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# *Comparison of the Direct Effects of Halothane and Isoflurane on Large and Small Coronary Arteries Isolated from Dogs*

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**Relaxant responses to halothane and isoflurane were compared in helical strips of dog epicardial coronary arteries of different sizes: proximal large coronary arteries with outside diameters (OD) larger than 2.5 mm and distal small arteries with 0.7–0.9 mm OD. Responses to pharmacologic vasodilators, including nitroglycerin (NTG) and adenosine, were also studied for comparison. The relaxation induced by halothane in concentrations of 0.8–2.3% and by NTG ($10^{-9}$–$10^{-5}$ M) was greater in proximal large coronary arteries than in distal small ones contracted with 20 mM KCl. In contrast, the relaxation by isoflurane (1.2–3.5%) and by adenosine ($10^{-8}$–$10^{-4}$ M) was greater in small coronary arteries than in large ones. These results suggest that isoflurane is, like adenosine, preferentially a small artery dilator. (Key words: Anesthetics, volatile: halothane; isoflurane. Arteries: coronary; vascular muscle. Heart: coronary vasodilation. Pharmacology: adenosine; nitroglycerin.)**

ALTHOUGH it has been suggested that both halothane and isoflurane are systemic and coronary vasodilators,[1–4] only isoflurane has been reported to cause "coronary steal."[3,5–8] Coronary steal is defined as increasing flow to normal myocardium by diverting it away from a collateralized ischemic area[9] and is caused by preferential dilatation of resistance vessels in the nonischemic area.

Proximal large coronary arteries and distal coronary arterioles (resistance vessels) differ considerably from one another in terms of structure, function, and regulation.[10] On the other hand, *in vitro* studies suggest that there are differences in responses to vasodilators between proximal large and distal small epicardial arteries, and that small epicardial arteries *in vitro* have similar reactivity with that of resistance arterioles *in vivo*.[11–14] For example, nitroglycerin (NTG) is a large coronary dilator, and in contrast, adenosine is preferentially a dilator of resistance arterioles *in vivo* and small epicardial arteries *in vitro*. Despite these facts, no comparison of the effects of anesthetics on isolated large and small coronary arteries has been made.

In the current study, we compared the effects of halothane and isoflurane on proximal large and distal small epicardial coronary arteries isolated from the dog. In addition, the effects of coronary vasodilators, NTG, and adenosine were examined as a comparative study.

## Methods

The study protocol was approved by the Kyoto University Animal Use Committee. Sixteen mongrel dogs of either sex weighing 6–17 kg were anesthetized with intravenous ketamine in a dose of 20 $mg \cdot kg^{-1}$ and were killed by bleeding from the common carotid arteries. The heart was rapidly removed, and the left anterior descending and circumflex branches of the left coronary artery were isolated. Proximal portions with outside diameters (OD) of greater than 2.0 mm and distal portions with 0.7–0.9 mm OD were isolated; mean values of OD were 2.61 ± 0.09 mm (n = 14) and 0.89 ± 0.01 mm (n = 14), respectively, for arteries exposed to anesthetics, and 2.73 ± 0.08 mm (n = 7) and 0.89 ± 0.01 mm (n = 7), respectively, for arteries exposed to vasodilators. The arteries were cleaned and cut into helical strips that measured approximately 17 mm in length. Each strip was fixed vertically between hooks in a 10-ml muscle bath containing the nutrient solution that was aerated with a mixture of 95% $O_2$ and 5% $CO_2$ and maintained at 37 ± 0.5° C. The hook anchoring the upper end of the strip was connected to the lever of a force-displacement transducer (Toyo Baldwin, Tokyo, Japan). The resting tension was adjusted to 2.0 g for large arteries and 1.5 g for small arteries.[15] Constituents of the nutrient solution (in mM) were as follows: NaCl, 118.2: KCl, 4.6: $NaHCO_3$, 24.8: $CaCl_2$, 2.5: $MgSO_4$, 1.2: $KH_2PO_4$, 1.2: and dextrose, 10. The *p*H of the solution was 7.35–7.45 when the solution was aerated with the gas mixture. Before the start of the experiments, all preparations were allowed to equilibrate for 60–90 min in the control media, during which time the fluids were replaced every 10–15 min.

Isometric contractions and relaxations were displayed on an ink writing oscillograph (Nihondenki Sanei Co., Tokyo, Japan). The contractile response to KCl (30 mM) was first obtained, with the average values in large and small coronary arteries being 1,902 ± 287 mg (n = 21) and 614 ± 88 mg (n = 21), respectively. To examine the effect of anesthetics on coronary vascular smooth muscle with intact endothelial cells,[16,17] the preservation of en-

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dothelial cell function of each strip was confirmed by testing relaxation induced by $10^{-6}$ M acetylcholine[18] in KCl (20 mM)-contracted strips; the acetylcholine-induced relaxation relative to the relaxation induced by $10^{-4}$ M papaverine averaged 47.7 ± 4.4% (n = 14) and 46.4 ± 6.7% (n = 7) in large coronary arteries for anesthetics and vasodilators, respectively, and 55.7 ± 3.1% (n = 14) and 60.9 ± 3.8% (n = 7) in small coronary arteries for anesthetics and vasodilators, respectively.

In the preliminary study, the contraction of some small coronary arteries induced by prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) or serotonin (but not by KCl) was not sustained for more than 60 min, which was necessary for obtaining the dose-response relationship of anesthetics. Thus, before the dose-response curves for inhalation anesthetics and vasodilators were obtained, arterial strips had been previously contracted with 20 mM KCl. Halothane and isoflurane were introduced in the oxygen-carbon dioxide mixture through Fluotec 3 (Cyprane Keighley, England) for halothane and Fortec (Cyprane Keighley, England) for isoflurane. The concentration in the resulting gas mixture was monitored and adjusted using a Capnomac Multicap (Datex, Finland). The muscle bath was covered with plastic to prevent the aerating gas from immediately escaping into the atmosphere. The actual concentrations of these volatile anesthetics in the bathing medium were determined by gas chromatography (Hewlett Packard 5890A Gas Chromatograph, Palo Alto, CA).[19] Saturation of bathing medium by each concentration of anesthetic gas was attained within 5–7 min. The concentrations for 1.5% halothane and 2.3% isoflurane were 10.74 ± 0.43 mg/100 ml (n = 10) and 7.57 ± 0.41 mg/100 ml (n = 10), respectively. Nitroglycerin and adenosine were added directly to the bathing media in cumulative concentrations. Dose–response curves for halothane and isoflurane or NTG and adenosine were obtained in the same preparation in random sequence. At the end of each experiment with an anesthetic, NTG, adenosine, or acetylcholine, papaverine in a concentration of $10^{-4}$ M was added to attain maximum relaxation. Relaxation induced by anesthetics or vasodilators was compared with that produced by papaverine.

Values are expressed as means ± SEM. To compare the effects of halothane *versus* isoflurane, NTG *versus* adenosine, or the large *versus* small coronary arteries, Student's *t* test for paired data was used. Other data were analyzed statistically by analysis of variance (ANOVA) and Newman-Keuls multiple range test. $P < 0.05$ was considered statistically significant.

Drugs used were halothane (Imperial Chemical Industries, England), isoflurane (Dainabot, Osaka, Japan), nitroglycerin (Nihon Kayaku, Tokyo, Japan), adenosine (Kohjin, Tokyo), and papaverine hydrochloride (Dainippon Seiyaku, Osaka, Japan).

## Results

### Response to Anesthetics

In helical strips of proximal large coronary arteries contracted with KCl, halothane in concentrations of 0.8–2.3% produced a concentration-dependent relaxation. However, halothane failed to significantly affect the tension of small coronary arteries partially contracted with KCl; halothane produced slight relaxation in six of 14 strips and slight contraction in the remaining eight small coronary arterial strips (fig. 1, left). Thus, halothane-induced relaxation was significantly greater in large than in small coronary arteries ($P < 0.05$). In contrast, isoflurane in concentrations of 1.2–3.5% produced a concentration-dependent relaxation in small coronary arteries. In large coronary arteries, isoflurane at 1.2% produced a slight contraction, but at 2.3 and 3.5%, it produced a concentration-dependent relaxation. Isoflurane-induced relaxation was significantly greater in small coronary arteries than in large ones ($P < 0.05$; fig. 1, right). The actual recordings of the response of large and small coronary arteries to halothane and isoflurane are presented in figure 2. The responses of large and small coronary arteries to halothane and isoflurane at each concentration stabilized within 20–30 min; thus, it took about 60–70 min to complete the concentration-response relationship. After the response to 2.3% halothane or 3.5% isoflurane had been obtained and the anesthetics had been removed from aerating gas mixture, the arterial tension returned to the level prior to administration of anesthetics.

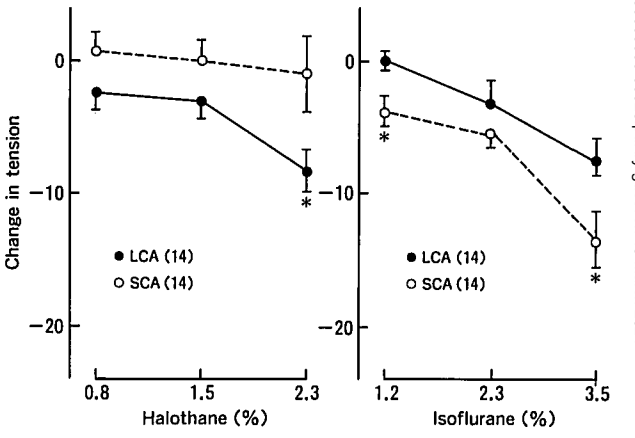


FIG. 1. Responses to halothane (*left*) and isoflurane (*right*) of large and small coronary arteries previously contracted with 20 mM KCl. The absolute value of relaxation induced by $10^{-4}$ M papaverine was taken as 100%; mean values in large and small coronary arteries were 2473 ± 317 mg and 946 ± 136 mg, respectively. Minus (−) represents relaxation. LCA = large coronary artery; SCA = small coronary artery. Figures in parentheses indicate the number of preparations studied. *$P < 0.05$ and **$P < 0.01$ large coronary artery *versus* small coronary artery.

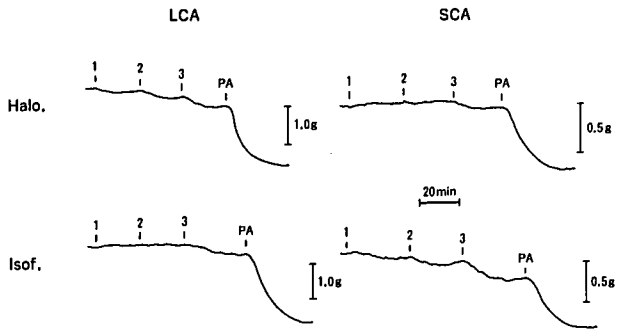


FIG. 2. Comparison of the response to halothane (*upper tracing*) and isoflurane (*lower tracing*) of large and small coronary arteries contracted with 20 mM KCl. Halo = halothane; Isof. = isoflurane. Markers 1, 2, and 3 for halothane represent 0.8, 1.5, and 2.3%, respectively, and markers for isoflurane represent 1.2, 2.3, and 3.5%, respectively. PA represents papaverine $10^{-4}$ M.

In comparing the relaxant effects of halothane *versus* isoflurane at clinically relevant concentrations, the relaxation induced by halothane at 0.8% was significantly greater than that induced by isoflurane at 1.2% in large coronary arteries ($P < 0.05$), although in small coronary arteries the relaxation by isoflurane (1.2%) was slightly, but not significantly, greater than that by halothane (0.8%). At higher concentrations of 2 or 3 MAC, the relaxation of small coronary arteries induced by isoflurane (2.3% and 3.5%) was significantly greater than that induced by halothane (1.5 and 2.3%; $P < 0.05$).

### Response to NTG and Adenosine

Nitroglycerin ($10^{-9}$–$10^{-5}$ M) and adenosine ($10^{-8}$–$10^{-4}$ M) rapidly relaxed dog coronary arteries of different sizes in a dose-dependent manner; thus, a series for the dose-response relationship was completed within 15 min. There were significant differences in the relaxation response of large and small coronary arteries to NTG and to adenosine. Nitroglycerin-induced relaxation was significantly greater in large than in small coronary arteries (fig. 3, left). In contrast, adenosine relaxed small coronary arteries to a significantly greater extent than large coronary arteries (fig. 3, right). The maximum relaxation induced by NTG of large coronary arteries and that induced by adenosine of small coronary arteries were significantly greater than the relaxations of large or small coronary arteries induced by anesthetics at the highest concentrations tested.

## Discussion

There have been numerous *in vivo* studies concerning the effects of halothane or isoflurane on coronary circulation in humans and in animals; however, there is still disagreement as to whether isoflurane is a small vessel-type coronary vasodilator with the potential to cause regional myocardial ischemia in the patient with coronary disease.[6,7,20,21] The disagreements in the results of the effects of isoflurane on coronary circulation obtained in *in vivo* studies may be derived in part from different experimental conditions; coronary circulation is inevitably affected by anesthetic-induced changes in systemic hemodynamics, myocardial metabolism, or contractility, and further by the direct vascular effects of opiates or barbiturates.[22,23] Among these *in vivo* studies, Sill *et al.*,[6] using quantitative coronary angiography, clearly showed that isoflurane at 0.75–2.25% produced no change in the caliber of the epicardial coronary arteries, concomitant with a doubling of myocardial flow, and concluded that the coronary vasodilating effect of isoflurane is limited to the small coronary vessels.

Studies using isolated coronary arteries, devoid of the influence secondary to hemodynamic changes, suggest that both halothane and isoflurane are direct coronary vasodilators. Bollen *et al.*[24] compared the direct effects of halothane and isoflurane on isolated porcine epicardial segments of coronary artery with outside diameters of 1.5–2.0 mm and demonstrated that halothane, at clinically relevant concentrations, relaxed arteries previously contracted with U44069, a prostaglandin (PG) $H_2$ analog, or with KCl to a greater extent than relaxation following isoflurane. Blaise *et al.*,[25] using isolated coronary arteries from left circumflex and proximal left anterior descending coronary arteries from the dog, demonstrated that isoflurane at a concentration of 2.3% attenuated the contractile responses of arteries to $PGF_{2\alpha}$, serotonin, and phenylephrine. Our findings of the effect of halothane and isoflurane on isolated large coronary arteries are in good

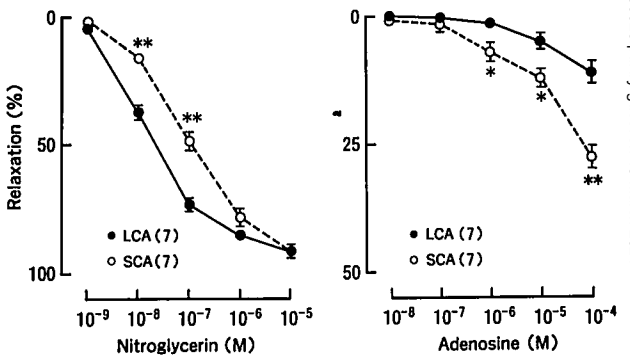


FIG. 3. Responses to nitroglycerin (*left*) and adenosine (*right*) of large and small coronary arteries previously contracted with 20 mM KCl. The absolute value of relaxation induced by $10^{-4}$ M papaverine was taken as 100%; mean values in large and small coronary arteries for nitroglycerin were 2,370 ± 239 mg and 528 ± 105 mg, respectively, and those for adenosine were 2,012 ± 354 mg and 663 ± 125 mg, respectively. Figures in parentheses indicate the number of preparations studied. *$P < 0.05$ and **$P < 0.01$, large coronary artery *versus* small coronary artery.

agreement with those of previous studies; however, the effects of anesthetics on the isolated distal small coronary arteries have not been examined previously.

Using isolated dog epicardial arteries of different sizes, the current study revealed that vasodilators and volatile anesthetics produced a quantitatively different magnitude of relaxation in the proximal large coronary arteries and the distal small coronary arteries. Nitroglycerin and halothane relaxed proximal large coronary arteries to a greater extent than the distal small arteries, whereas adenosine and isoflurane produced an opposite effect: greater relaxation in small coronary arteries than in large ones.

Vessels of different size, width, or length have different optimal resting tensions when they are subjected to *in vitro* studies in which the changes in isometric tension are measured. The relaxant effects of vasodilators are related directly to passive resting tensions developed by stretching of arterial strips.[15] We differentiated the large and small epicardial coronary arteries according to the outside diameter (greater than 2.0 mm as large artery and less than 1.0 as small artery), and the resting tension was adjusted to 2.0 and 1.5 g, respectively, although the sizes of arteries were slightly variable within the groups. Schnarr and Sparkes[12] used large and small coronary arteries with outside diameters of 2.0 and less than 0.55 mm, respectively, and the resting tensions were 1.6 and 0.12 g, respectively. Miwa and Toda[14] used arteries with inside diameters of greater than 1.5 mm, 0.5–0.8 mm, and less than 0.3 mm as large, medium, and small coronary arteries, respectively, and added the resting tensions of 3.0, 1.5, and 0.6 g, respectively. Despite different experimental conditions, a similar finding is that NTG preferentially dilates large coronary arteries, and in contrast, adenosine preferentially dilates small coronary arteries. Thus, the regional difference of relaxation of isolated coronary arteries induced by halothane and isoflurane, as well as NTG and adenosine, is likely to result from the functionally different responsiveness of large and small coronary arteries to anesthetics but not from the difference in resting tensions used in the current study.

It has been demonstrated that resistance vessels *in vivo* have similar reactivity to small epicardial arteries *in vitro*.[11,13,26] For example, Cohen and Kirk,[13] using cannulated dog coronary vessels, showed that NTG preferentially reduces large coronary artery resistance under normal and ischemic conditions, and adenosine has its principal action on resistance coronary vessels under normal perfusions, resulting in a reduction of the total coronary vascular resistance. Thus, although we examined the effect of anesthetics on small epicardial arteries that are anatomically different from coronary arterioles, one might extrapolate that selective actions of anesthetics on small coronary arteries are likely to occur in resistant arterioles *in vivo*.

Although *in vivo* and *in vitro* studies suggest that adenosine is a potent coronary vasodilator, adenosine at $10^{-4}$ M produced only about 25% of relaxations relative to those induced by $10^{-4}$ M papaverine in small coronary arteries contracted with KCl. Potassium chloride-induced constriction appears to be less susceptible to adenosine than prostanoid-induced constriction. In fact, our previous study demonstrated that adenosine at $10^{-4}$ M induced about 80% of relaxations in small coronary arteries contracted with $PGF_{2\alpha}$.[27] Such is the case with inhalation anesthetics. Both halothane and isoflurane have been demonstrated to inhibit prostanoid- or serotonin-induced constriction to a greater extent than KCl-induced constriction of large epicardial coronary arteries isolated from the dog[25] and pig.[24] Thus, it is possible that isoflurane produces more profound relaxation in small coronary arteries contracted with $PGF_{2\alpha}$ than with KCl as observed in the current study; however, isoflurane-induced relaxation even at 3.4%, which is well beyond clinical relevant concentrations, probably would be less than adenosine-induced relaxation, whatever agents may be used for preconstriction. Further work in this area is needed.

Although seemingly paradoxical, agents such as adenosine, which preferentially dilate coronary arterioles, can induce myocardial ischemia. The peripheral coronary arteries that are expected to dilate maximally under the ischemic condition could not be dilated any more by vasodilators, while vessels in the nonischemic region would be dilated, resulting in decrease of regional blood flow to the ischemic area.[9] In the clinical setting, dipyridamole,[28,29] an adenosine potentiator, is a drug potentially causing transient myocardial ischemia by such "coronary steal" due to its vasodilating action on coronary arterioles in patients with significant organic stenosis. Our finding that the effects of isoflurane on coronary artery resemble those of adenosine supports the possibility that isoflurane at concentrations higher than those usually used clinically produces "coronary steal." In fact, Buffington *et al.*,[7] in a canine model of chronic coronary occlusion, clearly showed that isoflurane, like adenosine, could produce a flow maldistribution with a decrease in the collateral-dependent region and an increase in the normally perfused region, concomitant with a deterioration in collateral zone function.

In conclusion, we demonstrated the regional difference of relaxation induced by halothane and isoflurane in isolated dog epicardial coronary arteries previously contracted with KCl; halothane, like nitroglycerin, preferentially relaxed the proximal large coronary artery, and in contrast, isoflurane, like adenosine, preferentially relaxed the distal small coronary artery.

## References


1. Domenech RJ, Macho P, Valdes J, Penna M: Coronary vascular resistance during halothane anesthesia. ANESTHESIOLOGY 46: 236–240, 1977
2. Cromwell TH, Stevens WC, Eger EI II, Shakespeare TF, Halsey MJ, Bahlman SH, Fourcade HE: The cardiovascular effects of compound 469 (Forane*) during spontaneous ventilation and $CO_2$ challenge in man. ANESTHESIOLOGY 35:17–25, 1971
3. Reiz S, Balfors E, Sorensen MB, Ariola S Jr, Friedman A, Truedsson H: Isoflurane—A powerful coronary vasodilator in patients with coronary artery disease. ANESTHESIOLOGY 59:91–97, 1983
4. Priebe H-J: Differential effects of isoflurane on regional right and left ventricular performances, and on coronary, systemic, and pulmonary hemodynamics in the dog. ANESTHESIOLOGY 66: 262–272, 1987
5. Priebe H-J, Foëx P: Isoflurane causes regional myocardial dysfunction in dogs with critical coronary artery stenosis. ANESTHESIOLOGY 66:293–300, 1987
6. Sill JC, Bove AA, Nugent M, Blaise GA, Dewey JD, Grabau C: Effects of isoflurane on coronary arteries and coronary arterioles in the intact dog. ANESTHESIOLOGY 66:273–279, 1987
7. Buffington CW, Romson JL, Levine A, Duttlinger NC, Huang AH: Isoflurane induces coronary steal in a canine model of chronic coronary occlusion. ANESTHESIOLOGY 66:280–292, 1987
8. Moffitt EA, Barker RA, Glenn JJ, Imrie DD, DelCampo C, Landymore RW, Kinley CE, Murphy DA: Myocardial metabolism and hemodynamic responses with isoflurane anesthesia for coronary artery surgery. Anesth Analg 65:53–61, 1986
9. Gross GJ, Warltier DC: Coronary steal in four models of single or multiple vessel obstruction in dogs. Am J Cardiol 48:84–92, 1981
10. Epstein SE, Cannon III RO, Talbot TL: Hemodynamic principles in the control of coronary blood flow. Am J Cardiol 56:4E–10E, 1985
11. Fam WM, McGregor M: Effect of nitroglycerin and dipyridamole on regional coronary resistance. Circ Res 22:649–659, 1968
12. Schnaar RL, Sparks HV: Response of large and small coronary arteries to nitroglycerin, $NaNO_2$, and adenosine. Am J Physiol 223:223–228, 1972
13. Cohen MV, Kirk ES: Differential response of large and small coronary arteries to nitroglycerin and angiotensin. Circ Res 33: 445–453, 1973
14. Miwa K, Toda N: The regional difference of relaxations induced by various vasodilators in isolated dog coronary and mesenteric arteries. Jpn J Pharmacol 38:313–320, 1985
15. Toda N, Hatano Y, Hayashi S: Modifications by stretches of the mechanical response of isolated cerebral and extra-cerebral arteries to vasoactive agents. Pflugers Arch 374:73–77, 1978
16. Muldoon SM, Hart JL, Bowen KA, Freas W: Attenuation of endothelium-mediated vasodilation by halothane. ANESTHESIOLOGY 68:31–37, 1988
17. Stone DJ, Johns RA: Endothelium-dependent effects of halothane, enflurane, and isoflurane on isolated rat aortic vascular rings. ANESTHESIOLOGY 71:126–132, 1989
18. Furchgott RF, Zawadzki JV: The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 288:373–376, 1980
19. Muldoon SM, Vanhoutte PM, Lorenz RR, Van Dyke RA: Venomotor changes caused by halothane acting on the sympathetic nerves. ANESTHESIOLOGY 43:41–48, 1975
20. Merin RG: Are the myocardial functional and metabolic effects of isoflurane really different from those of halothane and enflurane? ANESTHESIOLOGY 55:398–408, 1981
21. Cason BA, Verrier ED, London MJ, Mangano DT, Hickey RF: Effects of isoflurane and halothane on coronary vascular resistance and collateral myocardial blood flow: Their capacity to induce coronary steal. ANESTHESIOLOGY 67:665–675, 1987
22. Toda N, Hatano Y: Alpha-adrenergic blocking action of fentanyl on the isolated aorta of the rabbit. ANESTHESIOLOGY 46:411–416, 1977
23. Hatano Y, Nakamura K, Moriyama S, Mori K, Toda N: The contractile responses of isolated dog cerebral and extracerebral arteries to oxybarbiturates and thiobarbiturates. ANESTHESIOLOGY 71:80–86, 1989
24. Bollen BA, Tinker JH, Hermsmeyer K: Halothane reflexes previously constricted isolated porcine coronary artery segments more than isoflurane. ANESTHESIOLOGY 66:748–752, 1987
25. Blaise G, Sill JC, Nugent M, Van Dyke RA, Vanhoutte PM: Isoflurane causes endothelium-dependent inhibition of contractile responses of canine coronary arteries. ANESTHESIOLOGY 67: 513–517, 1987
26. Brown BG, Bolson E, Petersen RB, Pierce CD, Dodge HT: The mechanisms of nitroglycerin action: Stenosis vasodilatation as a major component of the drug response. Circulation 64:1089–1097, 1981
27. Toda N, Hatano Y: Antagonism by droperidol of dopamine-induced relaxation in isolated dog arteries. Eur J Pharmacol 57: 231–238, 1979
28. Brown BG, Josephson MA, Petersen RB, Pierce CD, Wong M, Hecht HS, Bolson E, Dodge HT: Intravenous dipyridamole combined with isometric handgrip for near maximal acute increase in coronary flow in patients with coronary artery disease. Am J Cardiol 48:1077–1085, 1981
29. Ando Y, Yasuda H, Kobayashi T, Miyamoto A, Kanamori K, Murakami R, Matsumura N: Conditions for "coronary steal" caused by coronary vasodilator in man. Jpn Heart J 23:79–95, 1982