Fluorinated Hydrocarbons and the Heart

Inhalation of fluorinated hydrocarbons has become a widespread phenomenon. Fluoroalkanes are used in aerosol dispensers for bronchodilators, cosmetics, paints, and a variety of household products. To a degree presently unknown, cardiac toxicity due to fluoroalkane inhalation may be a potential hazard to frequent users of aerosol dispensers. Studies by Taylor and Harris\(^1\) show that the Freons and related propellant gases are not "inert" compounds. Evidence from experiments with mice support their inference that a large number of the reported sudden deaths of asthmatics using pressurized nebulizers resulted from the cardiotoxic effect of the propellant. The report states that the experimental bradyarrhythmias induced in the mice probably reflect a direct action of the fluorinated hydrocarbons on the SA node and A-V conduction of the heart. Bass\(^2\) has reported on 110 cases of sudden death in youths who "turn on" by sniffing the vapors of aerosol propellants, airplane glue, and various solvents. The negative autopsy findings and rapid death suggest that a cardiac arrhythmia might be the fatal mechanism in most of these cases. Even the clinically used fluorinated hydrocarbon, halothane, may occasionally produce cardiac arrhythmias when given in concentrations needed for anesthesia.\(^3\) Relatively little is known, however, about the mechanism behind the electrophysiologic effects of fluorinated hydrocarbons on the heart. Therefore, work on this problem, which appears to be of public health importance, is needed.

In this month's issue of Anesthesiology two different animal studies involving halothane are reported, one dealing with the influence of halothane on cardiac conductance and the other with halothane's effect on automaticity in the intact dog heart. Using catheter electrocardiography, Atlee and Rusy showed that arrhythmias seen with halothane may be due to a depressant effect on A-V conductance. This finding provides further experimental evidence supporting the inference of Bass\(^2\) and Taylor and Harris\(^1\) that sudden death from inhalation of fluorinated aerosol propellants is due to severe cardiac arrhythmia. In a search for a mechanism to control anesthesia-induced arrhythmia, studies of the effects of diphenylhydantoin-type chemical agents on halothane-induced conduction depression should be carried out. A clinical report by Katz and Bigger\(^3\) showed diphenylhydantoin capable of terminating ventricular arrhythmias during anesthesia after other antiarrhythmic drugs had failed. It is also known that diphenylhydantoin, unlike other antiarrhythmic drugs, negligibly affects intraventricular conduction while enhancing A-V conduction.\(^4\) Helfant et al.\(^5\) showed that diphenylhydantoin reversed both the slowed A-V and intraventricular conduction induced in the dog heart by procainamide, a local anesthetic-type drug. Electrophysiologic manipulations of this type have potential clinical importance.

The article by Logic and Morrow in this issue describes an antiarrhythmic property of halothane which is shared by drugs of the local anesthetic type frequently used in the treatment of clinical arrhythmias.\(^1\) Halothane clearly suppressed experimentally-induced latent automaticity of subnodal pacemaker cells in the intact dog heart. The ionic mechanism behind the diastolic depolarization of cardiac cells has been studied by Vassalle\(^6\) by means of the "voltage-clamp" technique. He found that the automaticity may be the result of a time-dependent, progressive fall in the potassium ion current across the cell membrane.

It is of interest to speculate on the possible mechanism of the suppression of diastolic depolarization by halothane at the cardiac membrane level. Halothane and the other related general anesthetics are electroneutral and chemically relatively inactive. The high lipid solubility of these structures suggests that the site of action may be in the lipid portion of the excitable cell membrane, but their chemical mechanism of action has not yet been explained. Membrane-bound calcium, however, has long been considered a regulator of monovalent cation flux across cell membranes. There is some evidence for the hypothesis that local anesthetic-type drugs, which are organic
cations, act on cell membranes by displacing calcium ions from critical membrane sites, and thus modify specific ion fluxes. Therefore, the question should be asked: can the electro-neutral anesthetics which apparently affect the same membrane functions as local anesthetics also disturb calcium binding in membranes? Very recent studies on calcium-anesthetic interactions at erythrocyte membranes and at artificial model surfaces indicate that electro-neutral anesthetics are capable of modifying the calcium content of such interfaces. Instead of displacing membrane calcium in the manner of local anesthetic-type drugs, the electroneutral anesthetics were found to increase the calcium affinity of the membranes. Thus, the same critical membrane-calcium complex may be involved in the mechanisms of the general and local anesthetic drugs. However, the disturbances of this critical calcium complex appear to differ in nature.

Of interest in this regard is the recent report by Brown and Crout, in which it is postulated that the depressant effects of halothane and other inhalation general anesthetics on myocardial contractility may be due to drug interference with calcium-membrane binding. The similar depressant effect on myocardial contractility caused by cationic local anesthetic-type drugs has long been considered to be related to a modification of normal calcium movement across the membrane system of muscle fibers.

Per T. Thyrum, Ph.D.
Assistant Professor
Division of Myocardial Biology
Baylor College of Medicine
Houston, Texas

References