Title: MYOCARDIAL BETA-ADRENOCEPTOR DENSITY IS DECREASED BY HALOTHANE IN DOGS AS ASSESSED BY POSITRON EMISSION TOMOGRAPHY

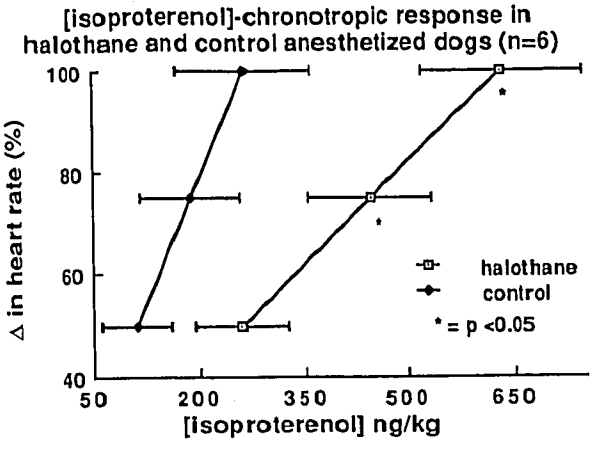
Authors: M. Maze, M.B. Ch.B, J. Marty, M.D., M. Seto, M.D., C. Crouzel, Ph.D., J.M. Valloise, B.S., M. Crouzel, J.P. Lancon, M.D., A. Syrota, M.D.

Affiliations: Département d' Anesthésie- Réanimation, Université Paris VII Hopital Bichat and Service Hospitalier Frédéric-Joliot Departement de Biologie, du Commissariat à l'Energie Atomique, Orsay, France

Introduction: Halothane exerts a multiplicity of effects on the autonomic nervous system resulting in qualitatively and quantitatively abnormal adrenergic responsiveness. While depressed ganglionic transmission and inhibition of transmitter release explain some of these alterations, halothane may also perturb the postsynaptic effector cell. Recently, we demonstrated that halothane, *in vitro*, diminishes beta-adrenoceptor density in circulating human lymphocytes[1], a finding which is in apparent conflict with data from earlier canine myocardial studies[2]. To delineate the effect of halothane on beta-adrenoceptors *in vivo* we have used positron emission tomography (PET) to visualize and quantify myocardial beta-adrenoceptors. This methodology uses molecules labeled with isotopes of natural elements, such as carbon. It can be compared to quantitative autoradiographic techniques used for imaging receptors *in vitro*[3]. CGP 12 177, a potent beta-adrenoceptor antagonist, was labeled with ^{11}C, a short-lived positron-emittor produced by a cyclotron[4], to correlate the *in vivo* effects of halothane on myocardial beta-adrenoceptors with adrenergic responsiveness.

Methods: Beagle dogs (n=6) were induced with sodium thiopental (STP) and ventilated with oxygen via an endotracheal tube. Anesthesia was maintained with a constant STP infusion at a calculated steady-state plasma level of 30 ug·ml^{-1} (control). On a separate occassion, at least a week apart, these animals were similarly induced and the anesthesia was supplemented with halothane, 1.0 % v/v end-tidal (halothane). Right atrial (for fluid/drug administration and intracardiac blood sampling) and femoral arterial (for continuous pressure/rate monitoring and arterial blood sampling) catheterizations were performed. After a 60 min equilibration period the chronotropic response to incremental infusions (1 min) of isoproterenol was assessed[5]. Thirty min later, ^{11}C-CGP 12 177(200 MBq) was injected into the right atrium and sequential transverse sections of the heart were imaged for 70 min by PET[4]. A region of interest was selected over the interventricular septum or the free wall of the left ventricle for deriving the myocardial concentration of ^{11}C-CGP 12 177. Simultaneously ^{11}C-CGP 12 177 blood radioactivity concentration was determined by a gamma-counting system. The myocardial to blood concentrations ratio (m/b), in halothane-anesthetized dogs was compared to control dogs at equilibrium (70 min) by paired t-test. Linear regression analysis was used to compare the chronotropic responses to isoproterenol between the two anesthetized states.

Results: Arterial blood gas analysis confirmed that the animals were maintained within physiologic acid-base range. The halothane dogs required significantly more isoproterenol for the same heart-rate response when compared to the control animals, indicative of beta-adrenergic hyporesponsiveness.



The m/b ratio in the halothane dogs (4.65 ± 0.69 ; mean ± SD) was significantly lower ($p<0.01$) than in the control animals (5.82 ± 0.50) indicating a decrease in the concentration of the beta-adrenoceptor ligand in the myocardial tissue.

Discussion: Adrenergic responsiveness in the target organ is dependent on the state of beta-adrenergic membrane receptors, "coupling" between receptor and effector within the membrane, and the intracellular effector system. PET provides a unique opportunity to study, *in vivo* and non-invasively, the effect of anesthetic agents on the adrenergic binding sites. The decrease in ^{11}C-CGP m/b ratio suggests that halothane diminishes beta adrenoceptor density *in vivo*. Thus this decrease may be a cause for the observed myocardial beta-adrenergic hyporesponsiveness.

References: 1. Marty J, Nimier M, Rochiccioli C, Luscombe F, Henzel D, Desmonts JM: Beta-adrenergic receptor density in human lymphocytes is decreased by halothane. Clin Res 34:402A, 1986

2. Bernstein K, Gangat Y, Verosky M, Vulliemoz Y, Triner L: Halothane effect on beta-adrenergic receptors in canine myocardium. Anesth Analg 60:401-405, 1981

3. Charbonneau P, Syrota A, Crouzel C, Vallois J-M, Prenant C, Crouzel M: Peripheral-type benzodiazepine receptors in the living heart characterized by positron emission tomography. Circulation 73:476-483, 1986

4. Seto M, Syrota A, Crouzel C, Charbonneau P, Vallois JM, Cayla J, Boullais C: Beta adrenergic receptors in the dog heart characterized by ^{11}C-CGP 12 177. J Nucl Med 27:949, 1986

5. Spiss CK, Maze M, Smith C: Alpha-adrenergic responsiveness correlates with epinephrine dose for arrhythmias during halothane anesthesia in dogs. Anesth Analg 63:297-300, 1984