

THE CHRONOTROPIC AND INOTROPIC EFFECTS OF HALOTHANE

A Comparison of Effects in Normal and Chronically Cardiac Denervated Dogs

DEAN H. MORROW, M.D., THOMAS E. GAFFNEY, M.D., JOHN E. HOLMAN, D.V.M.

BRADYCARDIA is commonly produced by halothane anesthesia, but the mechanism responsible for this negative chronotropic effect has not been clearly defined. Many clinical reports¹⁻⁴ have stated that the bradycardia produced by halothane in man is antagonized by atropine, and this finding suggests that it may be, at least in part, of vagal origin. Others, however, have reported that halothane may produce a decrease in heart rate even after the administration of effective doses of atropine.^{2, 3} This latter observation implies that halothane may have a non-vagal, direct cardiac, negative chronotropic effect.

The present experimental study was designed to determine the role of cardiac innervation in the mechanism of halothane-induced bradycardia. The chronotropic effect of halothane was determined before and after large doses of atropine in intact dogs and in dogs in which complete cardiac denervation had been previously performed. In addition, the inotropic effects of this agent under these conditions was assessed by measurement of myocardial contractile force.

METHOD

Seven healthy mongrel dogs averaging 11.5 kg. in weight were studied. Four were normal animals and 3 had previously been subjected to ablation of all extrinsic sympathetic and parasympathetic neural structures within the mediastinum resulting in total cardiac denervation as described by Cooper and associates.⁵ These denervations were carried out at least seven days prior to the present studies. Each animal was anesthetized with chloralose 100 mg./kg., and following endotracheal intubation, respiration was maintained with 100 per cent

oxygen at 5 l./minute total flow on a semi-closed circle absorption system utilizing a Jefferson controller. The arterial blood pressure was continuously recorded from a catheter in the femoral artery attached to a Statham pressure transducer and direct-writing oscillograph. The heart rate was measured from either the blood pressure record or from lead 2 of the electrocardiogram. Myocardial contractile force was measured with a Walton-Brodie strain gauge arch⁶ sutured to the right ventricle. Halothane in concentrations ranging from 1/2 to 3 per cent was administered to the animals before and following atropine, 2 mg. intravenously. ~~The halothane vapor was delivered from a calibrated Fluotec vaporizer.~~

RESULTS

Heart Rate. Halothane in concentrations up to 1.5 per cent had a variable effect upon heart rate; 1 per cent produced a 34 and 38 per cent increase and a 4 and 25 per cent decrease in heart rate in 4 normal dogs. Halothane concentrations greater than 1 per cent produced a dose-dependent decrease in heart rate in each of these same dogs. The maximal decreases in heart rate produced by 2 1/2 per cent halothane in the 4 normal dogs were 21, 26, 27 and 29 per cent below control levels. Atropine, 2 mg., had no effect on these dose effect relationships (fig. 1). In each of 3 chronically cardiac denervated dogs, halothane in concentrations greater than 1 per cent decreased heart rate to levels indistinguishable from those seen in the normal dogs and which were unaffected by atropine administration (fig. 2).

Myocardial Contractile Force. In 3 normal dogs halothane in all concentrations studied produced decreases in myocardial contractile force. In the 3 dogs with denervated hearts quantitatively similar responses were observed (fig. 3). The administration of atropine

Received from the Department of Anesthesiology, The Clinical Center; The Cardiology Branch and The Laboratory of Kidney and Electrolyte Metabolism, National Heart Institute, National Institutes of Health, Bethesda 14, Maryland, and accepted for publication June 14, 1961.

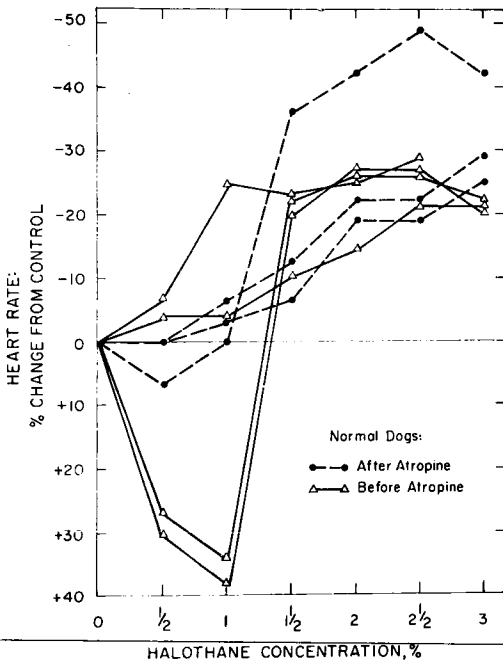


FIG. 1. Percentage change in heart rate from control of normal dogs with halothane administration before and after atropine (2 mg.).

(2 mg.) to both groups had no effect on the observed decreases in contractile force produced by halothane.

Systemic Arterial Pressure. Halothane produced similar dose-dependent decreases in the mean arterial blood pressure in 4 normal dogs and in the 3 cardiac denervated dogs (fig. 4).

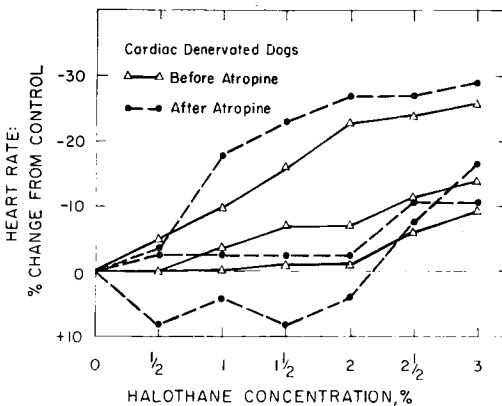


FIG. 2. Percentage change in heart rate from control of chronically cardiac denervated dogs with halothane administration before and after atropine (2 mg.).

COMMENT

The present observations demonstrate that halothane, in concentrations used clinically, produces a clear-cut, dose-dependent negative chronotropic effect on the heart of the intact dog, and that this effect is not abolished by a large dose of atropine. This finding suggests that the decrease in heart rate produced by halothane in normal dogs is not dependent upon an intact vagal system. This is confirmed by the persistent negative chronotropic effect of halothane seen in the dogs with totally denervated hearts.

However, in man, the effectiveness of atropine in the treatment of halothane-induced

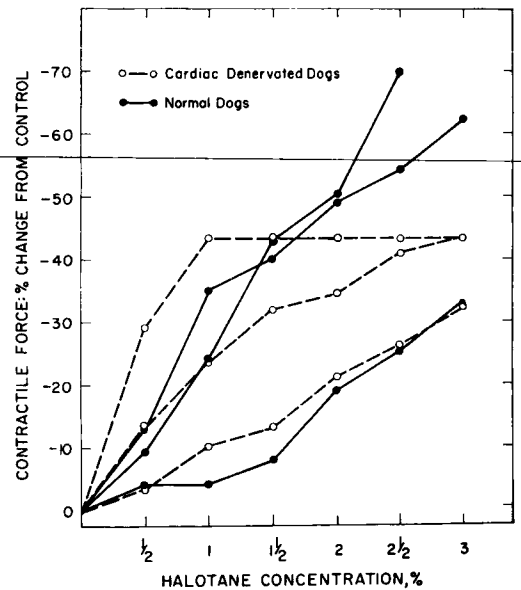


FIG. 3. Percentage change from control of heart contractile force of normal and chronically cardiac denervated dogs with the administration of halothane.

bradycardia is well established and is evidence that reflex vagal activity is important. These two observations, in man and dogs, are not inconsistent with each other since atropine would be expected to increase the heart rate of any patient by releasing tonic vagal activity.

The negative inotropic effect of halothane observed in the denervated dogs was quantitatively indistinguishable from the decrease in myocardial contractile force observed in the normal dogs. This indicates that the absence

of stored myocardial catecholamines, which are known to be depleted by cardiac denervation,⁵ and which may affect myocardial contractility,⁷ does not increase the sensitivity of the dog heart to the negative inotropic effect of halothane. This observation may be of clinical significance in view of the increased use of drugs, such as the Rauwolfia alkaloids⁸ and guanethidine,⁹ which are known to produce myocardial catecholamine depletion.

SUMMARY

The effects of halothane on heart rate, myocardial contractile force and systemic arterial pressure were studied in normal dogs and dogs which had been previously subjected to total chronic cardiac denervation. This agent, in concentrations ranging from 1/2 to 3 per cent, produced essentially identical decreases in all these parameters in both the normal and cardiac denervated animals. The administration of 2 mg. of atropine intravenously did not affect the responses. These observations indicate that the negative chronotropic effect of halothane, in the dog, is a direct cardiac effect rather than of vagal origin and that myocardial catecholamine depletion produced by chronic cardiac denervation does not increase the sensitivity of the heart to the negative inotropic effect of halothane.

REFERENCES

1. (A) Burn, J. H., Epstein, H. G., Feigan, G. A. and Paton, W. D. M., (B) Burns, T. H. S., Mushin, W. W., Oragane, G. S. W. and Robertson, J. D.: "Fluothane": A Report to the Medical Research Council by the Committee on Non-explosive Anesthetic Agents, *Brit. Med. J.* Part 2: 479, 1957.
2. Johnstone, M.: Human cardiovascular response to Fluothane anaesthesia, *Brit. J. Anaesth.* 28: 392, 1956.
3. Serveringhaus, J. W., and Cullen, S. C.: Depression of myocardium and body oxygen consumption with Fluothane, *ANESTHESIOLOGY* 19: 165, 1958.

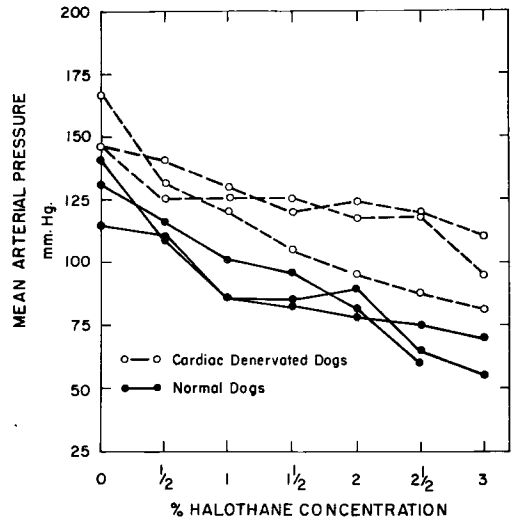


FIG. 4. Mean arterial blood pressure changes in normal and chronically denervated dogs with halothane administration.

4. Wyant, G. M., Merriman, J. E., Kilduff, C. J., and Thomas, E. T.: Cardiovascular effects of halothane, *Canad. Anaesth. Soc. J.* 5: 384, 1958.
5. Cooper, T., Gilbert, J. W., Bloodwell, R. B., and Crout, J. R.: Chronic extrinsic cardiac denervation by neural ablation, *Circulat. Res.* 9: 275, 1961.
6. Boniface, K. J., Brodie, O. J., and Walton, R. P.: Resistance strain gauge arches for direct measurement of heart contractile force in animals, *Proc. Soc. Exp. Biol. Med.* 84: 263, 1953.
7. Kako, K., Choudhury, J. D., and Bing, R. J.: Possible mechanism of decline in mechanical efficiency of the isolated heart, *J. Pharmacol. Exp. Ther.* 130: 46, 1960.
8. Ward, D. R., Kottogoda, S. R., and Krayner, O.: Threshold dose and time course of norepinephrine depletion of mammalian heart by reserpine, *J. Pharmacol. Exp. Ther.* 124: 340, 1958.
9. Cass, R., Kuntzman, R., and Brodie, B. B.: Norepinephrine depletion as possible mechanism of action of guanethidine (Su 5864), new hypotensive agent, *Proc. Soc. Exp. Biol. Med.* 103: 871, 1960.