TITLE: NITROUS OXIDE AND CORONARY ARTERY CONSTRICTION IN PIGS

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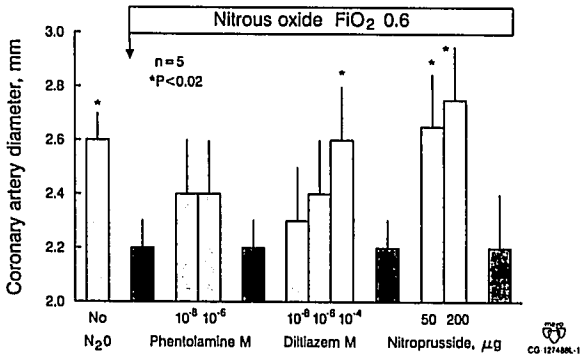
Nitrous oxide (N_2O) constricts epicardial coronary arteries in dogs. In pigs the effect is endothelium dependent. The mechanism is unknown and was addressed here by asking three questions: (a) Does N_2O increase norepinephrine overflow in isolated pig coronary arteries? (b) Is endothelin concentration in pig great cardiac vein blood elevated by N_2O? (Endothelin is a constrictor secreted by endothelial cells.) (c) Is coronary artery constriction evoked by N_2O in intact pigs reversed by coronary dilators with specific mechanisms of action--phentolamine (α receptor block), diltiazem (Ca^{2+} entry block) and nitroprusside (cGMP elevation)?

Three protocols were used. (a) Coronary artery strips ± endothelium from 5 pigs were suspended in a superfusion apparatus, aerated with either 70% N_2O or 70% nitrogen in oxygen, stimulated electrically and norepinephrine overflow measured. (b) Great cardiac vein blood was removed from 5 open chest anesthetized pigs before, during and following 60% N_2O and assayed for endothelin. (c) Coronary artery constriction was induced with 60% N_2O in 5 intact pigs and the effects of intracoronary vasodilators on vessel diameter were measured using computerized angiography.

Results indicate: (a) N_2O effect on norepinephrine overflow was minimal--0.05±0.002 without, versus 0.1±0.01 ng.100 $mg^{-1}.min^{-1}$ with N_2O ($p < 0.05$); (b) N_2O had no effect on endothelin release, concentrations remaining unchanged at 16±2 pg ml^{-1}; (c) sustained constriction evoked by N_2O was partially reversed by phentolamine and completely reversed by diltiazem and nitroprusside. Vessels reconstricted between administration of dilators (Fig.).

The mechanism of N_2O effect remains uncertain. N_2O had minimal or no effect on norepinephrine and endothelin release. Vasodilator studies indicate that N_2O constriction is in part α-adrenergic receptor dependent, is partially dependent upon Ca^{2+} entry and can be reversed by nitroprusside.

CORONARY VASODILATORS AND CONSTRICTION EVOKED BY NITROUS OXIDE



TITLE: ISOFLURANE, HALOTHANE AND SECOND MESSENGER PATHWAYS IN ISOLATED PIG CORONARY ARTERIES

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Contractile agonists constrict coronary arteries. They act at the cellular level by stimulating second messenger systems. Contraction is initiated and maintained, in part, by two pathways--inositol phosphate formation and by protein kinase C (PKC) activity. Here the effects of the anesthetics on the two pathways were investigated by asking if they inhibit contractions (a) evoked by a protein kinase C activator (PDBu), (b) evoked by acetylcholine and serotonin and if they continue to do so when a PKC inhibitor (H7) is present; (c) if they inhibit agonist induced inositol phosphate formation.

Coronary artery rings without endothelium were studied in organ chambers and changes in tension measured in the presence and absence of 1% and 2% isoflurane and halothane. Contractions were evoked by (a) the phorbol ester PDBu--a PKC activator; (b) acetylcholine and serotonin with and without H7, an inhibitor of PKC; (c) in a third experiment inositol phosphate formation induced by acetylcholine was measured using ^3H-inositol labeled rings with and without halothane 1.0%.

Results indicate (a) neither isoflurane 2% nor halothane 2% attenuate contractions evoked by PKC activation (Fig. 1); (b) isoflurane 2% and halothane 1% attenuated contractions evoked by acetylcholine and serotonin. Attenuation persisted in the presence of the PKC inhibitor H7 (Fig. 2); (c) halothane 1% inhibited agonist induced inositol phosphate formation (Fig. 3).

The results provide insight into the mechanisms of isoflurane and halothane effects on coronary artery contraction. The anesthetics appear to lack an effect on contractions mediated by PKC, but interact with the inositol phosphate limb of contraction.

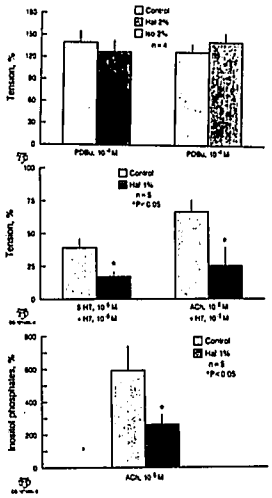

Figure 1: Protein kinase C activation with PDBu

Figure 2: Agonists plus PKC inhibition with H7

Figure 3: Increases in inositol phosphates evoked by ACh