

Amiodarone Causes Endothelium-Dependent Vasodilation in Canine Coronary Arteries

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Objective

To assess the vasodilating effects of amiodarone on canine coronary arteries by using solutions of amiodarone dissolved in polysorbate 80 or water.

Methods

Rings of coronary arteries, with or without intact endothelium, were immersed in Krebs solution and connected to a transducer for measuring the isometric force promoted by a vascular contraction. The arteries were exposed to increasing concentrations of polysorbate 80, amiodarone dissolved in water, amiodarone dissolved in polysorbate 80, and a commercial presentation of amiodarone (Cordarone). The experiments were conducted in the presence of the following enzymatic blockers: only indomethacin, *N* ω -nitro-L-arginine associated with indomethacin, and only *N* ω -nitro-L-arginine.

Results

Polysorbate 80 caused a small degree of nonendothelium-dependent relaxation. Cordarone, amiodarone dissolved in water, and amiodarone dissolved in polysorbate 80 caused endothelium-dependent relaxation, which was greater for amiodarone dissolved in polysorbate and for Cordarone. Only the association of indomethacin and *N* ω -nitro-L-arginine could eliminate the endothelium-dependent relaxation caused by amiodarone dissolved in polysorbate 80.

Conclusion

The results obtained indicate that vasodilation promoted by amiodarone in canine coronary arteries is mainly caused by stimulation of the release of nitric oxide and cyclooxygenase-dependent relaxing endothelial factors.

Key words

endothelium, amiodarone, nitric oxide, cyclooxygenase, coronary circulation

Currently, amiodarone is exclusively used as an antiarrhythmic agent. However, it was primarily introduced as a vasodilator for the treatment of angina pectoris¹. Although its vasodilating effect is well known and frequently evidenced as hypotension after its intravenous use^{2,3}, the mechanisms responsible for vasodilation have not been totally clarified. Amiodarone and its metabolite, *N*-desethylamiodarone, have been shown to cause endothelium-dependent relaxation in human veins^{4,5}. However, information about the mechanisms involved in relaxation of systemic arteries, mainly coronary arteries, is still scarce.

In addition to the intrinsic effects of amiodarone, polysorbate 80, a solvent used in commercial amiodarone, may influence the effect of other drugs⁶⁻⁸, cause histamine release⁹, and be potentially harmful to the endothelium^{10,11}. These effects may be clinically relevant, and have led to the search for other aqueous presentations of amiodarone¹².

The present investigation aimed at assessing the vasodilating effects of amiodarone, as well as those of polysorbate 80, in canine coronary arteries, by using a solution of amiodarone dissolved in polysorbate 80, a solution of amiodarone diluted in water, and a solution of polysorbate 80 diluted in water. To separately assess each of the 2 major pathways of production and release of vasodilating endothelial factors (nitric oxide and prostacyclins), the experiments were performed in the presence of the nitric oxide synthetase inhibitor (*N* ω -nitro-L-arginine), of cyclooxygenase (indomethacin), and of both.

Methods

Crossbred dogs (weight, 25-30 kg), of both sexes, and with no verminous disease, were anesthetized with intravenous thio-pental sodium (30 mg/kg; Abbott Lab, Chicago, IL, USA), had their carotids sectioned, and died of bleeding. Their chests were rapidly opened, and their hearts, still active, were removed and immersed in cold Krebs solution with a molar composition (NaCl, 118.3; KCl, 4.7; MgSO₄, 1.2; KH₂PO₄, 1.22; CaCl₂, 2.5; NaHCO₃, 25.0; and glucose, 11.1). The investigation was approved and performed according to the recommendations in the Guide for Care and Use of Laboratory Animals published by the US National Institutes of Health [DHHS Publication No. (NIH) 85-23, revised 1996], and the guidelines of the Institutional Committee for Animal Care and Use of the Mayo Foundation, Rochester, MN, USA.

The circumflex coronary artery was dissected and one segment was removed. Four- to 5-mm long vascular rings were carefully obtained from that arterial segment. The rings were suspended in 25-mL chambers containing Krebs solution at 37°C and aired

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with a gas mixture composed of 95% O₂ and 5% CO₂ (pH = 7.4). Each vascular ring was suspended by 2 stainless steel hooks passed through the lumen of the vessels. One hook was attached to the end of the chamber and the other to the force transducer Statham UC 2 (Gould, Cleveland, Ohio, USA). After stabilization of the preparation, the rings were progressively stretched until the pre-established tension of 10 g.

In all experiments, the absence or presence of intact endothelium was assessed through the response to a single dose of acetylcholine (10⁻⁶ M) after contraction induced by 20 mM of potassium chloride. Removal of the endothelium was mechanically performed by introducing the arm of a delicate tweezers in the lumen of the vessel, and by rolling the vessel under that arm of the tweezers.

After assessing the functional status of the endothelium, the vessels were maintained in the chambers immersed in Krebs solution with no drug for 30 minutes before beginning the experiments.

All experiments were performed in parallel, using pairs of vascular rings composed of one ring with endothelium and another ring without endothelium. Initially, concentration-response curves were obtained for the following solutions: amiodarone dissolved in distilled water (AMA) at concentrations from 10⁻⁹ M to 10⁻⁴ M; amiodarone dissolved in polysorbate 80 (AMPO) at concentrations from 10⁻⁹ M to 10⁻⁴ M of amiodarone and 10⁻¹³ M to 10⁻⁸ M of polysorbate; polysorbate 80 (10⁻¹³ M to 10⁻⁸ M of polysorbate); and a commercial preparation of amiodarone (Cordarone, 10⁻⁹ M to 10⁻⁴ M of amiodarone). All solutions were simultaneously tested in rings with and without endothelium.

The first group of concentration-response curves was obtained without blocking the cyclooxygenases or nitric oxide synthetase. Afterwards, concentration-response curves were built for amiodarone in water (AMA) and in polysorbate 80 (AMPO) in the presence of indomethacin (2x10⁻⁵ M), indomethacin (2x10⁻⁵ M) in combination with N ω -nitro-L-arginine (L-NA) (2x10⁻⁴ M), and L-NA (2x10⁻⁴ M) only. The enzymatic blockers were added 1h before beginning to build the concentration-response curves. Prostaglandin F2 α (2x10⁻⁶ M) was used to contract the vessels in all experiments.

Acetylcholine, indomethacin, prostaglandin F2 α , amiodarone, polysorbate 80, and N ω -nitro-L-arginine were acquired from Sigma Chemical Company (St. Louis, Mo, USA). Cordarone (150 mg/3 mL) was provided by Wyeth Laboratories Inc., USA. All drugs were prepared with distilled water, except for indomethacin, which was dissolved in a solution of NaHCO₃ (10⁻⁵ M), and amiodarone, when dissolved in polysorbate 80.

The solution of amiodarone in polysorbate 80 (AMPO) was obtained by dissolving polysorbate 80 in distilled water to obtain a solution with an initial concentration of 10⁻⁹ M of polysorbate. Then, amiodarone was added to the solution to obtain an amiodarone concentration of 10⁻⁴ M. That initial solution of amiodarone and polysorbate was used to obtain the subsequent dilutions, and that initial concentration of polysorbate 80 (10⁻⁹ M) chosen was obtained by diluting 1 flask of Cordarone (150 mg/3 mL, Wyeth Laboratories, Inc.), aiming at an amiodarone concentration of 10⁻⁴ M.

Amiodarone dissolved only in water was obtained by diluting amiodarone in distilled water at 40°C and agitating with ultrasound in a warmed bath until obtaining a clear solution.

The results are expressed as mean \pm standard deviation of the percentage of the plateau of contraction induced by prostaglandin F2 α . The plateau of contraction, the initial point of the

concentration-response curve, was considered as 0% of relaxation. "n" indicates the number of animals from which the vascular rings were obtained.

The following statistical tests were used: 2-way ANOVA followed by the Bonferroni post-test, the Kruskal-Wallis test, and the Dunn multiple comparisons test. GraphPad Prism software, version 3.03 (GraphPad Software Inc.) was used. The differences were considered significant when P < 0.05.

Results

No significant difference was observed between the plateaus of contraction (tab. I) when comparing arteries with and without endothelium within the same experimental group or between groups.

The relaxation caused by AMA (fig. 1, n=9) in arteries with endothelium ranged from 0% to 57.0% \pm 17.9%, and, in arteries without endothelium, from 0.37% \pm 1.11% to 17.2% \pm 15.56%. The differences were significant (P < 0.001) for the concentrations of 3.16x10⁻⁵ M and 10⁻⁴ M.

Cordarone (fig. 1, n=6) caused relaxation that ranged from 0.4% \pm 1.02%, at the minimum concentration, to 94.40% \pm 10.10%, at the maximum concentration, in vessels with endothelium. In vessels without endothelium, the relaxation ranged from 0% to 40.26% \pm 18.44%. The differences between relaxation of the vessels with and without endothelium were significant (P<0.001) for the concentrations of amiodarone of 3.16x10⁻⁵ and 10⁻⁴ M.

The solution of amiodarone in polysorbate (AMPO) (fig. 1, n=6) caused relaxation in arteries with endothelium that ranged from 0%, at the minimum concentration, to 100% \pm 0%, at the maximum concentration. In arteries without endothelium, relaxation ranged from 0% to 28.46% \pm 13.87%. The differences between the arteries with and without endothelium were significant (P < 0.001) for the concentrations from 10⁻⁵ M to 10⁻⁴ M.

Polysorbate 80 caused a mild relaxation in arteries with and without endothelium (fig. 2, n=6). The maximum relaxation in arteries with and without endothelium was 27.43% \pm 24.10% and 18.35% \pm 15.08%, respectively. The difference was not significant. It is worth noting that the addition of a single dose of amiodarone dissolved in water (10⁻⁴ M) after the last dose of the concentration-response curve for polysorbate 80 (10⁻⁸ M) caused immediate relaxation of 99.37% \pm 1.39% in arteries with endothelium and of 24.55% \pm 15.28% in arteries without endothelium (P<0.001).

Comparing the curves obtained with Cordarone with those obtained with amiodarone in polysorbate (AMPO), a difference in relaxation was observed only for the concentration of 10⁻⁵ M, and AMPO caused greater relaxation than that provided by commercial amiodarone (P < 0.01) in the arteries with endothelium.

Thus, as polysorbate 80 caused mild relaxation independently of the endothelium, and as the relaxation provided by AMPO was similar to that caused by commercial amiodarone, the subsequent experiments were performed only with amiodarone dissolved in water (AMA) and amiodarone dissolved in the polysorbate 80 solution (AMPO).

The presence of indomethacin (2 x 10⁻⁵ M) caused a significant deviation to the right of the concentration-response curve (P<0.05) for AMA (fig. 3, n=6); however, at the maximum concentration (10⁻⁴ M), the relaxation observed in vessels with endo-



Table I - Plateau of contraction, in g, of the concentration-response curves

Solution	Plateau of contraction (g)			
	No blockers	Indomethacin	L-NA	Indomethacin + L-NA
Commercial amiodarone with endothelium	10.22±4.32	-	-	-
Commercial amiodarone without endothelium	9.80±3.76	-	-	-
Amiodarone in water with endothelium	6.75±3.60	8.20±4.36	8.10±2.70	8.68±1.210
Amiodarone in water without endothelium	6.93±1.93	8.56±2.70	6.00±3.87	7.28±2.958
Amiodarone in polysorbate 80 with endothelium	10.00± 2.88	7.02±2.81	9.26±4.41	7.50±1.57
Amiodarone in polysorbate 80 without endothelium	8.840±2.39	7.28±2.20	9.22±3.08	7.65±2.03
Polysorbate 80 with endothelium	5.62±2.90	-	-	-
Polysorbate 80 without endothelium	7.13±2.28	-	-	-

The results are expressed as mean ± standard deviation. The differences are not significant.

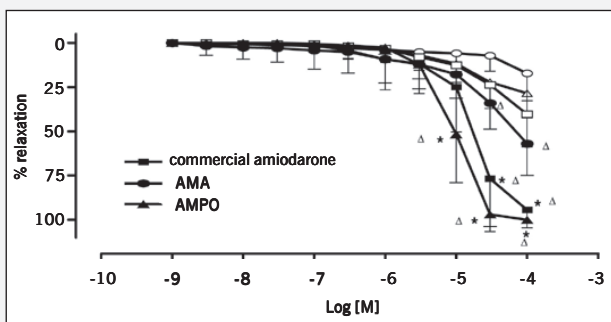


Fig. 1 - Concentration-response curve for the commercial presentation of amiodarone (Cordarone), amiodarone dissolved in water (AMA) and in polysorbate 80 (AMPO) in canine coronary arteries with (solid symbols) and without (clear symbols) endothelium, contracted with prostaglandin F_{2α} (2.5 x 10⁻⁶ M). The results are expressed as mean ± standard deviation. * indicates P<0.001 compared with AMA, and Δ indicates P<0.001 comparing arteries with and without endothelium.

thelium was still significantly greater (38.81%±15.07%, P<0.001) than that observed in vessels without endothelium (13.35%±6.63%).

Indomethacin did not significantly affect the relaxation caused by AMPO (fig. 3, n=6). Relaxation in the arteries with endothelium ranged from 0% to 85.76%±19.90%, and from 0% to 16.75%±8.30% in the vessels without endothelium. The difference in relaxation between the vessels with and without endothelium was significant (P<0.001) for the concentrations from 10⁻⁵ to 10⁻⁴ M.

Nω-nitro-L-arginine (L-NA) (2x10⁻⁴ M) eliminated the endothelium-dependent relaxation caused by AMA (fig. 4, n=6), because no significant differences in relaxation were observed in vessels with and without endothelium. Although Nω-nitro-L-arginine has caused some deviation in the concentration-response curve to the right, it has not inhibited endothelium-dependent relaxation caused by AMPO (n=6, maximum of 88.73%±15.67%). The relaxation obtained with the AMPO concentrations of 3.16x10⁻⁵ M and 10⁻⁴ M was significantly greater in arteries with endothelium (P<0.001).

The combination of Nω-nitro-L-arginine (2x10⁻⁴ M) with indomethacin (2x 10⁻⁵ M) eliminated completely the endothelium-dependent relaxation caused by both AMA and AMPO (fig. 5, n=6), because no significant difference was observed between relaxation of arteries with and without endothelium for both drugs, although some endothelium-independent relaxation occurred.

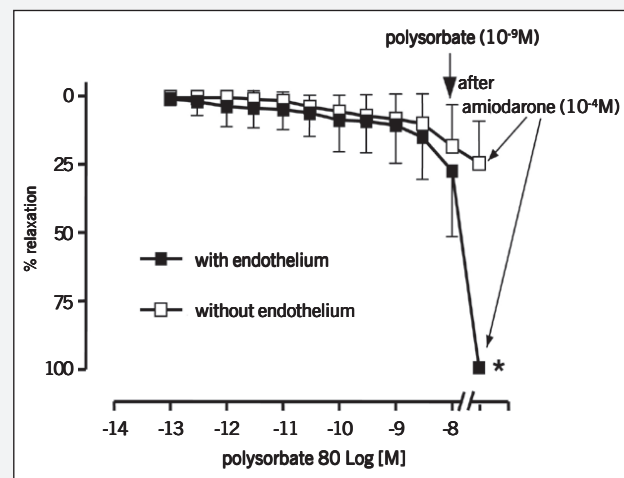


Fig. 2 - Concentration-response curve for polysorbate 80 in canine coronary arteries. The arrow points to the relaxation caused by a single dose of amiodarone dissolved in water (10⁻⁴ M) after the addition of the last concentration of polysorbate (10⁻⁹ M). The results are expressed as mean ± standard deviation. * indicates P<0.001 comparing arteries with and without endothelium.

Discussion

As already emphasized, amiodarone and its metabolite, N-desethylamiodarone, have already been shown to cause endothelium-dependent relaxation in human veins similarly to that observed in canine coronary arteries, although only amiodarone dissolved in polysorbate was used in those investigations^{4,5}.

Our results show that amiodarone causes relaxation, which is mainly endothelium-dependent in canine coronary arteries. However, although polysorbate 80 alone does not cause endothelium-dependent relaxation, it seems that the presence of the solvent polysorbate influences that vasodilation, because its association with amiodarone significantly influences the magnitude of endothelium-dependent relaxation.

Considering the results obtained with amiodarone dissolved in water, it is evident that the isolated blockage of cyclooxygenases decreased, but did not eliminate, vasodilation. However, the isolated blockage of nitric oxide synthetase blocked vasodilation promoted by amiodarone in water. Such a fact emphasizes the greater importance of nitric oxide in the vasodilation promoted by amiodarone. However, only the simultaneous inhibition of cyclooxyge-

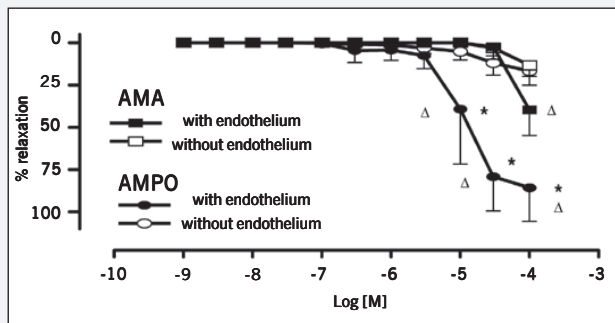


Fig. 3 - Concentration-response curve for amiodarone diluted in water (AMA) and in polysorbate 80 (AMPO) in canine coronary arteries in the presence of indomethacin (2×10^{-5} M) and contracted with prostaglandin F 2α (2.5×10^{-6} M). The results are expressed as mean \pm standard deviation. * indicates $P < 0.001$ compared with AMA and Δ indicates $P < 0.001$ comparing arteries with and without endothelium.

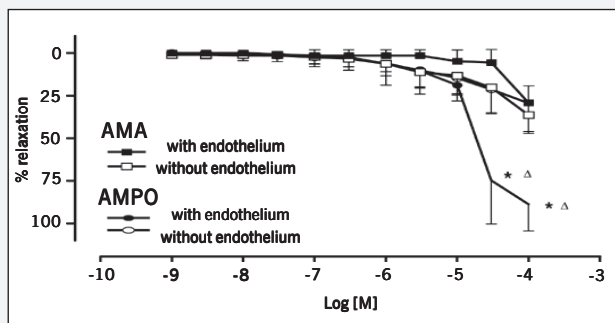


Fig. 4 - Concentration-response curve for amiodarone diluted in water (AMA) and in polysorbate 80 (AMPO) in canine coronary arteries in the presence of N ω -nitro-L-arginine (2×10^{-4} M) and contracted with prostaglandin F 2α (2.5×10^{-6} M). The results are expressed as mean \pm standard deviation. * indicates $P < 0.001$ compared with AMA, and Δ indicates $P < 0.001$ comparing arteries with and without endothelium.

nases and nitric oxide synthetase eliminated vasodilation promoted by amiodarone dissolved in polysorbate 80. Whether polysorbate 80 acted merely promoting better solubilization of amiodarone or whether it also modulated the effects of amiodarone, in both situations propitiating amplification of the vasodilating effect of amiodarone, is still questionable.

Evidence suggests that surfactants, such as polysorbates, may influence the enzymatic activity of the arachidonic acid. Surfactants have been shown to significantly reduce the inhibition promoted by the substrate of 15-lipoxygenases¹³ and promote the release of arachidonic acid^{14,15}. In addition, polysorbate 80 has been shown to facilitate the transportation of several ions (K^+ , Na^+ , NH_4^+ , Ca^{++}) and inorganic molecules through membrane models¹⁶⁻¹⁹. Evidence exists that polysorbates may also modulate sensitivity to certain antitumor agents, increasing the transportation of those agents through the membrane or facilitating their interaction^{6,19}, considering that amiodarone is a highly lipophilic drug²⁰.

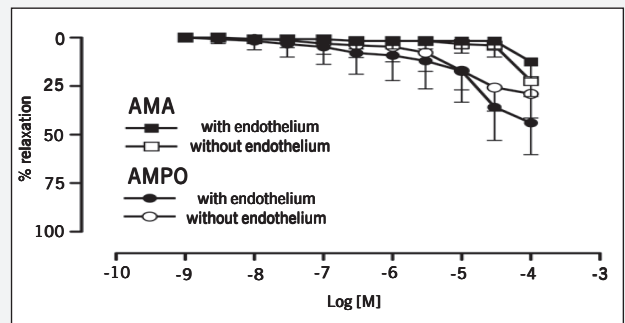


Fig. 5 - Concentration-response curve for amiodarone diluted in water (AMA) and in polysorbate 80 (AMPO) in canine coronary arteries in the presence of N ω -nitro-L-arginine (2×10^{-4} M) in combination with indomethacin (2×10^{-5} M) and contracted with prostaglandin F 2α (2.5×10^{-6} M). The results are expressed as mean \pm standard deviation. No significant differences were observed between the arteries with and without endothelium.

In vivo studies have also suggested that polysorbates are not inert and may influence the systemic effects of amiodarone^{7,8,21}, although other authors have shown that polysorbate may damage the vascular endothelium at concentrations greater than those used in our study^{4,5,10,11}.

The exact mechanism by which amiodarone causes the release of relaxing endothelial factors has not been completely clarified, but amiodarone²² and N-desethylamiodarone²³ have been shown to promote a sustained increase in the concentrations of cytoplasmic calcium in endothelial cells. Such calcium elevation may trigger the activation of the calmodulin-dependent pathway, which results in the release of vasodilating factors. In addition, evidence exists that amiodarone stimulates protein-G type receptors²⁴.

Although the results have clearly shown that the release of endothelial factors is the major mechanism of vascular relaxation, the results obtained with the simultaneous inhibition of the cyclooxygenases and nitric oxide synthetase have also shown that amiodarone causes some nonendothelium-dependent vasodilation (fig. 5), because a similar discreet relaxation is observed in arteries with and without endothelium. This fact may be related to its calcium channel blocking properties²⁵.

Although hypotension after the intravenous use of amiodarone is a well-known side effect^{2,3,26}, several mechanisms may be involved in vivo, in addition to the release of endothelial relaxing factors. Amiodarone has been shown to cause a reduction in cardiac performance or to induce a state of low peripheral vascular resistance due to an alpha-adrenergic blocking effect^{27,28}. In addition, polysorbate, present in the commercial formulation of amiodarone, may cause the release of histamine⁹, and result in hypotension.

In conclusion, our results show that vasodilation promoted by amiodarone in canine coronary arteries is mainly caused by the stimulation of the release of nitric oxide and cyclooxygenase-dependent endothelial relaxing factors.



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