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Effect of Topical Application of Nitroglycerin on
Cochlear Blood Flow

(ニトログリセリン局所投与における蝸牛血流への影響)

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論 文 目 録

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<p>副 論 文</p> <p style="text-align: right;">冊</p> <p>題 目</p> <p style="margin-top: 20px;">(同 上)</p>			
<p>参 考 論 文</p> <p style="text-align: right;">冊</p> <p>題 目</p> <p style="margin-left: 20px;">1. 舌根部髓外形質細胞腫 耳鼻咽喉科. 頭頸部外科, 63巻12号, 平成3年11月発行 医学書院</p> <p style="margin-left: 20px;">2. A Case of Acute Onset with Allergic Aspergillus Sinusitis (急性経過を以てAASの一例) Auris Nasus Larynx, 22巻2号, 1995年6月発行, 掲載予定, 9枚 Society for Promotion of International Otorhinolaryngology (SPIO)</p> <p style="margin-top: 10px;">(同 上)</p>			

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Effect of Topical Application of Nitroglycerin on Cochlear Blood Flow

(ニトログリセリン局所投与における蝸牛血流への影響)

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ABSTRACT

Purpose: To investigate whether topical application of the vasodilator nitroglycerin would increase cochlear blood flow without adversely affecting inner ear function.

Materials and Methods: The effect of topical application of nitroglycerin to the round window membrane on cochlear blood flow was measured in 33 guinea pigs by laser Doppler flowmetry.

Endocochlear potential, as an indicator of inner ear function, was recorded by a glass microelectrode inserted through the round window membrane in a second series of 27 guinea pigs. Blood pressure was also monitored in both experiments.

Results: Low doses (0.0001 to 1 μ g) of nitroglycerin induced an increase in cochlear blood flow with no change in blood pressure. The cochlear blood flow was maximally increased by approximately 50%. A high dose (50 μ g) of nitroglycerin induced a significant decrease in blood pressure but did not significantly affect endocochlear potential.

Conclusions: Topical application of nitroglycerin may be useful in increasing cochlear blood flow in various inner ear diseases.

Vascular disorders of the inner ear that reduce cochlear blood flow (CBF) may be involved in the pathogenesis of sudden deafness and other forms of sensorineural hearing loss¹⁻⁴. Many vasodilators have been administered to patients to increase CBF⁵⁻⁷, however the oral and intravenous administration of these drugs is complicated by cardiovascular side effects such as a decreased in blood pressure (BP) that may limit local effectiveness and general utility⁸. Recently studies were conducted to assess the effect of topical application of vasodilators in the middle ear cavity. Although topical applications of sodium nitroprusside or hydralazine on the round window membrane (RWM) increases CBF without decreasing BP⁹, both of these drugs exhibit ototoxic effects^{10,11}. New drugs that increase CBF without side effects are thus needed for clinical use.

Nitroglycerin (C₃H₅N₃O₉, MW: 227) was first synthesized by Sobrero in 1847 and has been used clinically as a vasodilator since then¹³. Nitroglycerin acts on both arterial and venous smooth muscle but at low concentrations its effect on veins is more marked than that on arterioles¹⁴.

We examined the effects of the topical application of nitroglycerin to the RWM on CBF, BP and inner ear function. CBF was measured by laser Doppler flowmetry¹² and inner ear function was assessed by measurements of endocochlear potential (EP).

MATERIALS AND METHODS

Sixty Hartley guinea pigs of both sexes, with body weight of 180 to 370 g, were used in these investigations. All animals demonstrated a normal Preyer reflex and were free of middle ear infection, as assessed directly under the surgical microscope.

Each guinea pig was anesthetized with sodium pentobarbital (40 mg per kilogram of body weight, i.p.) and succinylcholine (5 mg per animal, i.m.) and was then immobilized in the supine position. Stable anesthesia and a normal BP were maintained by injecting an additional half-dose of succinylcholine every hour and by injecting a half-dose of sodium pentobarbital every 2 hours. Body temperature was maintained at $38 \pm 1^\circ \text{C}$ with a heating pad and the head was covered to prevent cooling of the cochlea. Following tracheotomy, the animal was ventilated with pure oxygen and an artificial respirator. Measurement of BP was done by a catheter inserted in the right carotid artery and connected to a pressure transducer (Toyoda, PMS-5M-0.5H) and an amplifier (Toyoda, AA3000).

Measurement of CBF

A ventrolateral surgical approach was used to expose the left bulla of 33 guinea pigs. The tympanic membrane and ossicles were kept intact. The middle ear mucosa and periosteum overlying the otic capsule were carefully removed with a cotton pledget.

CBF was monitored with a laser Doppler flowmeter (Advance, ALF

21). A probe with an outer diameter of 1 mm was placed over the lateral wall of the basal turn of the cochlea to ensure tight attachment and to provide efficient laser-light coupling to the cochlea. All recordings were performed under stable illumination from the surgical microscope.

After recording stable BP and CBF baselines, 1 μ l of nitroglycerin was applied topically to the RWM with a microsyringe under the surgical microscope.

The nitroglycerin was dissolved in 99.5% ethanol at concentrations of 0.0001, 0.001, 0.01, 0.1 and 1 μ g/ μ l. Six guinea pigs received 1 μ g of the drug and five animals received each of the lower doses. In addition, three guinea pigs received 1 μ l of 99.5% ethanol and four received 1 μ l of physiological saline as controls. CBF and BP were recorded simultaneously for up to 1 hour after drug administration. CBF values are expressed as a percentage of the initial baseline.

Measurement of EP

EP was recorded in 27 guinea pigs with a glass micropipette (tip diameter, 0.1 μ m; resistance, 40 megaohms) filled with 0.5 M KCl. The electrode was inserted through the RWM into the scala media, the scala tympani and the basilar membrane. Potentials were amplified by an electrometer amplifier (World Precision Instrument, Duo 773). A circular Ag-AgCl ground wire with a diameter of 10 mm was placed in the neck muscles. Nitroglycerin was administered as described above in doses of 1 μ g (six animals), 10 μ g (five animals) or 50 μ g (six

animals). In addition, five guinea pigs received 99.5% ethanol and five received physiological saline.

RESULTS

Effects of Nitroglycerin on CBF

Neither 99.5% ethanol nor physiological saline significantly affected CBF or BP. The topical administration of nitroglycerin induced a dose-dependent response in CBF (Fig.1). A high dose (50 μ g) of nitroglycerin induced a significant decrease in BP. The increase in CBF was maximal within 10 min after application of the drug and the effect was still apparent after 60 min; the effect of 0.1 μ g nitroglycerin was most persistent, continuing for more than 90 min. The maximal CBF response for all 26 guinea pigs is shown in Figure 2. The dose-dependent response was maximal (approximately 50% increase) at 0.1 μ g of nitroglycerin; the response to nitroglycerin showed marked inter-individual variability.

Effects of Nitroglycerin on EP

EP tended to decrease slightly and transiently after topical application of nitroglycerin (1, 10, or 50 μ g). However this decrease was not significant statistically compared with responses to either 99.5% ethanol or physiological saline (Fig.3A). Mean BP decreased by about 15% after topical application of 50 μ g of nitroglycerin (Fig.3B) but subsequently showed a tendency to recover.

DISCUSSION

Systemic application of vasodilators as a treatment for vascular pathologies of the inner ear is complicated by general side effects such as decreased BP. Systemic administration of sodium nitroprusside or hydralazine markedly increases CBF but also reduces BP. Topical application of these drugs on the RWM induces a persistent increase in CBF without affecting BP⁹. Although the cochlea exhibits an autoregulatory mechanism^{15,16}, CBF is susceptible to changes in systemic BP. Thus topical administration of vasodilating agents is most effective in increasing CBF without systemic effects.

While the RWM is primarily a physical barrier to the inner ear, it is also the main route for the passage of potentially ototoxic substances from the middle ear cavity into the inner ear¹⁷. Substances of low molecular weight pass freely from the middle ear through the RWM, diffusing into the inner ear^{18,19}. Topical application of sodium nitroprusside or hydralazine to the RWM has been associated with a reduced auditory gross neural response and reduced EP^{10,11}. Thus vasodilating drugs that increase CBF without damaging the inner ear are required. Nitroglycerin acts on vascular smooth muscle and has vasodilative effects similar to those of sodium nitroprusside.

Nitroglycerin is also effective when applied topically via skin tape.

We have now shown that low concentrations of nitroglycerin induced a dose-dependent increase in CBF with no change in BP. The CBF was maximally increased by approximately 50% from the initial

baseline value and the effect persisted for more than 60 min. Because topical application of high concentrations of nitroglycerin induced only a slight transient decrease in EP, administration of nitroglycerin to the inner ear via this route may prove effective in increasing CBF without inducing damage to the functions of the inner ear.

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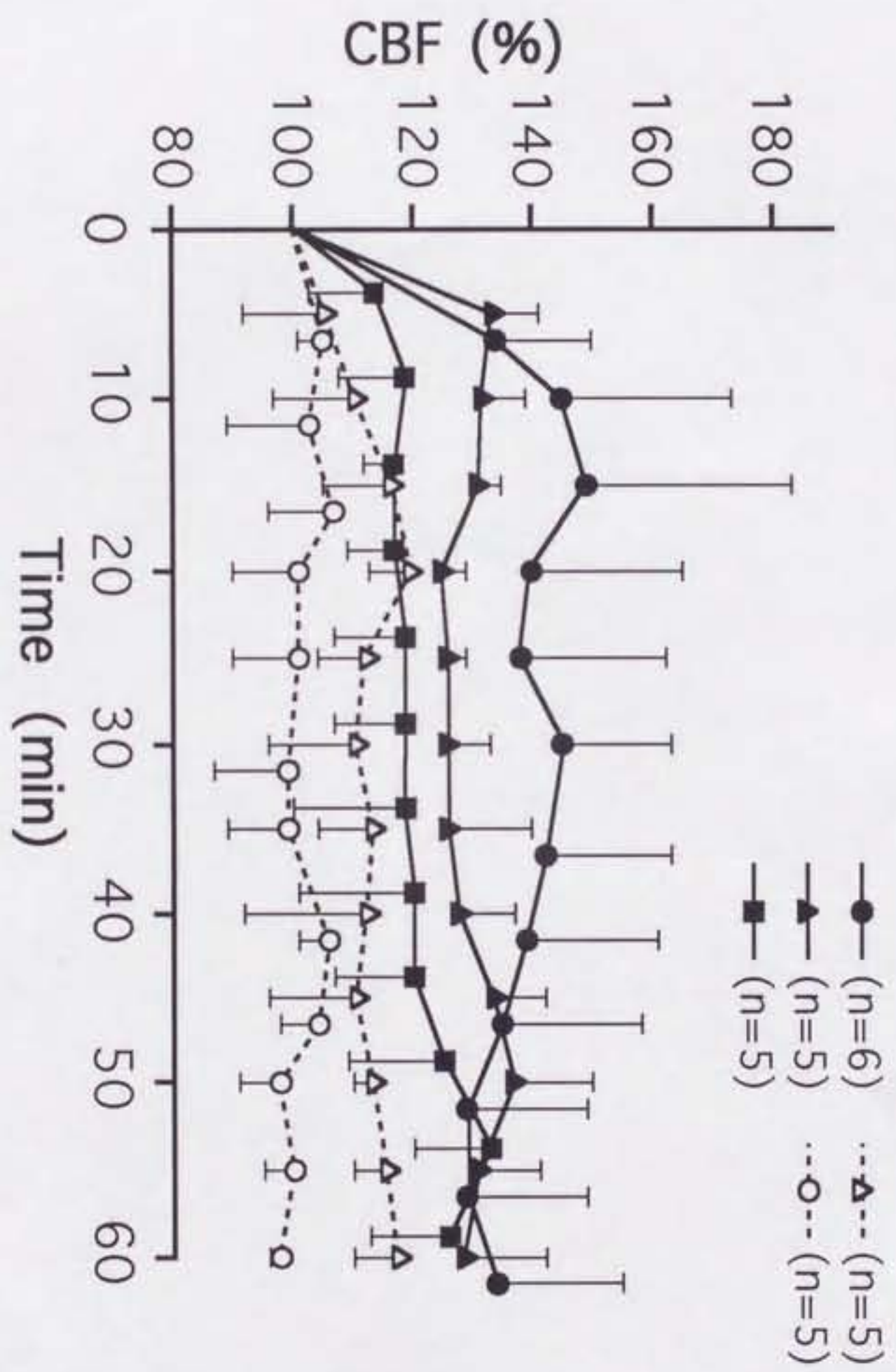


Fig 1. Ito et al.

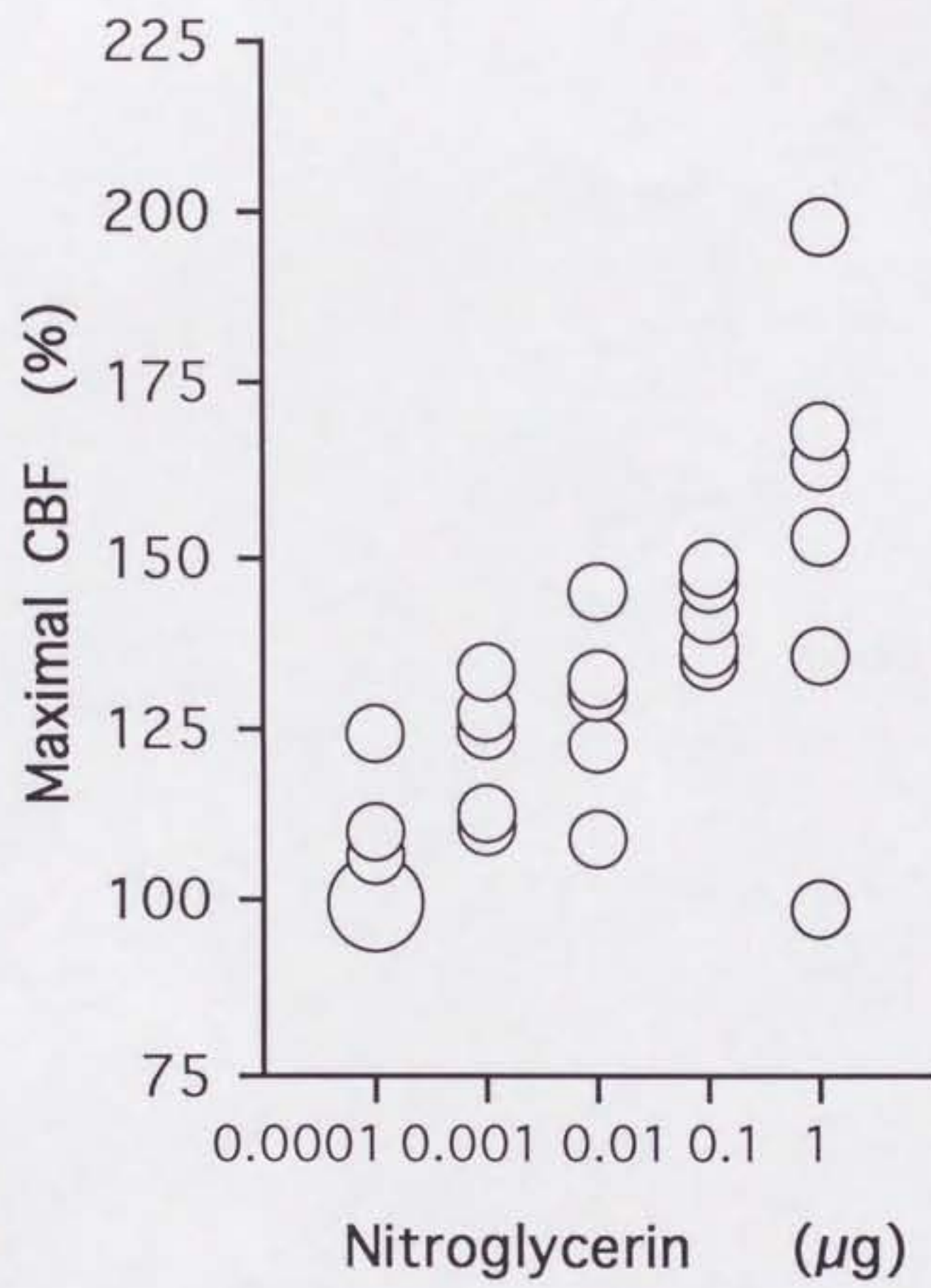


Fig 2. Ito et al.

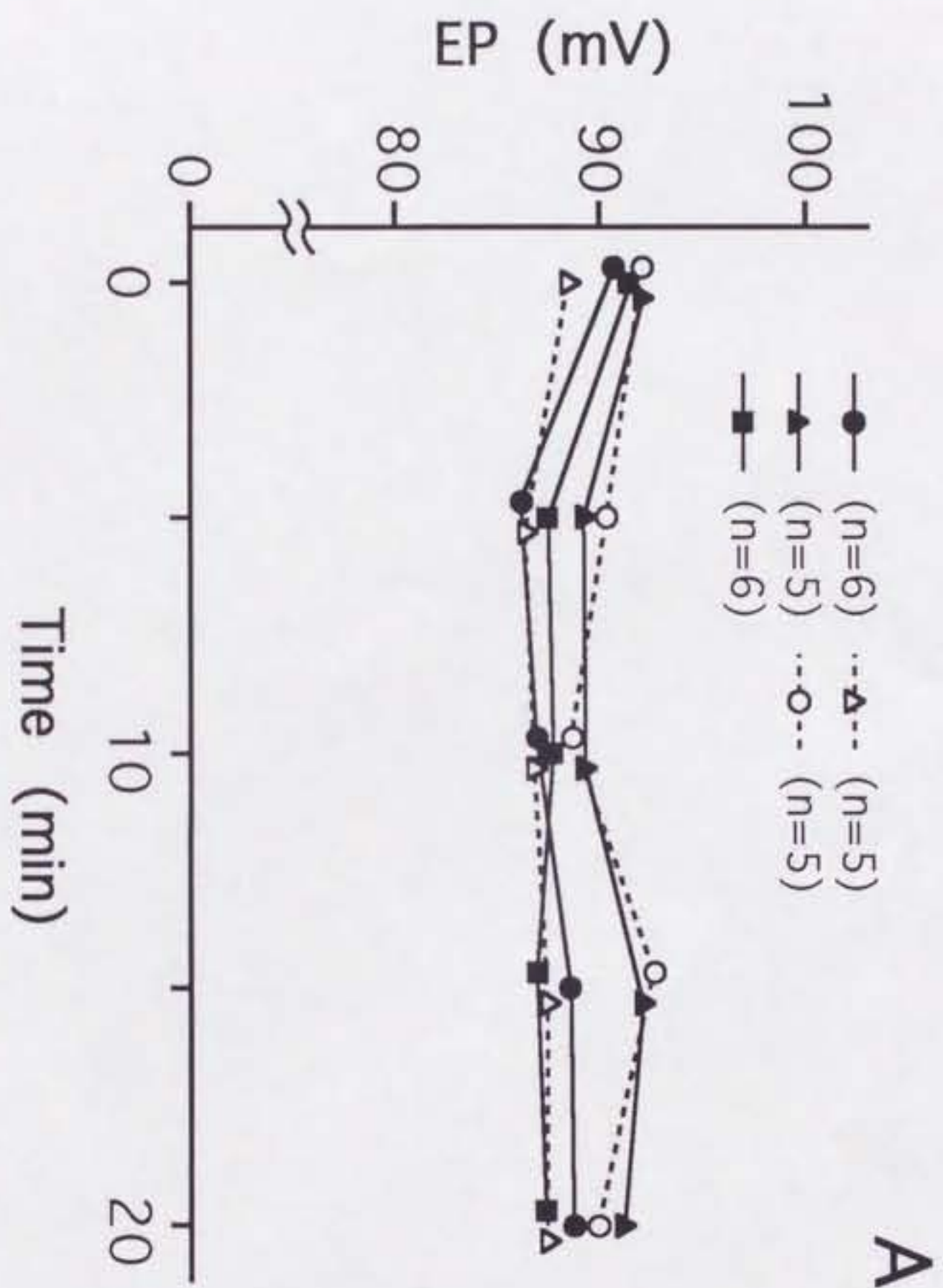


Fig 3A. Ito et al.

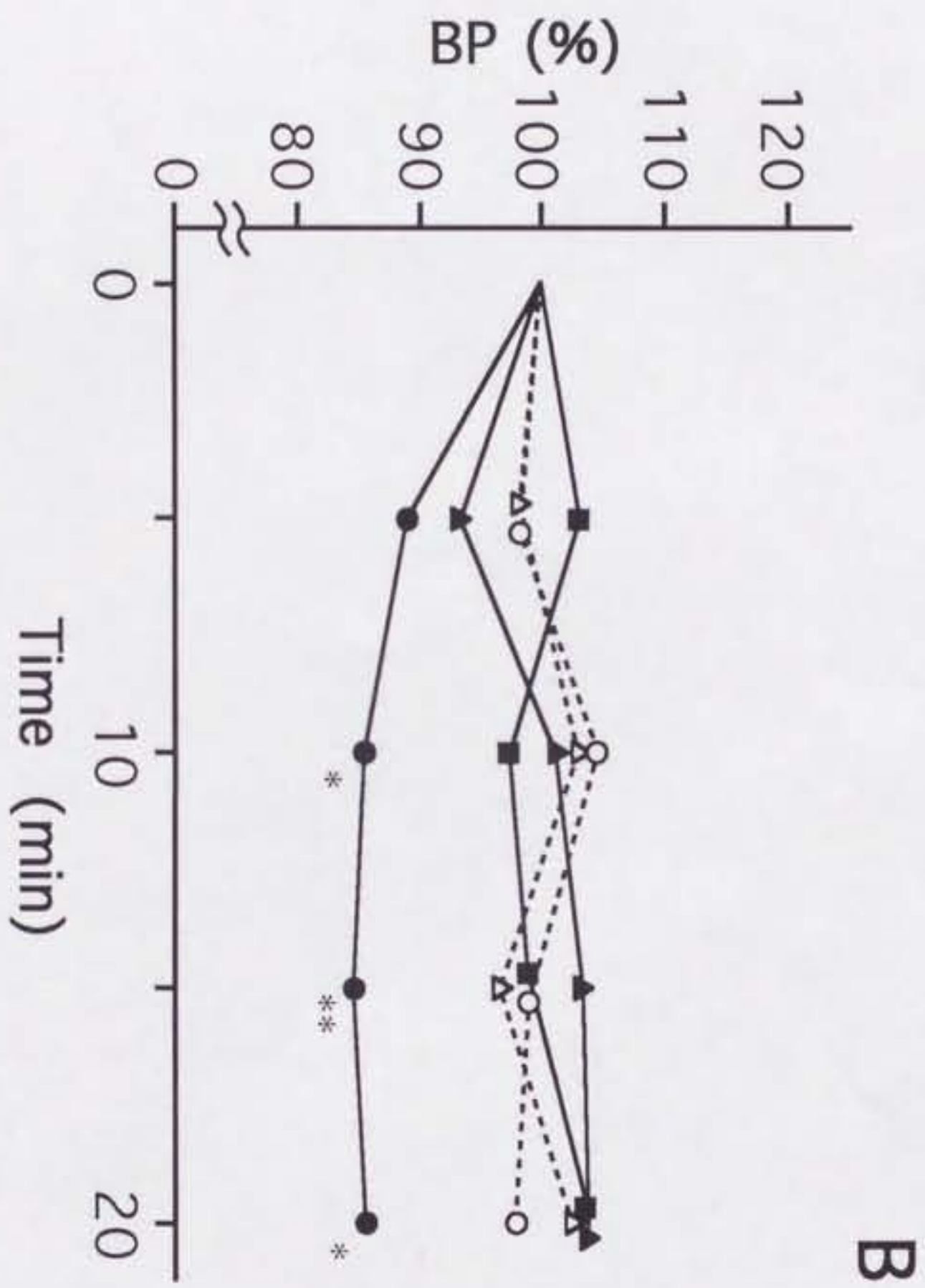


Fig 3B. Ito et al.

FIGURE LEGENDS

Fig 1. CBF response to topical application of nitroglycerin. (●) 1 μ g, (▲) 0.1 μ g, (■) 0.01 μ g, (Δ) 0.001 μ g and (○) 0.0001 μ g of nitroglycerin. Values are means \pm SD.

Fig 2. Dose-response relation for the maximal CBF observed within 1 hour of topical application of nitroglycerin. Small circles, one guinea pig; large circle, two guinea pigs with the same value.

Fig 3. Effect of topical application of nitroglycerin on EP (A) and BP (B). (●) 50 μ g, (▲) 10 μ g and (■) 1 μ g of nitroglycerin; (Δ) physiological saline and (○) 99.5% ethanol. Values are means. *P < 0.05, **P < 0.01.

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Kodak Color Control Patches

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