multiple groups was made by using a one-way ANOVA followed by Scheffe's post hoc procedure to determine significant differences among the means of the data groups. Statistical significance between two groups was evaluated by Student's *t* test for paired data when it's suitable. A probability of $p<0.05$ was considered statistically significant. In all experiments, n represents the number of RA segments from different patients.

## RESULTS

KCl (45 mM) elicited marked contractions with stable plateau upon the basal resting tone of RA preparations. However, cumulative concentrations of taurine (20, 40, 80 mM), with 10 min intervals after each concentration, did not significantly influence the basal resting tone (n=6, data not shown).

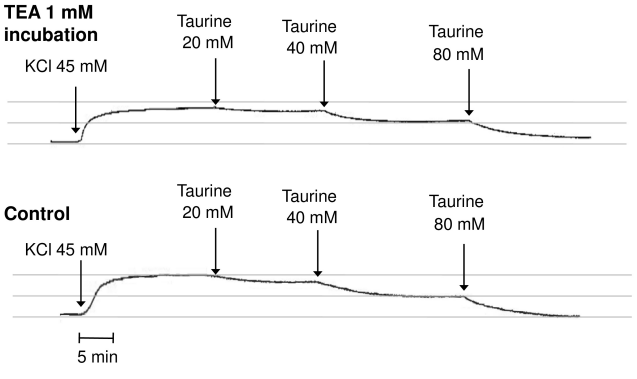


**Fig. 1.** Original tracings showing vasorelaxations to taurine (20, 40, 80 mM) in KCl (45 mM) -precontracted human radial artery rings in the absence (control) and presence of tetraethylammonium (TEA, 1 mM).

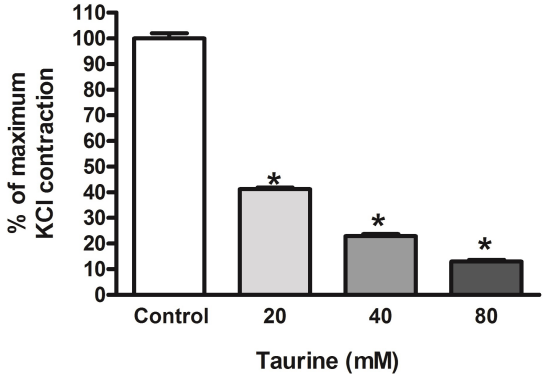


**Fig. 2. Effects of incubation with taurine (20, 40 or 80 mM) for 20 min on contractions induced by KCl (45 mM) in human radial artery rings (n=6).** Each value represents mean±S.E.M. and it is calculated as the percentage of the first KCl (45 mM) -induced contraction in the same ring. Vertical bars represent S.E.M. *p<0.001 compared with control.

In another experimental protocol, cumulative concentrations of taurine (20, 40, 80 mM) produced significant relaxations after precontraction of KCl (p<0.001, n=6) (Fig. 1). Moreover, incubation of taurine (20, 40 or 80 mM) for 20 min decreased KCl (45 mM)-induced contractions in a concentration dependent manner (Fig. 2). In addition, 5-HT (30 μM) evoked strong contractions in RA. Incubation with taurine (20, 40 or 80 mM) for 20 min significantly decreased 5-HT-induced contractions in correlation with the increasing concentrations of taurine (p<0.001, n=6) (Fig. 3).

Additionally, incubation with taurine (80 mM) significantly antagonized KCl (11, 22, 45, 68 mM) induced contractions (p<0.001, n=6) (Fig. 4).

In another experimental protocol, cumulative concentrations of $CaCl_2$ (10 μM to 10 mM) contracted RA preparations in a concentration-dependent manner. Incubation with 20, 40, 80 mM taurine inhibited $CaCl_2$-induced contractions significantly (p<0.001, n=6) (Fig. 5).

In endothelium-intact RA segments, relaxations to taurine (20, 40, 80 mM) were similar with endothelium-denuded preparations (n=3, data not shown). Additionally, COX inhibitor indomethacin or NOS inhibitor L-NAME did not affect taurine-induced relaxations (n=4, data not shown).

The roles of $K^+$ channels in vasodilation mechanism were evaluated in detail by using selective $K^+$ channels antagonists. While the $K^+$ channel inhibitors glibenclamide, 4-AP and $BaCl_2$ did not effect taurine-induced relaxations in KCl-precontracted RA preparations, TEA inhibited taurine responses significantly (p<0.01 and p<0,001, n=6) (Figs. 1 and 6).

## DISCUSSION

In the present study, we have demonstrated for the first time

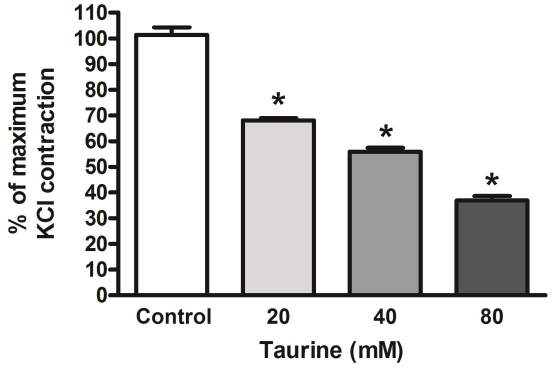


**Fig. 3. Effects of 20 min incubation with taurine (20, 40, 80 mM) on contractions induced by 5-HT (30 μM) in human radial artery preparations (n=6).** Each value represents mean±S.E.M. and it is calculated as the percentage of the first KCl (45 mM)-induced contraction in the same ring. Vertical bars represent S.E.M. *p<0.001, compared with control.

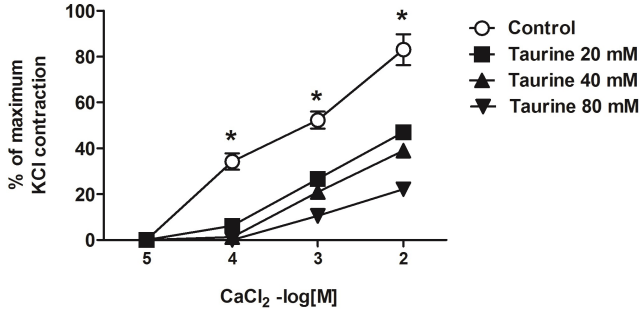


**Fig. 5. Inhibitor effects of 20 min incubation with taurine (20, 40, 80 mM) on contractions induced by $CaCl_2$ ($10^{-5}$ to $10^{-2}$ M) in human radial artery preparations (n=6).** Each value represents mean±S.E.M. and it is calculated as the percentage of the first KCl (45 mM)-induced contraction in the same ring. Vertical bars represent S.E.M. *p<0.001 compared with taurine (20, 40, 80 mM).

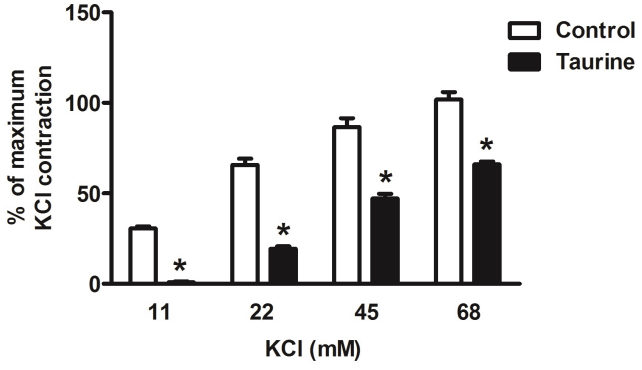


**Fig. 4. Inhibitor effects of 20 min incubation with taurine (80 mM) on contractions induced by KCl (11, 22, 45, 68 mM) in human radial artery preparations (n=6).** Each value represents mean±S.E.M. and it is calculated as the percentage of the first KCl (45 mM)-induced contraction in the same ring. Vertical bars represent S.E.M. *p<0.001, compared with corresponding control.

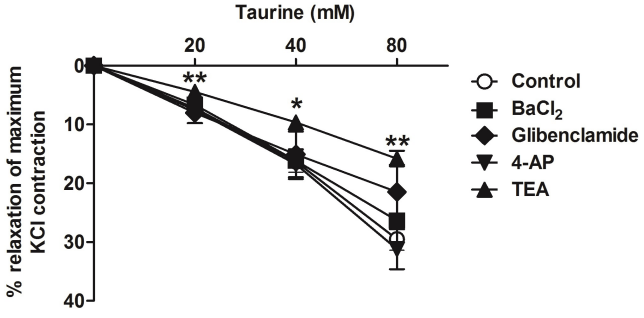


**Fig. 6. Vasorelaxations to cumulative concentrations of taurine (20, 40, 80 mM) in human radial artery rings precontracted with 45 mM KCl in the presence of tetraethylammonium (TEA, 1 mM), 4-aminopyridine (4-AP, 1 mM), barium chloride ($BaCl_2$, 30 μM) and glibenclamide (GLI, 10 μM).** Each value represents mean±S.E.M. and it is calculated as the percentage of the first KCl (45 mM)-induced contraction in the same ring (n=7~11). Vertical bars represent S.E.M. *p<0.01, **p<0.001 compared with corresponding control.

that taurine may induce relaxation in RA in vitro. While taurine did not significantly change the basal resting tone of RA, it relaxed KCl, 5-HT or $CaCl_2$-precontracted RA preparations. Taurine-induced relaxations might be mediated through opening of $BK_{Ca}$, since the vasorelaxations were nearly abolished by $BK_{Ca}$ and $K_v$ inhibitor TEA, and selective $K_v$, $K_{ATP}$ and $K_{IR}$ inhibitors did not affect taurine responses. Additionally, endothelial denudation did not effect taurine responses, and the vasorelaxant effect of taurine was not mediated via endothelium dependent nitric oxide (NO) or prostanoid-mediated mechanisms.

Previously, the vasorelaxant effects of taurine were reported in some animal arteries such as REA, RTA, RMA, RRA, and PCA [6,8-10,20,21]. Recently, we have reported that taurine antagonizes and relaxes the contractions of IMA [11]. While all of these studies are in conformity that taurine relaxes contracted arteries, there are differences on whether taurine affects the basal resting tone. While taurine did not affect the basal resting tone in REA and PCA, it reduced the basal tone in RTA [6,7,10]. In our recent study, we have shown that taurine does not influence the basal tone in IMA [11]. Likewise, in the present study; incubation with taurine did not significantly change the basal resting tone in RA. Moreover, the maximum magnitude of taurine-induced relaxation in RA (30~40%) was similar to those observed in some animal arteries and IMA [6,10,11].

Previous studies are also consistent in that taurine may induce relaxation of animal and human arteries precontracted by various stimuli. Previously, depolarizing substance KCl and/or α-adrenoceptor agonist noradrenaline were used to produce precontraction, and taurine induced relaxations were observed in RTA, RMA, RRA and REA [6,7,9,21]. Moreover, Liu et al. showed that taurine relaxed precontractions with histamine, 5-HT, $CaCl_2$ and thromboxane $A_2$ analog U46619 in PCA [10]. Likewise, we have recently shown that taurine relaxes IMA precontracted with KCl, 5-HT or $CaCl_2$ [11]. The present study adds to previous studies, since we have shown that taurine may relax RA contraction induced by various stimuli.

The present study, together with the previous reports, shows that taurine is not selective against various precontracted stimuli. The reason of this nonselective action of taurine could be related to its interference with a common contractile pathway. $Ca^{2+}$ is the common activator of vascular contraction, and it may be originated from different sources related to various mechanisms. The millimolar concentrations of KCl depolarize the smooth muscle cell membrane, and it causes activation of voltage-operated $Ca^{2+}$ channels. Histamine, 5-HT or U46619 are coupled to their specific receptors, which specifically activate receptor operated calcium channels (ROCC) [22]. The agonist mentioned above are coupled to their receptors which activate both $Ca^{2+}$ influx through ROCC and $Ca^{2+}$ release from the intracellular stores [22]. Thereupon, a common mechanism shared by the various stimuli related to intracellular $Ca^{2+}$ concentrations may be involved in taurine-induced relaxations.

To date, several researchers have studied the exact mechanism of taurine-induced relaxation, and recent evidence suggests that $K^+$ channel-mediated mechanisms may be relevant to vasodilator effects of taurine. Liu et al. suggested that activation of some $K^+$ channels, specifically $K_{IR}$, $K_{ATP}$, and $BK_{Ca}$ might be relevant to taurine-induced relaxation of PCA [10]. In RRA, RMA and RTA, it was suggested that vasodilator effect of taurine was mediated through TEA-sensitive $K^+$ channel namely $BK_{Ca}$ [9,21]. Involvement of $BK_{Ca}$ was also shown in RTA obtained from either normal or insulin-resistant rats, although taurine-induced vasodilation was altered in insulin-resistant rats compared to normal rats [23]. We have recently shown that $BK_{Ca}$ might be relevant to the vasodilator effect of taurine in IMA [11]. In the present study, we have demonstrated that vasorelaxation to taurine may be mediated by increasing $K^+$ efflux through $BK_{Ca}$, but not via $K_{ATP}$ or $K_v$, since the vasorelaxations were nearly abolished by $BK_{Ca}$ and $K_v$ inhibitor TEA, and selective $K_v$, $K_{ATP}$ and $K_{IR}$ inhibitors did not affect taurine responses. The present experiments also showed that the relaxation induced by taurine of precontracted RA was not affected by endothelial denudation or pretreatment with L-NAME or indomethacin. Therefore, these results suggest that endothelium, NO or prostanoid-mediated mechanisms are not relevant to vasodilator effect of taurine.

Taurine may have myocardial protective effects. In some tissues, when cells are damaged, the concentrations of taurine may increase over 10 mM, and huge amounts of taurine may be released in to the adjacent interstitial fluid [24-26]. It is well known that excessive amounts of $K^+$ is released from damaged cells when myocardium or other tissue is ischemic or injured. Thereupon, elevation of extracellular $K^+$ may lead to membrane depolarization in nearby cells, which eventually results in $Ca^{2+}$ influx, parenchymal cell $Ca^{2+}$ overload and/or vasoconstriction. Eventually, this contractile status induced by increased $K^+$ concentrations would further decrease blood flow to the ischemic tissue area. On the other hand, excessive amounts of taurine, released from damaged cells, may antagonize $Ca^{2+}$ overload and contractile status, and it may even induce vasodilation. Hence, taurine may be an important local endogenous factor with anti-ischemic effects in key processes in ischemia-reperfusion mediated cell death. For this reason, the results of the present study may contribute to our knowledge about roles of taurine in cardiovascular events, and its clinical implications in avoiding cardiac damage during bypass surgery, heart transplantation and myocardial infarction [27,28].

Due to above mentioned properties of taurine, and in consistence with our findings, it may be used for graft protection in the early period after graft harvesting, early and long-term postoperative period. Since RA grafts are prone to vasospasm in the harvesting period, taurine may be added to graft protection solutions in combination with several other vasodilatory agents such papaverine, verapamil, diltiazem and nitroglycerin. Furthermore, taurine may be used as an adjuvant treatment agent in

combination with $Ca^{2+}$ channel blockers in long term period either as a drug or as a dietary supplement in order to increase long term patency rates. However, further studies needed to prove its mentioned effects.

The main findings of our study should be assessed though within the study limitations, i.e. we studied with RA only, and we cannot extrapolate our results to other human arteries. We have shown that $BK_{Ca}$ may be involved in vasodilator effect of taurine, and we have used specific $K^+$ channel antagonists to reach this conclusion. Further studies, especially with cellular patch-clamp techniques, are crucial to clarify the exact mechanism of taurine–induced vasodilation.

## CONCLUSION

In conclusion, our study is unique to show taurine-induced vasodilation in a human artery, the RA. The underlying mechanism of relaxant effect of taurine in RA may be through opening of $BK_{Ca}$. Pathophysiological role of taurine in cardiovascular events needs to be explored further. From clinical standpoint, taurine may be used for prevention of early graft spasm and for better long-term patency rates.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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