Contrast Medium-Induced Vasoconstrictions

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CONTRAST MEDIUM-INDUCED VASOCONSTRICTIONS

An investigation of the vasoconstrictive action of iohexol in isolated rabbit coronary arteries

J. Karstoft, L. Bååth, I. Jansen and L. Edvinsson

Abstract

Angiographic contrast media (CM) may cause both vasodilatation and vasoconstriction. This study evaluates a contrast medium-induced vasoconstriction that occurs when isolated arteries are exposed directly to a CM. Segments of rabbit coronary arteries were mounted in tissue baths containing buffer solution. During the experiments the buffer solution was exchanged with iohexol iso-osmolar with plasma, which caused a temporary vasoconstriction of the vessel segments. The constriction did not depend on the degree of oxygenation of iohexol. The endothelium was not involved in the vasoconstriction. Prazosin slightly decreased the vasoconstriction and a small part of the constriction might thus depend on liberation of norepinephrine by iohexol. The constriction was totally inhibited by the calcium antagonist nifedipine, while it was augmented by addition of low concentrations of KCl to iohexol. It is concluded that the otherwise safe CM iohexol causes vasoconstriction in vitro by depolarizing the smooth muscle cells and the nerve terminals in the vessel wall.

Key words: Arteries, coronary; contrast medium, iohexol; calcium; experimental.

A change in vessel tone is a well known side effect from contrast media (CM) and generally CM cause vasodilatation. The tendency of a CM to cause vasodilation is related to its hyperosmolality, chemotoxicity and ion content (15-17, 23). However, during angiography vasospasm may also occur (5, 8, 25). This may be due to the manipulation of the angiographic catheter, but a vasospasm can also be provoked by the CM itself. The frequency of CM-induced vasospasm during angiography varies; in earlier studies a frequency of 10% has been observed (20). The mechanism causing the vasospasm is unknown. In isolated vessels vasospasm (vasoconstriction) has been provoked by exposure to hyperosmolar CM solutions (4, 10, 26). In these investigations the constrictions were believed to be due to the hyperosmolality of the media and not related to their chemotoxicity or ion content.

In previous studies with isolated coronary arteries we have found that CM, isotonic with plasma, influence the actions of different vasoactive substances due to the chemotoxicity and the ion content of the CM (3, 17-19). During those experiments a temporary vasoconstriction was also noticed as soon as a CM was added to the vessel. Since the CM used were iso-osmolar with plasma, the constriction was not due to hyperosmolality as in the previous studies (4, 10, 26). The vasoconstriction might be related to the vasospasm seen clinically.

The aim of the present study was to investigate by what mechanism a CM iso-osmolar with plasma may cause this vasoconstriction.

Material and Methods

Rabbits of both sexes (weight 2.0-3.0 kg) were anesthetized i.v. with pentobarbital (Mebumal vet, ACO, Sweden). The heart was removed and placed in Krebs' buffer solution at 4°C. The buffer solution contained (mM) 119 NaCl, 4.6 KCl, 1.5 CaCl2, 1.2 MgCl2, 15 NaHCO3, 1.2 NaH2PO4 and 11 glucose. The left coronary artery was dissected free from surrounding tissue and cut into 8 cylindric segments (length 0.7-1.5 mm, diameter 0.5-1.0 mm when mounted in the baths). Four of the segments were used on day 1 while the...
other 4 were stored in buffer solution at 4°C and used the following day. There was no difference in the contractility of the vessel segments used day 1 compared to those used day 2.

Each segment was placed in a 2.5 ml tissue bath containing buffer solution at 37°C and continuously gassed with a mixture of 95% O₂ and 5% CO₂. The segment was mounted between 2 L-shaped metal prongs. One prong was connected to a FT 03C Grass transducer (Grass Instrument Co., Quincy, MA) measuring isometric contractions. The other prong was connected to a displacement device. The device was adjusted to a passive force of 2 mN, creating a tension in the vessel wall imitating the blood pressure in vivo (13). The signals were amplified on a Transbridge TBM 4 amplifier and recorded on a Mac Lab system (World Precision Instruments Inc., New Haven, CT).

After the vessel segments had stabilized for 1.5 hours, the buffer was exchanged with a K⁺-enriched buffer solution. This solution contained 63 mM KCl and 60 mM NaCl with unchanged concentrations of the other electrolytes and produced a stable tonic constriction. This procedure was repeated 2 to 4 times until the strength of the constriction was reproducible. A constriction was considered reproducible when the variation in 2 following constrictions was less than 10%. The constriction (K-Emax) was used as a reference constriction, to which the following experimental constrictions of the vessel segment were compared. The constriction was also performed prior to the last experiment with the vessel segment to evaluate its viability.

During the experiment the buffer solution in the bath was exchanged with a test solution and the reaction (contraction, mN) of the vessel segment was recorded. The contractile response in each experiment was registered and calculated in % K-Emax of the vessel segment. After each experiment the vessel segment was rinsed with buffer solution and allowed to rest for 1/2 hour before the next experiment.

All test solutions were preheated to 37°C. The following experiments were performed:

a) Test for sufficient oxygenation of the CM (n=18). The contractile response of the vessel segments when exposed to iohexol 140 mg I/ml (Omnipaque, Nycomed) was compared to the contractile response when exposed to iohexol saturated with oxygen. The oxygen saturation was performed by perfusing iohexol with 100% O₂ for 5 min prior to the addition to the vessel segments. This procedure increased the O₂ tension from approximately 25 to 75 kPa.

b) Test for involvement of the endothelium (n=18). The contractile response of the vessel segments, when exposed to iohexol, was compared to the contractile response of segments that had been pretreated with 0.1% Triton-X (Sigma Co., St. Louis, MO). Triton-X was infused over a few seconds by inserting a thin polyethylene catheter coupled to a 5 ml syringe into one end of the dissected coronary artery. The vessel was then thoroughly rinsed with buffer solution infused through the same catheter as the infusion of Triton-X. The procedure was performed before cutting the vessel in segments. Tests with addition of acetylcholine (Acetylcholine chloride, Sigma Co.) to Triton-X-treated vessels confirmed that the endothelium was removed.

c) Test for involvement of nerve terminals (n=12). The contractile response of the vessel segments, when exposed to iohexol, was compared to the contractile response of segments that had been pretreated with 10⁻⁸ M prazosin (Prazosin chloride, Fermion Orion Corp. Ltd., Helsinki, Finland). As prazosin has a delayed effect, it was added not only to the iohexol solution during the experiment, but also to the buffer solution in the baths 30 min prior to the experiment.

d) Test for involvement of calcium channels (n=8). The contractile response of the vessel segments, when exposed to iohexol, was compared to the contractile response of segments that had been pretreated with 10⁻⁸ M nifedipine (Adalat, Bayer). As nifedipine has a delayed effect, it was not only added to the iohexol solution during the experiment but also to the buffer solution in the baths 15 min prior to the experiment.

e) Test for agonistic effect of depolarization with KCl (n=8). The contractile response of the vessel segments, when exposed to iohexol, was compared to the contractile response of the segments when exposed to iohexol with addition of 5 mM or 10 mM KCl (Fluka AG, Buchs, Switzerland), as well as the contractile response to buffer solution with addition of 10 mM KCl.

The Wilcoxon signed rank test was used when comparing paired observations (experiments a and e), while the Mann-Whitney U-test was used when comparing unpaired observations (experiments b, c and d). A p-value <0.05 was considered significant.

Results

An example of a CM-induced constriction of a vessel segment is shown in Fig. 1. The duration of each vasoconstriction lasted between 1 and 10 min. The duration of the constriction was proportional to the strength of the constriction. It was reversible and the force always returned spontaneously to the baseline. Contraction only occurred when the buffer solution was changed to a test solution, and not when changing from test solution to buffer, or
when changing buffer solution to fresh buffer. The contractile response of the test solutions is given in % K-E_max (median and interquartile range).

Fig. 2 gives the contractile response of the vessel segments when exposed to iohexol and iohexol saturated with oxygen. The contraction to iohexol was 27% (17–70%) and the contraction to oxygenated iohexol was 26% (13–50%). The difference was not significant.

Fig. 3 gives the contractile response of untreated vessel segments and the contractile response of segments pretreated with Triton-X. In untreated segments the contraction was 52% (30–62%) and in Triton-X-treated segments it was 60% (51–78%), p<0.05.

Fig. 4 gives the contractile response of untreated vessel segments and the contractile response of segments pretreated with prazosin. In untreated segments the contraction was 123% (115–147%) and in prazosin-treated segments it was 100% (88–108%), p<0.001.

Fig. 5 gives the contractile response of untreated vessel segments and the contractile response of segments pretreated with nifedipine. In untreated segments the contraction was 25% (16–35%) and in nifedipine-treated segments it was 0% (0–0%), p<0.001.

Fig. 6 gives the contractile response of the vessel segments when exposed to iohexol, iohexol with 5 mM KCl, iohexol with 10 mM KCl, and buffer with 10 mM KCl. The contraction to iohexol was 31% (19–36%), to iohexol with 5 mM KCl 43% (39–51%), to iohexol with 10 mM KCl 72% (53–81%), and to buffer with 10 mM KCl 0% (0–0%).

Discussion

Previous in vitro studies found a vasoconstrictive effect of CM due to the hyperosmolality of the CM (4, 10, 26). In those studies, hypertonic mixtures of CM and buffer solution were used. In vivo, blood is for a short period of time
substituted with CM during angiography. To imitate this event in the present study, the nutrient buffer solution was completely substituted with CM during the experiments. Since nonionic CM are increasingly used clinically, iohexol was chosen as the test solution. Iohexol is a nonionic CM with low toxicity and is known to cause less vasodilatation than ionic media (1, 2).

Vasoconstriction was a constant finding that occurred every time iohexol was added to the vessel. However, the strength of the iohexol-induced constriction varied between 25% and 123% (Figs 4 and 5). The reason for this variation is unknown, but there seemed to be both interindividual and season-dependent variations. For that reason, vessels from the same animal were used in all the experiments in each of the series a to e.

Since iohexol was used in a concentration iso-osmolar with plasma the constriction was not due to hyperosmolality as in the previous in vitro studies, but had to be due to chemotoxicity or the nonionic nature of the CM. That the vessel began to contract within a few seconds after the exchange of buffer with CM (Fig. 1) was contrary to the previous studies, in which the constriction started more slowly and reached its maximum after 15 to 60 min (4, 26). Furthermore, the vasoconstriction in the present study did not develop when the CM was mixed with buffer. Thus, the vasoconstriction must be due to a different mechanism than the previously investigated vasoconstrictions mentioned above. The test conditions were therefore varied in an attempt to investigate the mechanism responsible for the vasoconstriction.

Hypoxia of isolated rabbit arteries causes vasoconstriction, probably due to liberation of vasoconstrictors from the endothelium (21). Iohexol was delivered equilibrated with air and was added to the baths in that form. In the baths, during the experiments, iohexol was gassed with a mixture of 95% O₂ and 5% CO₂ in the same way as the buffer solution. To insure that iohexol was sufficiently oxygenated in the form used, the contractile response of the segments when exposed to “normal” iohexol was compared with the contractile response to iohexol saturated with oxygen. The contractile response to iohexol was equal to the contractile response to iohexol saturated with oxygen (Fig. 2). Thus, the CM-induced constriction was not due to hypoxia.

During the last decade the endothelium has been extensively investigated due to its production of vasoactive substances. It has been shown to liberate both endothelium-derived contracting factors (EDCF) and endothelium-relaxing factors (EDRF) (11, 21). The endothelium can be removed chemically by dissolving it with Triton-X. In the present study the contraction of segments without endothelium was higher than the contraction of segments with endothelium (Fig. 3). Thus, the CM-induced contraction was not due to liberation of EDCF. EDRF (nitric oxide, NO) is a labile vasodilator which is constantly liberated from the endothelium, causing vasodilatation (11, 24). The higher contraction in the vessels without endothelium was most probably due to lack of EDRF.

The isolated vessel segments are of course denervated, but the nerve terminals connected with the smooth muscle cells of the vessel are preserved and may liberate vasoactive substances when stimulated (7, 12). Stimulation of the sympathetic nerves of the vessels have been shown to cause vasoconstriction by liberation of norepinephrine (7). It has previously been shown that CM can change the function of isolated nerve endings from the brain (22) and might thus theoretically be able to influence the function of nerve terminals in the vessels. Prazosin is an antagonist to norepinephrine, blocking its receptors (α₁-adrenergic receptors) on the smooth muscle cells (12). Iohexol caused powerful contractions of both the prazosin-treated and the untreated vessel segments (Fig. 4). However, the constriction of prazosin-treated segments was slightly, but significantly, lower than that of the untreated vessels. This means that liberation of norepinephrine may to some extent be involved in the CM-induced constriction. Nevertheless, the main component of the constriction is due to other mechanisms.

An increase in intracellular calcium is necessary for contraction of the smooth muscle cells. This can be accomplished by influx of calcium ions from the extracellular space through calcium channels into the cell cytosol or by liberation of calcium ions stored intracellularly (6). The calcium channels may be divided into potential-operated channels (POC) and receptor-operated channels (ROC). ROC open when the cell membrane depolarizes, while POC open when a vasoconstrictor binds to its receptor. The inhibitory effects on vasoconstriction from currently used calcium antagonists, like nifedipine, are due to inhibition of POC and ROC (9, 14, 27).

In the present study, the contraction was totally inhibited by treatment of the vessels with nifedipine (Fig. 5). Therefore,
the CM-induced contraction seems to be due to activation of the calcium channels.

KCl causes vasoconstriction by depolarizing the smooth muscle cell membrane, which in turn causes opening of POC (6). In buffer solution a concentration of approximately 20 mM KCl is needed to cause contraction (3). In the present study smaller concentrations of KCl (5–10 mM) markedly potentiated the concentration of iohexol whereas buffer with 10 mM KCl did not case vasoconstriction (Fig. 6). This synergistic effect of iohexol and KCl is believed to be due to opening of POC by iohexol. Since POC open when the smooth muscle cell membrane is depolarized, the vasoconstriction of iohexol must be due to a depolarizing effect on the smooth muscle cell membrane.

If iohexol causes depolarization of the smooth muscle cells, it might also depolarize the nerve cell membrane, just as KCl does (12). Depolarization of nerve terminals in the vessel wall would cause liberation of norepinephrine. The vasoconstrictive action of norepinephrine would be blocked in the prazosin-treated vessels, but not in the untreated vessel segments. A depolarizing effect of iohexol not only on the smooth muscle cells, but also on the nerve terminals, would therefore explain the slightly lower contraction of vessel segments treated with prazosin.

The corresponding clinical effect to the vasoconstriction has not as yet been investigated. It might be related to vessel spasm, but the constriction described in the present study occurred each time the CM was added to the vessel segments while vessel spasm during arteriography is a comparatively rare event. However, in vivo the vessel tone is determined by a balance between locally liberated, circulating and nervous mediated vasoconstrictive, and vasodilative substances as well as by the blood volume. CM are able to cause both vasodilatation and vasoconstriction in vitro, but they mostly cause vasodilatation. The vasoconstriction might therefore only occur during pathologic conditions, i.e. when there is an imbalance between the vasodilative and vasoconstrictive substances. Under those circumstances a certain depolarizing effect from the CM might cause a constriction. The CM used, iohexol, is safe compared to other CM and is not known to induce more spasm clinically than other CM. It is therefore of interest to compare the tendency of different kinds of CM to cause this type of vasoconstriction.

From the present investigation it can be concluded that, in vitro, CM iso-osmolar with plasma can cause vasoconstriction due to chemotoxicity or lack of ions. Iohexol seems to cause vasoconstriction by depolarizing the smooth muscle cells in the vessel wall. A small part of the constriction might also be due to stimulation (depolarization) of the nerve terminals, causing liberation of norepinephrine.

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REFERENCES


