

## Clinical Implications of Topographic Anatomy on the Ganglion Impar

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THE blockade of the ganglion impar, a single ganglion converged by the caudal ends of the two sympathetic trunks, has been described to relieve the intractable perineal pain of sympathetic origin in patients with rectal, anal, colon, bladder, or cervical cancer.<sup>1-3</sup> The success rate of this method depends on the anatomical variability of the location of the ganglion,<sup>4</sup> but its location has been variably reported from the anterior to the sacrococcygeal joint<sup>1-4</sup> or the coccyx,<sup>5-8</sup> to the tip of the coccyx.<sup>9</sup> Accordingly, this study was performed to identify the location of the ganglion impar and to determine its shape and size and its topographic relation with the branch of the sacral nerve, in the hope that this might facilitate a more successful blockade of the ganglion.

### Materials and Methods

Fifty sacra and coccyges were removed and dissected under the surgical microscope (Carl Zeiss, Oberkochen, Germany). Four to five pairs of sacral ganglia were found after removing the fascia and fat tissue. The caudal ends of the two trunks converged into a single ganglion at diverse sites on the coccyx. Distances of the ganglion impar along the medial line from the mid sacrococcygeal joint (X) to the tip of the coccyx (Y) were measured using a digital caliper (Mitutoyo, Kawasaki, Japan), and the relative index was calculated as  $X/X + Y$ . The distance from the mid sacrococcygeal joint to the tip of the coccyx was measured for the size of the coccyx. The Pearson correlation coefficient ( $r$ ) between the size of the coccyx and the distance of the ganglion impar from the tip of the coccyx was calculated.

### Results

The shape of the ganglion was classified as oval (26%), irregular (20%), triangular (14%), elongated (10%), rectangular (8%), and U shaped (8%). In 14% of the samples,

two caudal ends of the sympathetic trunks were connected without forming a recognizable ganglionic shape. The average long and short diameters of the ganglion were 2.5 and 1.1 mm for the oval type, 4.2 and 2.5 mm for the irregular type, 1.9 and 1.3 mm for the triangular type, 1.8 and 0.7 mm for the rectangular type. The average length of the elongated type was 4.4 mm.

The average distances of the midpoint of the sacrococcygeal joint and the tip of the coccyx to the ganglion impar were 8.6 mm (0-19.3 mm) and 25.0 mm (10.7-37.4 mm), respectively. The relative index of the location of the ganglion impar was calculated from the determined distances, as described in the Materials and Methods. Its value varied from 0 to 0.6, with a median and average value of 0.3 (fig. 1). The frequency according to the distance of the ganglion impar from the tip of the coccyx was also calculated (fig. 2). The size of the coccyx ranged from 18.2 to 48.1 mm, with a mean of 33.3 mm. The relation between the size of the coccyx and the distance of the ganglion impar from the coccygeal tip was statistically significant ( $P < 0.001$ ) (fig. 3).

The branch from the ventral ramus of the sacral nerve was observed to run close to the ganglion impar in one (4%) or both sides (2%). The shortest distance between the nerve branch and the ganglion impar ranged from 2.8 to 10.3 mm, with a mean of 6.3 mm. One or two coccygeal ganglia were observed in 12% of the samples.

### Discussion

Since the blockade of the ganglion impar was first introduced for the management of intractable perineal pain in 1990 by Plancarte *et al.*, a number of modified methods have been reported, including the transsacrococcygeal ligament placement of a needle,<sup>1</sup> the application of a curved needle,<sup>2</sup> and cryoablation through the sacrococcygeal disc.<sup>4</sup> However, the nature of the perineal pain that can be relieved by the ganglion blockade is neuropathic; hence, the perineal pain due to the somatic invasion of malignancies is not the appropriate indication for the blockade of the ganglion impar. Ganglion blockade was also reported to be effective in the treatment of hyperhidrosis in the perineum and buttock.<sup>10,11</sup> Although successful blockade of the ganglion impar depends on accurately locating the ganglion,<sup>4</sup> its location has been described inconsistently. Previous reports on the blockade of the ganglion depicted its location anterior to the sacrococcygeal joint,<sup>1-4</sup> but anatomy textbooks locate it anterior to the coccyx<sup>5-8</sup> or at the tip

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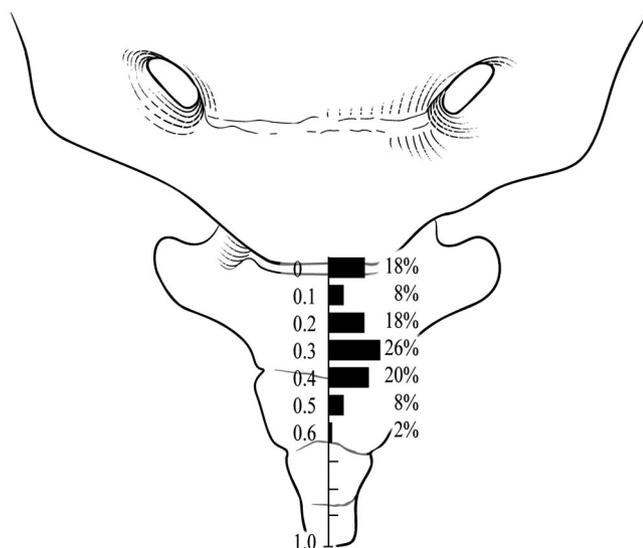


Fig. 1. The locations of the ganglion impar, in terms of relative index.

of the coccyx.<sup>9</sup> The current study makes plain the wide range of sizes of the coccyx and distances of the ganglion impar from the coccygeal tip, and the significant correlation between them. The diverse locations of the ganglion impar were represented by a relative index, and the value of this index varied from 0 (locating it at the sacrococcygeal joint) to 0.6 (below the midpoint of the line joining the midpoint of sacrococcygeal joint and the tip of the coccyx). The median and average index value was 0.3, which was the midpoint between the two sites with relative indexes of 0 and 0.6. This result implies that the needle for the blockade of the ganglion impar should be directed toward the site with an index value of 0.3 rather than at the sacrococcygeal junction, the conventional injection site in previous reports.<sup>1-4</sup>

The branches from the ventral ramus of the sacral

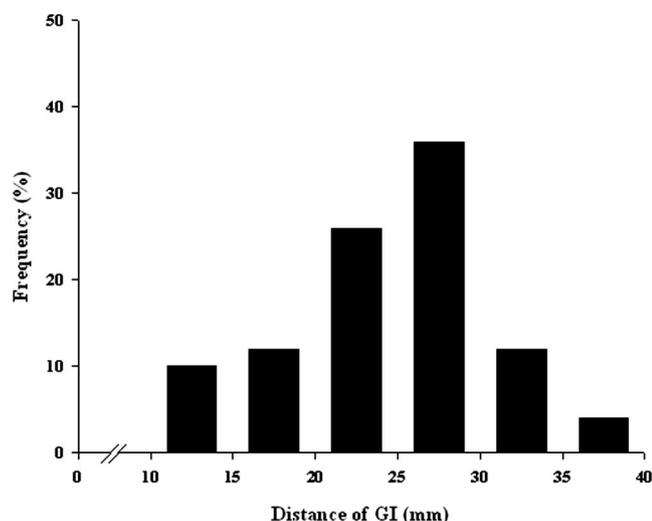


Fig. 2. Frequency of the distance of the ganglion impar (GI) from the tip of the coccyx.

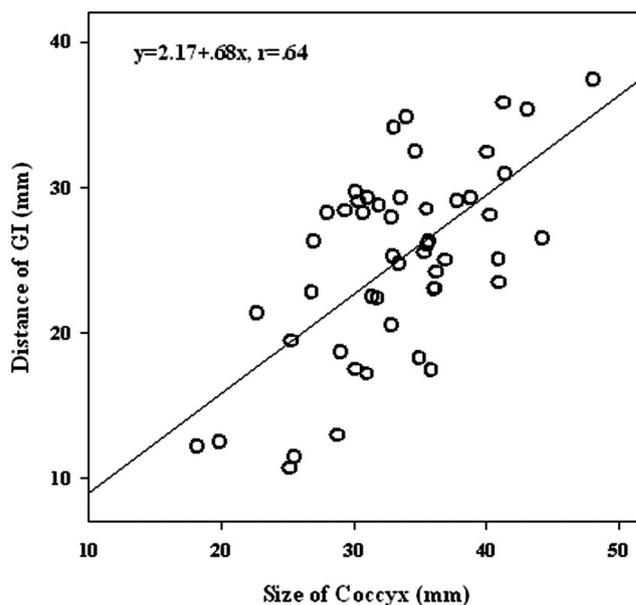


Fig. 3. Correlation between the size of the coccyx and the distance of the ganglion impar (GI) from the tip of the coccyx.

nerve were observed to run close to the ganglion impar in 3 of the 50 samples. Considering the risks of the development of neuritis and neuralgia after chemical neurolysis,<sup>12</sup> this finding suggests that the amount of blocking agents should be minimized to avoid possible injury of the sacral nerve branch. However, the determination of the minimal and optimal amounts of blocking agents requires further clinical investigation.

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## Effects of Bupivacaine Enantiomers and Ropivacaine on Vasorelaxation Mediated by Adenosine Triphosphate-sensitive $K^+$ Channels in the Rat Aorta

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THE actions of local anesthetics on the nervous system are reportedly related to their effects on  $K^+$  as well as  $Na^+$  channels in neurons.<sup>1</sup> Importantly, among these  $K^+$  channels in the nervous system, a voltage-insensitive flickering  $K^+$  channels has been found to be more sensitive than the  $Na^+$  channel to lipophilic, amide-linked local anesthetics, especially to the piperidine derivatives bupivacaine and ropivacaine.<sup>2,3</sup> The flickering  $K^+$  channel was mostly found in thin, myelinated nerve fibers, and it is a possible candidate for generating the resting potential of these fibers.<sup>4</sup> Therefore, these results indicate that the inhibition of  $K^+$  channels contributes to the action of bupivacaine and ropivacaine on the nervous system.

Cumulative findings have demonstrated that  $K^+$  channels play crucial roles in physiologic and pathophysiologic vasodilation.<sup>5-7</sup> Although *S*(-)-bupivacaine is less toxic on cardiac function or the central nervous system than racemic bupivacaine,<sup>8,9</sup> the effects of bupivacaine enantiomers on  $K^+$  channels of vascular smooth muscle have not been studied. In addition, whether the *S*(-)-enantiomer ropivacaine affects these channels of vascular smooth muscle has been unknown.

Therefore, the current study was designed to determine the potency of amide-linked long-acting local anesthetic drugs on  $K^+$  channels of vascular smooth muscle, by examining whether bupivacaine enantiomers as well as ropivacaine modify vasorelaxation induced by an adenosine triphosphate (ATP)-sensitive  $K^+$  channel opener in the isolated rat aorta.

### Materials and Methods

The institutional animal care and use committee (Wakayama, Japan) approved this study. Male Wistar rats

(weight, 250–350 g) were anesthetized with inhalation of 3% halothane. Under this anesthetic condition, the rats were killed by exsanguination, and thoracic aortas were harvested. Thoracic aortic rings of 2.5 mm in length were studied in modified Krebs-Ringer's bicarbonate solution (control solution) of the following composition: 119 mM NaCl, 4.7 mM KCl, 2.5 mM  $CaCl_2$ , 1.17 mM  $MgSO_4$ , 1.18 mM  $KH_2PO_4$ , 25 mM  $NaHCO_3$ , and 11 mM glucose. In some rings, the endothelium was removed mechanically, and the endothelial removal or preservation was confirmed by the absence or the presence of the relaxation in response to acetylcholine ( $10^{-5}$  M), respectively. Several rings cut from the same artery were studied in parallel. Each ring was connected to an isometric force transducer and suspended in an organ chamber filled with 10 ml control solution (37°C, pH 7.4) bubbled with 95%  $O_2$  and 5%  $CO_2$ . The artery was gradually stretched to the optimal point of its length-tension curve as determined by the contraction to phenylephrine ( $3 \times 10^{-7}$  M). In most of the studied arteries, optimal tension was achieved at approximately 1.5 g. During submaximal contraction to phenylephrine, the concentration-response curve to levromakalim or diltiazem was obtained. Some rings were treated with glibenclamide, *S*(-)- or *R*(+)-bupivacaine, or ropivacaine, which was given 15 min before addition of phenylephrine ( $3 \times 10^{-7}$  M). The vasorelaxation was expressed as a percentage of the maximal relaxation in response to papaverine ( $3 \times 10^{-4}$  M), which was added at the end of experiments to produce the maximal relaxation (100%) of arteries.

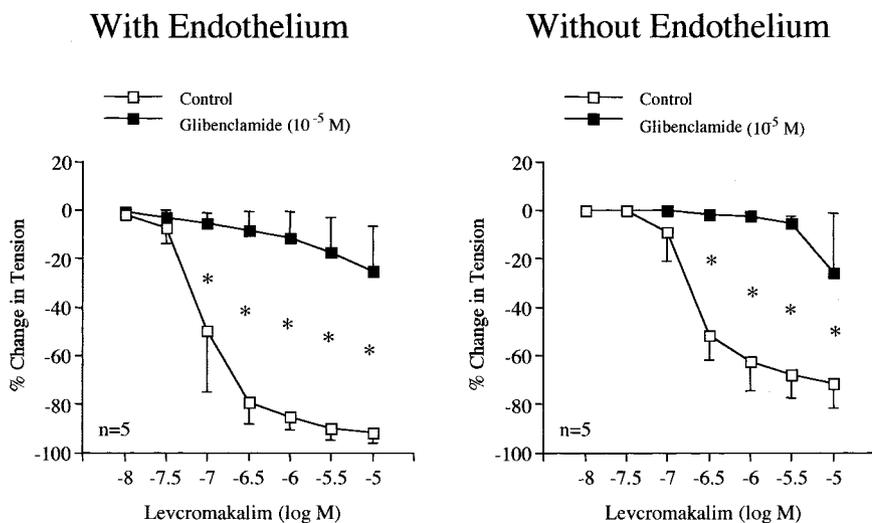
### Drugs

The following pharmacologic agents were used: diltiazem, dimethyl sulfoxide, glibenclamide, and phenylephrine (Sigma, St. Louis, MO). Levromakalim and *S*(-)-bupivacaine, *R*(+)-bupivacaine, and ropivacaine were gifts from GlaxoSmithKline plc (Greenford, United Kingdom) or AstraZeneca Pharmaceutical Co. (Södertälje, Sweden), respectively. Drugs, except for levromakalim and glibenclamide, were dissolved in distilled water such that volumes of less than 60  $\mu$ l were added to the organ chambers. Stock solutions of levromakalim ( $10^{-5}$  M) and glibenclamide ( $10^{-5}$  M) were prepared in dimethyl sulfoxide ( $3 \times 10^{-4}$  M).

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**Fig. 1.** Concentration–response curves to levcromakalim ( $10^{-8}$  to  $10^{-5}$  M) in the absence and in the presence of glibenclamide ( $10^{-5}$  M), obtained in the rat thoracic aorta with or without endothelium. Data are shown as mean  $\pm$  SD and expressed as percent of maximal vasorelaxation induced by papaverine ( $3 \times 10^{-4}$  M). \* Difference between control rings and rings treated with glibenclamide is statistically significant ( $P < 0.05$ ).

### Statistical Analysis

Data are expressed as mean  $\pm$  SD. Statistical analysis was performed using repeated-measures analysis of variance, followed by the Scheffé F test for multiple comparisons. Differences were considered to be statistically significant when  $P$  was less than 0.05.

## Results

During submaximal contraction to phenylephrine ( $3 \times 10^{-7}$  M), the selective ATP-sensitive  $K^+$  channel opener levcromakalim ( $10^{-8}$  to  $10^{-5}$  M) produced vasorelaxation of the rat aorta with or without endothelium in a concentration-dependent fashion (fig. 1). This relaxation was abolished by a selective ATP-sensitive  $K^+$  channel antagonist glibenclamide ( $10^{-5}$  M) (fig. 1). In the aortas with endothelium,  $R(+)$ -bupivacaine ( $10^{-6}$  to  $10^{-5}$  M) and  $S(-)$ -bupivacaine ( $3 \times 10^{-6}$  to  $10^{-5}$  M) inhibited vasorelaxation in response to levcromakalim in a concentration-dependent fashion, whereas ropivacaine did not affect this vasorelaxation (fig. 2A). In the aortas without endothelium,  $R(+)$ -bupivacaine ( $3 \times 10^{-6}$  to  $10^{-5}$  M) inhibited vasorelaxation to levcromakalim in a concentration-dependent fashion, whereas  $S(-)$ -bupivacaine reduced the relaxation only in the highest concentration used, and ropivacaine did not alter this vasorelaxation (fig. 2B).

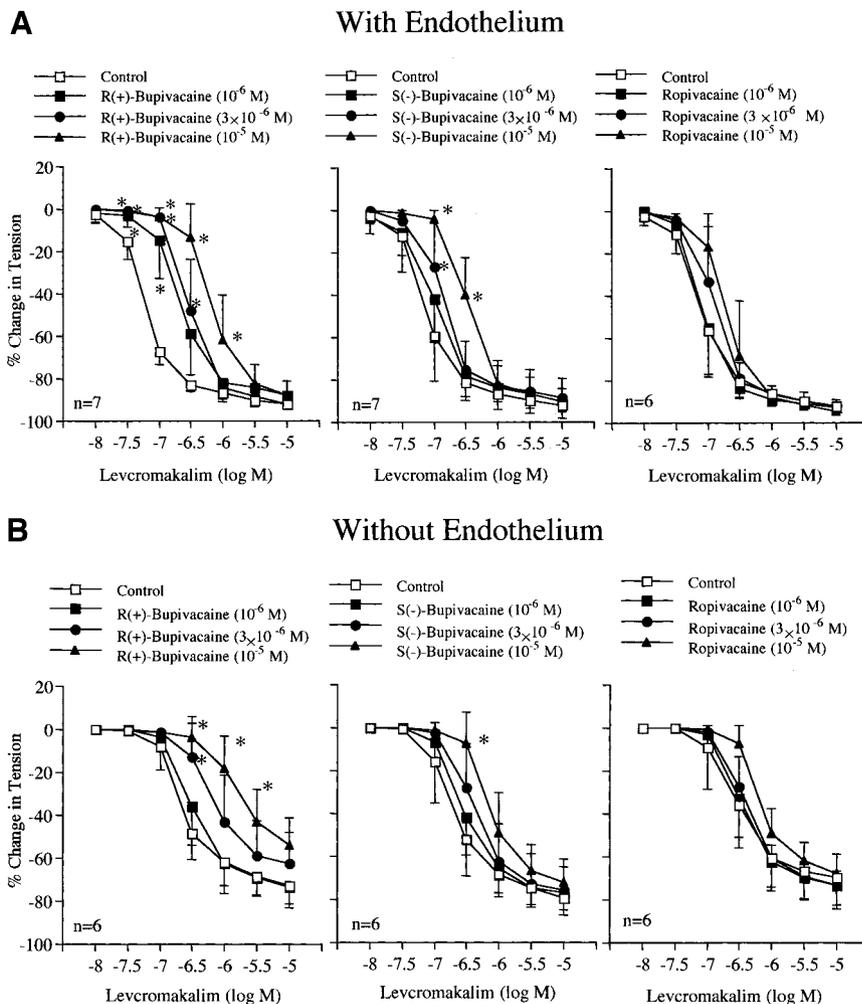
The highest concentration of each compound ( $10^{-5}$  M) did not affect vasorelaxation in response to the voltage-dependent  $Ca^{2+}$  channel antagonist diltiazem ( $10^{-8}$  to  $3 \times 10^{-4}$  M) (fig. 3).

## Discussion

Levcromakalim is a selective ATP-sensitive  $K^+$  channel opener in the rat aorta, suggesting that this preparation is a suitable model by which we can evaluate the role of ATP-sensitive  $K^+$  channels in vascular smooth muscle.<sup>7</sup>

In the rat aortas with and without endothelium,  $R(+)$ -bupivacaine caused the rather augmented inhibitory effect on the vasorelaxation *via* ATP-sensitive  $K^+$  channels, compared with  $S(-)$ -isomer, although both  $R(+)$ - and  $S(-)$ -bupivacaine inhibited the vasorelaxation in a concentration-dependent fashion. These results support the following conclusions. First, the effects of bupivacaine enantiomers on vasorelaxation *via* ATP-sensitive  $K^+$  channels are mostly mediated by their effects on these channels on vascular smooth muscle cells, because inhibitory actions of bupivacaine enantiomers were similar between the aortas with and without endothelium. Second, bupivacaine seems to stereoselectively reduce the vasorelaxation mediated by ATP-sensitive  $K^+$  channels. Previous studies on rat cardiac myocytes, bovine adrenal zona fasciculata cells, and native *Xenopus* oocytes demonstrated that racemic bupivacaine, containing  $R(+)$ - and  $S(-)$ -bupivacaine, reduces ATP-sensitive  $K^+$  currents.<sup>10–12</sup> These results obtained from studies performed using tissues other than blood vessels are certainly in agreement with our findings that bupivacaine enantiomers reduced vasorelaxation mediated by ATP-sensitive  $K^+$  channels. In the rat aorta, the pure  $S(-)$ -enantiomer ropivacaine did not alter vasorelaxation caused by an ATP-sensitive  $K^+$  channel opener. Considering the above findings regarding the inhibitory effects of bupivacaine enantiomers, it is likely that  $S(-)$ -enantiomers of local anesthetics show less potent effects on vasorelaxation mediated by ATP-sensitive  $K^+$  channels. In addition, ropivacaine, compared with  $S(-)$ -bupivacaine, seems to have less impact on these  $K^+$  channels of vascular smooth muscle cells.

The ATP-sensitive  $K^+$  channel is a complex of two proteins: the sulfonylurea receptor and Kir6.1 or 6.2, which belongs to the inward rectifier  $K^+$  channel family.<sup>13</sup> Because the sulfonylurea receptor of ATP-sensitive  $K^+$  channel is reportedly a primary target of the openers of this channel, it is most likely that bupivacaine enanti-



**Fig. 2.** (A) Concentration–response curves to levromakalim in the absence or in the presence of *R*(+)-bupivacaine, *S*(–)-bupivacaine, or ropivacaine ( $10^{-6}$ ,  $3 \times 10^{-6}$ ,  $10^{-5}$  M), obtained in the rat thoracic aorta with endothelium. Data are shown as mean  $\pm$  SD and expressed as percent of maximal vasorelaxation induced by papaverine ( $3 \times 10^{-4}$  M). \* Difference between control rings and rings treated with *R*(+)-bupivacaine ( $10^{-6}$ ,  $3 \times 10^{-6}$ ,  $10^{-5}$  M) or *S*(–)-bupivacaine ( $3 \times 10^{-6}$ ,  $10^{-5}$  M) is statistically significant ( $P < 0.05$ ). (B) Concentration–response curves to levromakalim in the absence or in the presence of *R*(+)-bupivacaine, *S*(–)-bupivacaine, or ropivacaine ( $10^{-6}$ ,  $3 \times 10^{-6}$ ,  $10^{-5}$  M), obtained in the rat thoracic aorta without endothelium. Data are shown as mean  $\pm$  SD and expressed as percent of maximal vasorelaxation induced by papaverine ( $3 \times 10^{-4}$  M). \* Difference between control rings and rings treated with *R*(+)-bupivacaine or *S*(–)-bupivacaine is statistically significant ( $P < 0.05$ ).

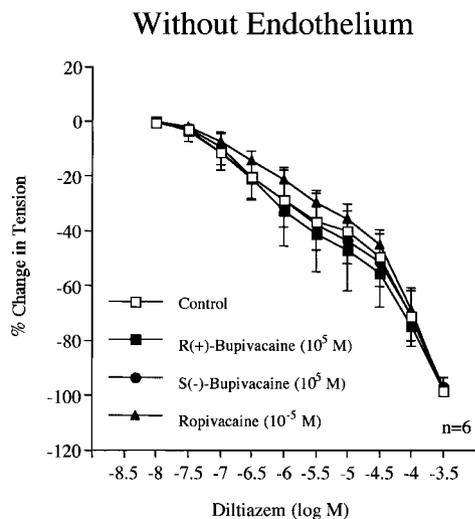
omers modify vasorelaxation in response to an ATP-sensitive  $K^+$  channel opener *via* the effect on the sulfonylurea receptor of these channels.<sup>14</sup> However, a recent study has found that racemic bupivacaine inhibits G protein-gated inward rectifier  $K^+$  channels by antagonizing the interaction of phosphatidylinositol 4,5-bisphosphate with the channel.<sup>15</sup> Therefore, we cannot rule out the possibility that bupivacaine may act on the compartment of inward rectifier  $K^+$  channel family in ATP-sensitive  $K^+$  channels. In any case, it is highly possible that bupivacaine, which is a lipophilic anesthetic, directly affects some channel compartments because recent studies have already reported such direct action of bupivacaine on voltage-dependent  $K^+$  channel proteins.<sup>16,17</sup>

Each compound evaluated in the current study, even in the highest concentration used, did not affect vasorelaxation in response to a voltage-dependent  $Ca^{2+}$  channel antagonist diltiazem. These results may support the concept that bupivacaine does not inhibit vasodilator responses in general. Our findings that neither bupivacaine enantiomers nor ropivacaine affect contraction in response to phenylephrine and maximal relaxation in-

duced by papaverine (data not shown) also neglect the possibility that the inhibitory effect of bupivacaine on vasorelaxation mediated by ATP-sensitive  $K^+$  channels is due to its vasoconstrictor effect on the aorta.

Thresholds of a free plasma concentration in humans for central nervous toxicity were reported up to  $1.5 \times 10^{-6}$  M and  $2.6 \times 10^{-6}$  M for racemic bupivacaine and ropivacaine, respectively.<sup>18</sup> A recent study has found that free plasma concentrations higher than  $1.5 \times 10^{-6}$  M are seen in infants during epidural infusion of bupivacaine because of a low  $\alpha$ -1 acid glycoprotein concentration.<sup>19</sup> Therefore, our results suggest that in clinical situations, bupivacaine enantiomers, especially *R*(+)-bupivacaine, impair vasodilation mediated by ATP-sensitive  $K^+$  channels, whereas ropivacaine does not alter the vasodilation.

During hypoxia, acidosis, and ischemia, ATP-sensitive  $K^+$  channels are activated, resulting in arterial dilation or increased tolerance of tissues to ischemia or both.<sup>6,20,21</sup> Although it is still unclear whether our results have relevance to vasodilation in resistance blood vessels, during pathophysiologic situations, bupivacaine enantiomers, especially *R*(+)-bupivacaine, but not ropiva-



**Fig. 3.** Concentration–response curves to diltiazem ( $10^{-8}$  to  $3 \times 10^{-4}$  M) in the absence or in the presence of *R*(+)-bupivacaine, *S*(–)-bupivacaine, or ropivacaine ( $10^{-5}$  M), obtained in the rat thoracic aorta without endothelium. Data are shown as mean  $\pm$  SD and expressed as percent of maximal vasorelaxation induced by papaverine ( $3 \times 10^{-4}$  M).

caine, may impair vasodilator effects induced by activation of ATP-sensitive  $K^+$  channels, which play an important role in regulation of circulation.

In conclusion, this is the first study evaluating the effects of amide-linked long-acting local anesthetics, including bupivacaine enantiomers and ropivacaine, on  $K^+$  channels of vascular smooth muscle. From our results, *S*(–)-enantiomers of amide-linked local anesthetics seem to show less potent effects on vasorelaxation mediated by ATP-sensitive  $K^+$  channels. In these *S*(–)-isomers, ropivacaine may not affect these  $K^+$  channels of vascular smooth muscle cells.

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