J Anesth (1996) 10:26–32

Journal of
Anesthesia



# Effects of phenol on vascular smooth muscle in rabbit mesenteric resistance arteries

TAKASHI AKATA, KENJI KODAMA, and SHOSUKE TAKAHASHI

Department of Anaesthesiology and Critical Care Medicine, Faculty of Medicine, Kyushu University, Fukuoka 812, Japan

**Abstract:** Although phenol has long been used clinically as a neurolytic agent or as a preservative for injections, little information is available regarding its direct vascular action. We therefore studied the effects of phenol (0.1 μM–2 mM) on isolated rabbit small mesenteric arteries, using isometric tension recording methods. All experiments were performed on endothelium-denuded strips. Phenol (≥10 μM) generated transient contractions in a concentration-dependent manner in both normal Krebs and $Ca^{2+}$-free solutions with $EC_{50}$ values (concentrations that produced 50% of the maximal response) of 39.8 μM and 99.7 μM, respectively. Depletion of intracellular $Ca^{2+}$ stores by A23187 or ryanodine completely eliminated the phenol-induced contractions. When caffeine (10 mM) and noradrenaline (NA, 10 μM) were consecutively applied in $Ca^{2+}$-free solution with an interval of 7 min (sufficient to prevent caffeine-induced inhibition of $Ca^{2+}$ sensitivity), caffeine eliminated the contractions induced by subsequent application of NA. In similar experiments where phenol (1 mM) and NA (10 μM) were consecutively applied in $Ca^{2+}$-free solution, phenol significantly inhibited contractions induced by subsequent application of NA. Phenol (0.1 mM, $\approx EC_{65}$), applied in the presence of either 128 mM $K^+$ or NA (10 μM), produced transient vasoconstrictions superimposed on both high $K^+$- and NA-induced contractions, but had a lesser effect on maintenance of these contractions. The vascular responses to high $K^+$, NA, and caffeine after washout of phenol were not significantly different from those before application of phenol (up to 2 mM). The results suggest that phenol stimulates $Ca^{2+}$ release from intracellular $Ca^{2+}$ stores, which are sensitive to both caffeine and NA in this resistance artery. The effect does not appear to reflect a toxic effect on vascular smooth muscle. It seems unlikely that phenol causes adverse hemodynamic changes because of the observed direct vascular action.

*Address correspondence to*: T. Akata

Received for publication on March 20, 1995; accepted on July 19, 1995

Presented in part at the annual meeting of the American Society of Anesthesiologists, Atlanta, Georgia, October 21–25, 1995

**Key words:** Phenol, Preservative for injections, Intracellular calcium stores, Vascular smooth muscle, Resistance artery, Protamine

## Introduction

Phenol, first introduced as an antiseptic by Lister more than a century ago [1], has been used clinically as a preservative for injections or as a neurolytic agent in the treatment of chronic pain to block permanently those sensory nerves which conduct pain [2]. In both the U.S. and Japan, phenol at a concentration of up to 0.5% has been approved as an additive to preparations for injection that are administered in a volume exceeding 5 ml because of its antimicrobial preservative properties [3,4]. For example, in Japan, phenol has been used as a preservative at a concentration of 0.25% for a protamine sulfate injection (Shimizu Pharmaceutical, Shimizu, Japan) which has been used to neutralize heparin-induced anticoagulation in cardiovascular surgery and is known to cause various adverse cardiovascular responses [5–7]. In addition, loss of consciousness and circulatory and respiratory collapse are known to occur following intravascular injection of phenol, which may inadvertently happen when used as the neurolytic agent [2].

To our knowledge, no study to date has examined the effects of phenol on vascular smooth muscle. In this study, we investigated the effects of phenol on isolated rabbit small resistance artery, using isometric tension recording methods. For the first time we demonstrate that phenol causes vasoconstriction as a result of $Ca^{2+}$ release from intracellular $Ca^{2+}$ stores in vascular smooth muscle.

## Materials and methods

### *Tissue preparation*

After we had received institutional approval for this animal study, male albino rabbits (2.0–2.5 kg) were given sodium pentobarbital (40 mg·kg$^{-1}$ i.v.) and exsanguinated. The mesentery in the jejunal region was immediately placed in a dissecting chamber filled with preoxygenated Krebs-bicarbonate solution, and the mesenteric artery was rapidly excised. The distal portion of the third- or fourth-order branches (≈150–250 μm in outside diameter), which are known to contribute substantially to vascular resistance [8], were used for the present experiments. Under a binocular microscope, the fat and adhering connective tissues were carefully removed, and thin transverse strips (400–600 μm long and 100–120 μm wide) were prepared. In all experiments, the endothelium was removed by gently rubbing the intimal surface with a small pin utilizing its round surface, and the functional removal of endothelium was confirmed by the lack of acetylcholine (ACh, 10 μM)-induced relaxation as previously reported [9,10]. The morphological removal of endothelium with this technique was previously documented in our previous immunohistochemical study [9].

### *Tension measurement*

Mechanical responses were measured by attaching the strip to a strain gauge (UI-2 type, Shinko, Tokyo, Japan) in a chamber of 0.9 ml capacity as previously described [9–13]. The strip was horizontally mounted in the chamber on a microscope stage, and then stretched to ≈1.1–1.2 times the resting length to obtain the maximum contractile response to high $K^+$. The solution was changed by perfusing it rapidly from one end while aspirating it simultaneously from the other end. All experiments were performed at 35°C.

### *Solutions and drugs*

The ionic concentrations of Krebs solution were as follows (mM): NaCl 111.9, KCl 3.7, $MgCl_2$ 1.2, $CaCl_2$ 2.6, $NaHCO_3$ 25.5, $KH_3PO$ 1.2, glucose 11.4. The high-$K^+$ solution was prepared by replacing NaCl with KCl isoosmotically. In $Ca^{2+}$-free solutions, $CaCl_2$ was replaced with $MgCl_2$, and 2 mM ethyleneglycol-bis-(β-amino-ethylether)-*N*,*N*,*N*′,*N*′-tetraacetic acid (EGTA) was added. The solution was bubbled with 95% $O_2$/5% $CO_2$, and its pH was adjusted to 7.3–7.4. All the experiments with high $K^+$ were performed in the presence of 3 μM guanethidine and 0.3 μM tetrodotoxin (TTX) to minimize the influence of peripheral nerve activity.

Noradrenaline (NA), ACh, and TTX were obtained from Sigma Chemical, St. Louis, MO, USA. A23187 (free acid) and ryanodine were obtained from Calbiochem (San Diego, CA, USA).

### *Calculation and statistical analysis*

The data points in concentration–response relationships for phenol-induced vasoconstriction were fitted according to a four-parameter logistic model described by De Lean et al. [14], and the $EC_{50}$ values (concentrations that produced 50% of the maximal response) were derived from these fits. The amplitude of phasic component of high-$K^+$- or NA-induced contraction was normalized as 1.0 to express the phenol-induced contraction.

All results are expressed as the means ± SEM; *n* denotes the number of animals (= number of strips). The statistical assessment of the data was made by analysis of variance (ANOVA), Scheffé's F test, and Student's *t*-test, where appropriate. A level of $P < 0.05$ was considered significant.

## Results

### *Characteristics of phenol-induced vasoconstriction*

The effects of phenol (0.1 μM–2 mM) were first examined in the absence of vasoconstrictors. As shown in Figs. 1 and 2, phenol (≥10 μM) generated transient vasoconstriction in a concentration-dependent manner similar to caffeine-induced contraction in both normal Krebs (2.6 mM $Ca^{2+}$) and $Ca^{2+}$-free (2 mM EGTA) solutions with $EC_{50}$ values of 39.8 μM and 99.7 μM, respectively; removal of extracellular $Ca^{2+}$ slightly but significantly attenuated the phenol-induced contraction (Fig. 2).

Exposure to A23187 (0.1 μM, 30 min) or ryanodine (10 μM, 20 min, applied with caffeine) almost completely eliminated both caffeine- (10 mM) and NA- (10 μM) induced contractions as previously reported in the same artery [9], suggesting that intracellular $Ca^{2+}$ stores are almost completely depleted by these treatments. The depletion of intracellular $Ca^{2+}$ stores by A23187 ($n = 3$) or ryanodine ($n = 4$) completely eliminated the phenol (1 mM, maximum)-induced contraction in both normal Krebs and $Ca^{2+}$-free (2 mM EGTA) solutions (not shown).

As shown in Fig. 3, in experiments where caffeine (10 mM) and NA (10 μM) were consecutively applied in $Ca^{2+}$-free (2 mM EGTA) solution with an interval of 7 min, caffeine completely inhibited the contraction induced by subsequent application of NA ($n = 3$). In similar experiments where phenol (1 mM) and NA (10 μM) were consecutively applied in $Ca^{2+}$-free solu-

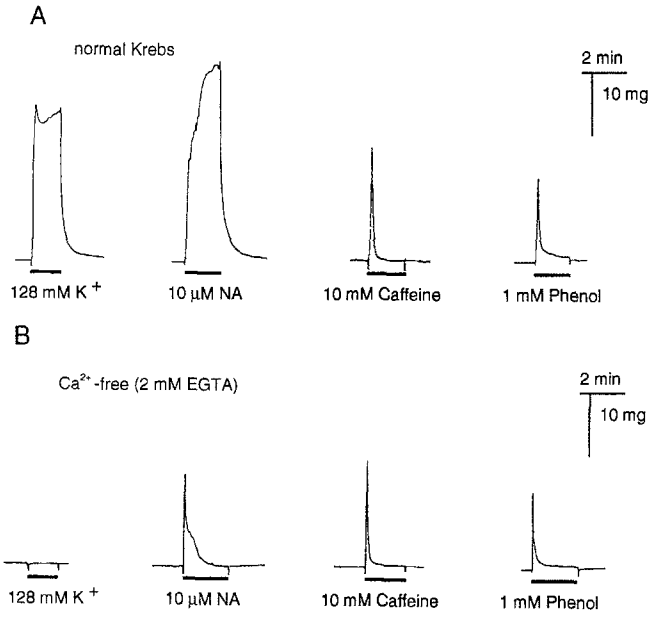


**Fig. 1.** Representative examples of 128 mM $K^+$-, noradrenaline (*NA*, 10 μM)-, caffeine (10 mM)-, and phenol (1 mM)-induced contractions evoked in both normal Krebs (2.6 mM $Ca^{2+}$) (**A**) and $Ca^{2+}$-free [2 mM ethyleneglycoltetraacetic acid (EGTA)] (**B**) solutions in endothelium-denuded strips. Removal of extracellular $Ca^{2+}$ completely eliminated 128 mM $K^+$-induced contraction, and strongly inhibited NA-induced tonic contraction. In contrast, both caffeine- and phenol-induced contractions were less affected by removal of extracellular $Ca^{2+}$. Similar observations were made in six other strips

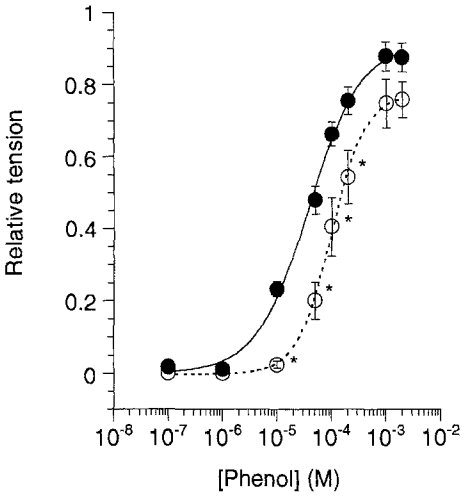


**Fig. 2.** Concentration–response relationship for phenol-induced vasoconstrictions in both normal Krebs (2.6 mM $Ca^{2+}$) (*closed circles*) and $Ca^{2+}$-free (2 mM EGTA) (*open circles*) solutions in endothelium-denuded strips. All values are expressed as means ± SEM ($n$ = 5–7). $^*P < 0.05$ *vs* normal Krebs

tion, phenol significantly inhibited the NA-induced contraction (Fig. 3B); the amplitude of NA-induced contraction after application of phenol was 0.71 ± 0.02 ($n$ = 4) times the control ($P < 0.05$). As shown in Fig. 4A,B, phenol failed to evoke contractions after repetitive application of either caffeine or NA in $Ca^{2+}$-free (2 mM EGTA) solution. In contrast, NA could evoke contractions after repetitive application of phenol in $Ca^{2+}$-free solution (Fig. 4C). In addition, caffeine still evoked contraction after repetitive applications of phenol and NA in $Ca^{2+}$-free solution (Fig. 4C). The inter-

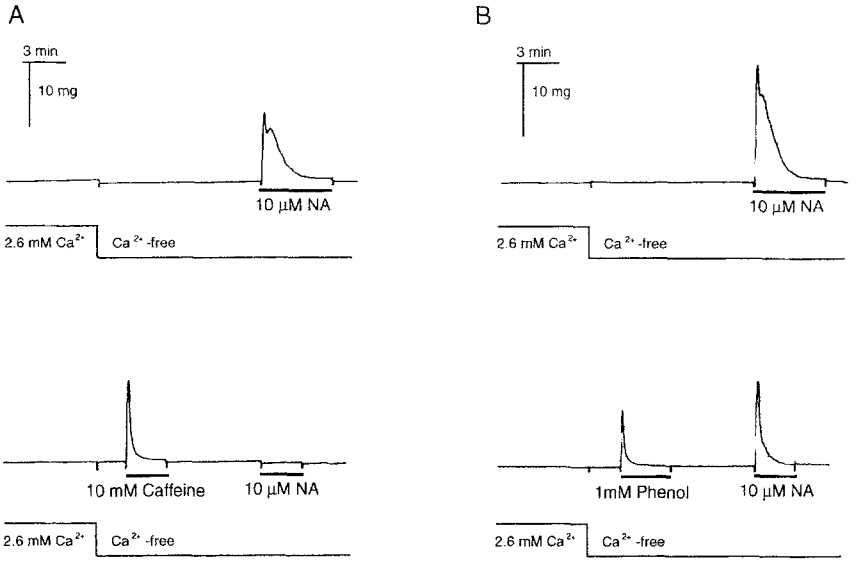


**Fig. 3.** Effects of preapplication of caffeine (10 mM) (**A**) and phenol (1 mM) (**B**) on noradrenaline (10 μM, *NA*)-induced contraction in $Ca^{2+}$-free (2 mM EGTA) solution. NA was applied to the strip 7 min after washout of caffeine or phenol. The *upper panel* in each figure shows the control NA-induced contraction. Identical results were obtained in several other strips ($n$ = 3–4)

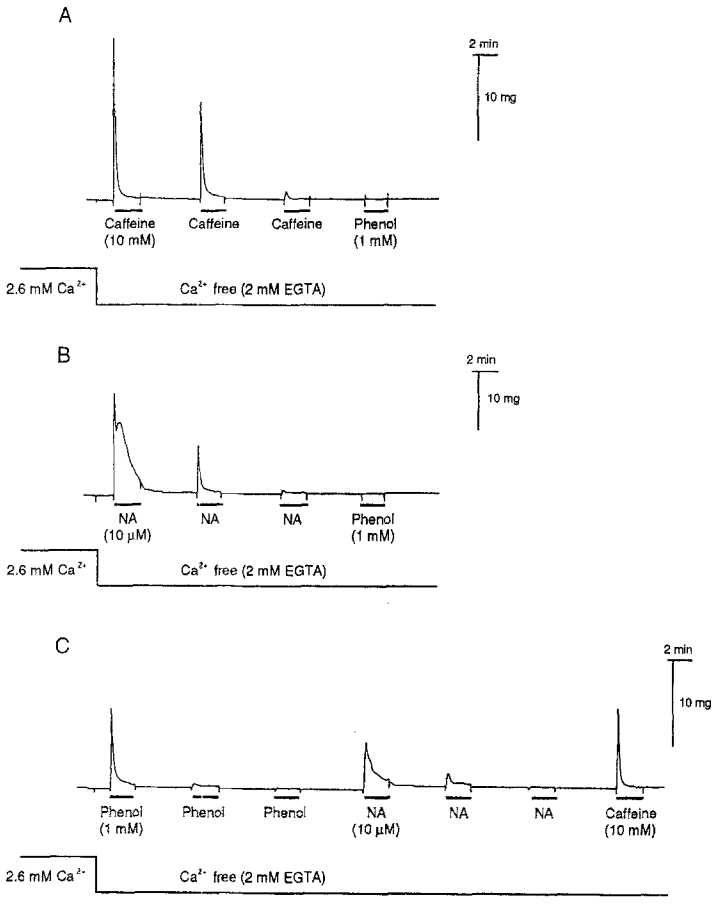


**Fig. 4. A,B** Effects of repetitive application of caffeine (10 mM) (**A**) or NA (10 μM) (**B**) on contractions induced by subsequent application of phenol (1 mM) in $Ca^{2+}$-free (2 mM EGTA) solution. **C** Effects of repetitive application of phenol (1 mM) on contractions induced by subsequent application of NA (10 μM) or caffeine (10 μM) in $Ca^{2+}$-free (2 mM EGTA) solution. Identical results were obtained in several other strips ($n$ = 3–4)

vals used in the above experiments in $Ca^{2+}$-free solution (Figs. 3, 4), i.e., 5 or 7 min, were considered sufficient to avoid the known inhibitory effect of caffeine or the enhancing effect of NA on $Ca^{2+}$ sensitivity; complete recovery from caffeine-induced inhibition or NA-induced enhancement of contraction was consistently achieved within 5 min after washout of caffeine or NA in the strips precontracted with high $K^+$. The effect of phenol on contraction after washout of phenol is shown in Fig. 5; it is unlikely that phenol significantly affected the $Ca^{2+}$ sensitivity 5–7 min after washout of phenol.

### *Effects of phenol on high-$K^+$- or NA-induced contraction*

The effects of phenol (0.1 mM, $\approx EC_{65}$ in Krebs solution) were then examined on contractions induced by 128 mM $K^+$ or NA (10 μM). Phenol, when applied in the presence of either 128 mM $K^+$ or NA, produced transient vasoconstrictions superimposed on both 128 mM $K^+$- and NA-induced contractions (Fig. 5); the amplitude of phenol contraction in the presence of 128 mM $K^+$ was 0.57 ± 0.15 ($n$ = 5) times that of 128 mM $K^+$-induced phasic contraction, while the amplitude of phenol contraction in the presence of NA was 0.40 ± 0.11 ($n$ = 4) times that of NA-induced phasic contraction. In addition, transient vasorelaxation was observed following the phenol-induced transient vasoconstriction and also after washout of phenol in the presence of either high $K^+$ or NA (Fig. 5). Similarly, caffeine, applied in the presence of either 128 mM $K^+$- or NA, produced transient vasoconstrictions superimposed on both high $K^+$- and NA-induced contractions; however, the vasoconstrictions were followed by complete vasorelaxation in the presence of either high $K^+$ or NA (Fig. 5).

## Discussion

The present study demonstrates that phenol causes transient vasoconstriction in both the presence and the absence of vasoconstrictors in small resistance arteries. The effect of removal of extracellular $Ca^{2+}$ on the phenol-induced contraction and the disappearance of phenol-induced contraction after depletion of intracellular $Ca^{2+}$ stores both suggest that phenol-induced contractions are due to $Ca^{2+}$ release from intracellular $Ca^{2+}$ stores. The slight but significant inhibition of phenol-induced contractions observed in $Ca^{2+}$-free (2-mM EGTA) solution may be explained by a possible decrease in the amount of $Ca^{2+}$ in intracellular $Ca^{2+}$ stores after removal of extracellular $Ca^{2+}$.

Both caffeine- and NA-induced contractions in $Ca^{2+}$-free solution were almost completely inhibited after

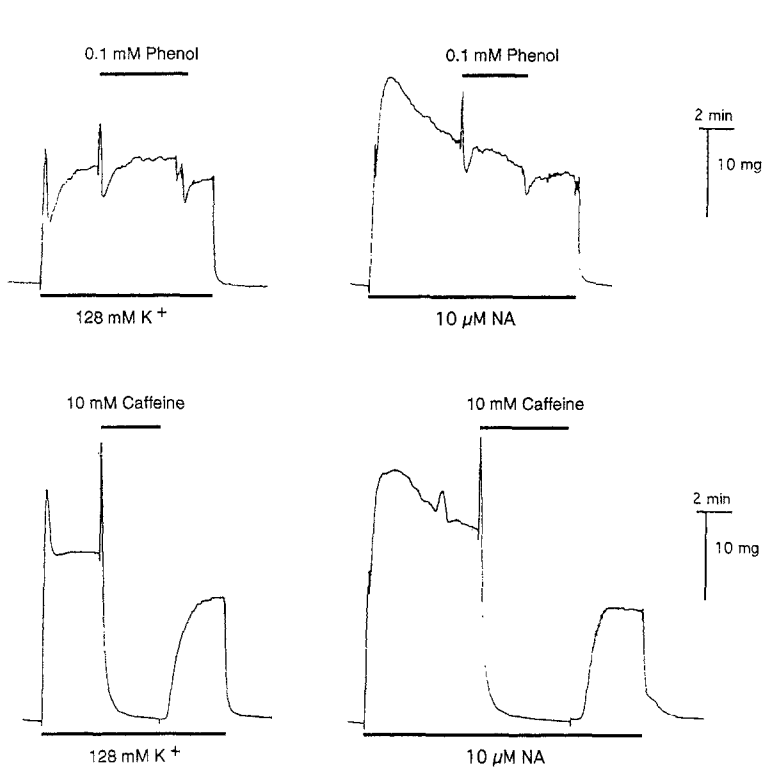


**Fig. 5.** Effects of phenol (0.1 mM, **A**) and caffeine (10 mM, **B**) on both 128 mM $K^+$- and NA (10 μM)-induced contractions in endothelium-denuded strips. Identical results were obtained in several other strips ($n$ = 4–5)

treatment with ryanodine, known to deplete caffeine-sensitive intracellular $Ca^{2+}$ stores [15]. In addition, preapplication of caffeine completely eliminated the contractions induced by subsequent application of NA in $Ca^{2+}$-free solution (Fig. 3A). These findings indicate that NA-sensitive intracellular $Ca^{2+}$ stores in this artery, believed to be $IP_3$-sensitive [16], are also sensitive to caffeine. However, caffeine still evoked contractions after depletion of the NA-sensitive intracellular $Ca^{2+}$ stores by repetitive application of NA (Fig. 4C), suggesting that a part of caffeine (or ryanodine)-sensitive intracellular $Ca^{2+}$ stores are insensitive to NA. Therefore, the intracellular $Ca^{2+}$ stores in this artery may consist of two kinds of stores, i.e., the intracellular $Ca^{2+}$ stores sensitive to both caffeine and NA, and those sensitive only to caffeine but not to NA.

Depletion of the NA-sensitive intracellular $Ca^{2+}$ stores by repetitive application of NA completely eliminated the phenol-induced contractions (Fig. 4B), suggesting that phenol stimulates the $Ca^{2+}$ release from the NA-sensitive intracellular $Ca^{2+}$ stores. In support of this, preapplication of phenol significantly inhibited the contractions induced by subsequent application of NA (Fig. 3B). However, NA still evoked contraction after repetitive application of phenol, which was supposed to deplete the phenol-sensitive intracellular $Ca^{2+}$ stores (Fig. 4C). This may suggest that the phenol-sensitive intracellular $Ca^{2+}$ stores are only a part of the NA-sensitive intracellular $Ca^{2+}$ stores. With this idea in mind, the intracellular $Ca^{2+}$ stores in this artery may be considered to consist of three kinds of stores, i.e., (1) the intracellular $Ca^{2+}$ stores sensitive to caffeine, NA, and phenol; (2) those sensitive to both NA and caffeine; and (3) those sensitive only to caffeine but not to NA or phenol. Alternatively, the phenol-induced $Ca^{2+}$ release mechanism might be readily desensitized.

Phenol appeared to cause transient vasoconstriction as a result of $Ca^{2+}$ release from intracellular $Ca^{2+}$ stores like caffeine. Both phenol and caffeine, when applied in the presence of either high $K^+$ or NA, similarly caused transient vasoconstriction superimposed on both high $K^+$- and NA-induced contractions (Fig. 5). However, significant differences in vascular response after the transient vasoconstriction in the presence of high $K^+$- or NA were observed between phenol and caffeine; that is, only transient vasorelaxation was observed following the phenol-induced vasoconstriction, while complete relaxation was observed following the caffeine-induced vasoconstriction (Fig. 5). The caffeine-induced relaxation was probably due to both a decrease in cytosolic $Ca^{2+}$ level and an inhibition of contractile proteins [17]. The mechanism(s) behind the transient vasorelaxation following the phenol contraction is (are) currently unknown. However, we speculate that they may reflect refilling of the intracellular $Ca^{2+}$ stores with $Ca^{2+}$, based on the assumption that the intracellular $Ca^{2+}$ stores actively contribute to maintenance of contraction as a

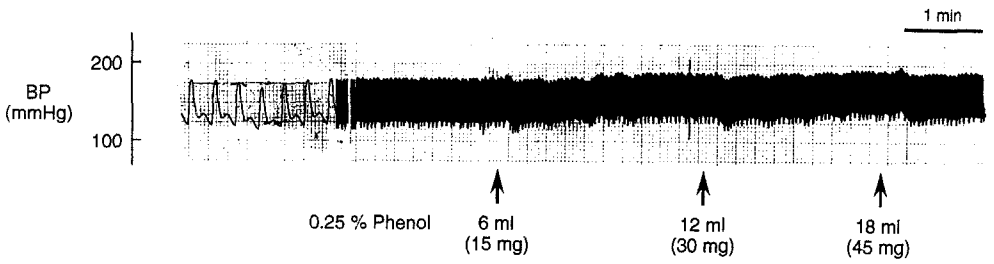


**Fig. 6.** Effects of intravenous injection of 6, 12, and 18 ml of 0.25% phenol from a central venous pressure (CVP) line (superior vena cava) on systemic blood pressure in a mongrel dog (12 kg). After obtaining an optimal anesthetic level with sodium pentobarbital, 30 mg·kg$^{-1}$ i.v., the animal was intubated and ventilated with room air using a positive pressure ventilator. Femoral arterial pressure and electrocardiography (ECG) were continuously monitored. Phenol was injected after obtaining a steady state. Blood pressure was affected little by the injections of phenol. No significant changes in ECG were observed (not shown). A similar result was obtained in one other dog (10 kg)

source of $Ca^{2+}$. In other words, the process of refilling might lead to a transient decrease in the cytosolic free $Ca^{2+}$ level, thereby causing transient vasorelaxation. Similarly, the transient vasorelaxation observed after washout of phenol might also reflect refilling of the intracellular $Ca^{2+}$ stores with $Ca^{2+}$; in spite of lack of apparent changes in tension, phenol might have depleted the intracellular $Ca^{2+}$ stores to some extent by continously stimulating $Ca^{2+}$ release until its washout. In support of this idea, we have observed similar transient vasorelaxation following washout of $Ca^{2+}$-releasing agents such as halothane or enflurane in the presence of agonists or high $K^+$ (unpublished data). Except for these transient vasoconstrictions and vasorelaxation, phenol had little effect on maintenance of the contraction induced by high $K^+$ or NA. It is therefore unlikely that phenol at this concentration (0.1 mM) adversely affects vascular tone because of the direct actions on vascular smooth muscle.

The present study does not address whether phenol causes significant changes in vascular tone through its action on the endothelium, which is believed to play a major role in the regulation of vascular tone in vivo [18,19]. Intracellular $Ca^{2+}$ stores in endothelial cells have been proposed to play an important role in regulation of endothelial function [20,21]. In addition, ryanodine-sensitive intracellular $Ca^{2+}$ stores have recently been reported to exist in endothelial cells [20]. Therefore, it may be conceivable that phenol affects vascular tone in an endothelium-dependent manner through action on the endothelial intracellular $Ca^{2+}$ stores. However, the action of phenol on intracellular $Ca^{2+}$ stores appears to be largely transient. In addition, our preliminary in vivo experiments in two mongrel dogs have shown that intravascular injection of 6–18 ml of 0.25% phenol from a central venous pressure (CVP) line had little effect on systemic blood pressure (Fig. 6). The injected amount of phenol (15–45 mg) would yield peak plasma concentrations of ≈0.27–0.80 mM (calculated from plasma volume [600 ml; a 12-kg dog] and injected doses), which are supposed to be larger than peak plasma concentrations of phenol when used as a preservative for injections. Therefore, it seems unlikely that phenol, when used as a preservative, causes significant hemodynamic changes in vivo, where the endothelium is present.

Phenol has long been used as a neurolytic agent in treatment of chronic intractable pain [2]. Rather high concentrations (6%–8%) have been used for this purpose, and the recommended maximal amount of phenol injected in one bolus shot was 66 mg [2]. Inadvertent intravascular injection of this amount of phenol into a 60 kg patient (plasma volume ≈31) would yield a peak plasma concentration of ≈0.23 mM. To our knowledge, there has been only one study which measured blood (serum) concentrations of phenol used clinically as the neurolytic agent [22]. The average peak serum concentrations of conjugated and unconjugated (free) phenol were 2.93 μg/ml (≈0.031 mM) and 4.19 μg/ml (≈0.045 mM), respectively, after lumbar or thoracic sympathetic block with 4–10 ml of 7% aqueous phenol [22]. In addition, blood concentrations of free phenol have previously been reported to increase to 7.7 μg/ml (0.082 mM) and 9.7 μg/ml (0.11 mM) in patients with chronic renal failure and hepatic coma, respectively [23]. Considering the concentrations of phenol tested in this study, phenol is unlikely to cause significant hemodynamic changes after nerve blockade or in patients with renal or hepatic failure because of its direct action on vascular smooth muscle.

Phenol is known to be toxic to living cells by acting as a protoplasmic poison [24]. However, the vascular responses to high $K^+$, NA, and caffeine after washout of phenol were all not significantly different from those before application of phenol (up to 2 mM), suggesting that the observed vascular action of phenol at concentrations up to 2 mM is not due to its toxic effect on vascular smooth muscle.

In conclusion, phenol causes transient vasoconstriction by releasing $Ca^{2+}$ from intracellular $Ca^{2+}$ stores, which are sensitive to both caffeine and NA in this resistance artery. It is unlikely that phenol, when clinically used as either a preservative for injections or a neurolytic agent, causes adverse hemodynamic changes because of its direct action on vascular smooth muscle.

## References


1. Nathan PW, Scott TG (1958) Intrathecal phenol for intractable pain: safety and dangers of the method. Lancet i:76–80
2. Budd K (1994) Ablative nerve blocks and neurosurgical techniques. In: Nimmo WS, Rowbotham DJ, Smith G (eds) Anaesthesia. Blackwell Scientific, London, pp 1665–1666
3. United States Pharmacopeial Convention (1995) The United States Pharmacopeia. The National Formulary. United States Pharmacopeial Convention, Rockville, p 1651
4. Nihon Koteisho Kyokai (1986) Nihon Yakkyokuhou Kaisetsusho (Pharmacopoeia Japonica). Hirokawa Shoten, Tokyo, A-116
5. Horrow JC (1985) Protamine: A review of its toxicity. Anesth Analg 64:348–361
6. Hobbhahn J, Conzen PF, Zenker B, Goetz AE, Peter K, Brendel W (1988) Beneficial effect of cyclooxygenase inhibition on adverse hemodynamic responses after protamine. Anesth Analg 67:253–260
7. Morel DR, Mo Costabella PM, Pittet J-F (1990) Adverse cardiopulmonary effects of increased plasm concentrations following the neutralization of heparin with protamine in awake sheep are infusion rate-dependent. Anesthesiology 73:415–424
8. Christensen KL, Mulvany MJ (1993) Mesenteric arcade arteries contribute substantially to vascular resistance in conscious rats. J Vasc Res 30:73–79
9. Akata T, Yoshitake J, Nakashima M, Itoh T (1991) Effects of protamine on vascular smooth muscle of rabbit mesenteric artery. Anesthesiology 75:833–846
10. Akata T, Nakashima M, Kodama K, Boyle III WA, Takahashi S (1995) Effects of volatile anesthetics on ACh-induced relaxation in the rabbit mesenteric resistance artery. Anesthesiology 82:188–204
11. Akata T, Kodama K, Takahashi S (1993) Effects of heparin on the vasodilator action of protamine in the rabbit mesenteric artery. Br J Pharmacol 109:1247–1253
12. Akata T, Kodama K, Yoshitake J, Takahashi S (1993) Heparin prevents the vasodilating actions of protamine on human small mesenteric arteries. Anesth Analg 76:1213–1221
13. Akata T, Kodama K, Takahashi S (1995) Effects of heparin on the inhibitory action of protamine on endothelium-mediated vasorelaxation. Acta Anaesthesiol Scand 39:698–704
14. De Lean AP, Munson PJ, Rodbard D (1978) Simultaneous analysis of families of sigmoidal curves: application to bioassay, radioligand assay, and physiological dose-response curves. Am J Physiol 235:E97–E102
15. Iino M, Kobayashi T, Endo M (1988) Use of ryanodine for functional removal of the calcium store in smooth muscle cells of the guinea pig. Biochem Biophys Res Commun 152:417–422
16. Hashimoto T, Hirata M, Itoh T, Kanmura Y, Kuriyama H (1986) Inositol 1,4,5-triphosphate activates pharmacomechanical coupling in smooth muscle of the rabbit mesenteric artery. J Physiol (Lond) 370:605–618
17. Ozaki H, Kasai H, Hori M, Ishihara H, Karaki H (1990) Direct inhibition of chicken gizzard smooth muscle contractile apparatus by caffeine. Naunyn Schmiedeberg Arch Pharmacol 341:262–267
18. Furchgott RF (1983) Role of endothelium in responses of vascular smooth muscle. Circ Res 53:557–573
19. Ignarro LJ (1989) Biological actions and properties of endothelium-derived nitric oxide formed and released from artery and vein. Circ Res 65:1–21
20. Ziegelstein RC, Spurgeon HA, Pili R, Passaniti A, Cheng L, Corda S, Lakatta EG, Capgrossi MC (1994) A functional ryanodine-sensitive intracellular $Ca^{2+}$ store is present in vascular endothelial cells. Circ Res 74:151–156
21. Nilius B (1991) Ion channels and regulation of transmembrane $Ca^{2+}$ influx in endothelium. In: Sperelakis N, Kuriyama H (eds) Ion channels of vascular smooth muscle cells and endothelial cells. Elsevier Science, New York, pp 317–325
22. Nomoto Y (1985) Pharmacokinetics of phenol following phenol block (in Japanese with English abstract). Masui (Jpn J Anesthesiol) 35:28–34
23. Warde EN, Wilkinson K (1976) Free phenols in chronic renal failure. Clin Nephrol 6:361–364
24. Dolley SR (ed) (1991) Therapeutic drugs, vol 2. Churchill Livingstone, Edinburgh, pp P68–P71 (no section author)