STUDIES ON CYCLOPROPANE SENSITIZATION TO ADRENALINE-INDUCED CARDIAC ARRHYTHMIAS

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ABSTRACT

Small doses of adrenaline (0.1-2.0 µg./kg.) injected over 60 seconds into thiopental-cyclopropane anaesthetized dogs produce bigeminal rhythms characterized by an exceptionally constant interval between the coupled beats. Phenylephrine also causes this arrhythmia but methoxamine does so rarely. An elevation in the systolic blood pressure is required for the appearance of the bigeminy but the arrhythmia can be elicited consistently only in the presence of an increase in blood pressure and a sympathomimetic amine with cardiac stimulant action. Thus, isoproterenol does not produce the arrhythmia unless the depressor response is reversed mechanically. The arrhythmia may be elicited in some dogs anaesthetized with either cyclopropane or thiopental, but both anaesthetic agents are required for the consistent production of this arrhythmia by adrenaline. Thiopental also modifies other arrhythmic responses to adrenaline so that multifocal ventricular rhythms and ventricular fibrillation occur at doses which animals anaesthetized with cyclopropane alone tolerate well. Tachyphylaxis to adrenaline-induced arrhythmias occurs more readily in the cyclopropane-anaesthetized animal than the animal receiving thiopental in addition to cyclopropane. The duration of the cardiac effects of thiopental greatly exceeds its expected anaesthetic action.

A parasystolic focus of automaticity has been excluded in the

genesis of the bigeminal rhythm by the demonstration of constancy of the coupling interval with sudden changes in the dominant rate. Bigeminal and multifocal rhythms are interconvertible through appropriate changes in the systemic blood pressure and both are abolished by injections of acetylcholine into the left circumflex coronary artery. Thiopental also acts in the distribution of this artery, presumably at the atrioventricular node or upper bundle of His.

Stimulation of the vagus in the presence of a sympathomimetic amine allows the emergence of ventricular foci of automaticity through inhibition of supraventricular centres. No difference was noted between the sensitized (cyclopropane) and the nonsensitized (pentobarbital) preparation when this technique was employed. The evidence indicates that the bigeminal and multifocal arrhythmias occurring with low doses of adrenaline in the sensitized preparation are not due to the emergence of ventricular foci of automaticity.

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SECTION I

INTRODUCTION

A. GENERAL INTRODUCTION

The administration of adrenaline during hydrocarbon anaesthesia remains one of the most useful pharmacological procedures for the experimental production of cardiac arrhythmias and one of the significant hazards of clinical anaesthesiology. Sudden death during hydrocarbon anaesthesia was noted as early as 1895 when Oliver and Schafer made the observation that administration of adrenal extracts to cats anaesthetized with chloroform resulted in death of the animals (1). This observation was not developed further and the lethality of the adrenal extract was not related to the anaesthetic agent by these authors. Five years later MacWilliam described sudden halving of the pulse rate and the appearance of pulse irregularities on applying pressure to the abdomen of the chloroformed cat but did not comment on this observation (2). In 1910 Blumenfeld presented a paper to the Anaesthesiology Section of the Royal Society of Medicine describing a case of sudden cardiovascular collapse following administration of adrenaline during light chloroform anaesthesia for nasal surgery (3). Blumenfeld attributed this phenomenon to "nasal reflexes" but the several discussants of the paper commented on similar responses in a variety of surgical procedures associated with the concomitant use of chloroform and adrenaline. This empirical association of adrenaline with chloroform in producing cardiovascular collapse was investigated by Goodman Levy who published his observations on animals in the following year (4,5). He noted that ventricular fibrillation occurred spontaneously in cats lightly anaesthetized with chloroform and that this arrhythmia could be produced consistently by the administration of adrenaline. The requisite conditions for spontaneous

and adrenaline-induced arrhythmias were investigated and an attempt was made to relate experimental observations to the hitherto unexplained deaths occurring during clinical chloroform anaesthesia (6,7).

The acceptance of Levy's experimental observations led to revision of anaesthetic techniques with chloroform and greater safety in administration of this agent. The importance of his contribution goes much beyond this. "Sensitization" of the heart to adrenaline had been demonstrated clearly and a technique was made available for the experimental study of cardiac arrhythmias and for the assessment of anti-arrhythmic agents.

In 1929 Lucas and Henderson described the anaesthetic properties of cyclopropane and noted the occurrence of pulse irregularities following administration of this agent to animals (8). The production of spontaneous arrhythmias by cyclopropane was confirmed (9,10) and in 1937 Meet et al. reported on sensitization of the heart to adrenaline by cyclopropane (11). This was the first of a series of communications and review articles by Meek and his group (12-18) which established the cyclopropane-adrenaline preparation as a basic tool in the study of cardiac arrhythmias. Acceptance of this preparation probably was predicated on several important considerations. Several authors found cyclopropane to sensitize the canine heart (9-11). The dog appeared to be closer phylogenetically to man than were the cat or rabbit which had previously been employed. Moreover, since cyclopropane was a gaseous anaesthetic it could be administered in known concentrations. The recognition by Meek that the arrhythmic response to adrenaline varied with the rapidity of injection probably was of major importance. His group demon-

strated that the intravenous administration of 10 µg./kg. of adrenaline over 50 seconds consistently produced ventricular rhythms but seldom ventricular fibrillation (11). In effect, they shifted interest from chloroform-adrenaline "syncope" (ventricular fibrillation) to less severe ventricular rhythms which lent themselves better to experimental investigation. In so doing they introduced a standardized test preparation (11).

B. SPONTANEOUS AND ADRENALINE-INDUCED ARRHYTHMIAS DURING HYDROCARBON ANAESTHESIA

1. The Role of Anaesthetic Concentrations

Observations made on chloroform-anaesthetized cats indicated that deep anaesthesia tended to abolish spontaneous arrhythmias (4,5) and that the ease with which adrenaline produced arrhythmias was inversely related to the depth of anaesthesia (7). It was later demonstrated that the production of arrhythmias during light anaesthesia was facilitated by an antecedent period of deep anaesthesia (19). In contrast, it is acknowledged generally that the production of spontaneous and adrenaline-induced arrhythmias under cyclopropane is directly related to the depth of anaesthesia (9,11,18). The only report to the contrary is that of Guedel who advanced the concept of an "arrhythmic range" for cyclopropane (20). He believed that spontaneous arrhythmias occurred only within a specific range of cyclopropane concentrations. Although Thienes et al. confirmed this experimentally in dogs (21), there is no mention in either communication of the adequacy of pulmonary ventilation. The extreme concentrations of cyclopropane required to exceed the "arrhythmic range" would be expected to produce severe hypoxia and hypercarbia (see follow-

ing section). Lee et al. were not able to demonstrate this phenomenon in adequately ventilated animals (18).

Close inspection of the literature suggests that the reported differences under light and deep anaesthesia with the two agents may be a function of the species employed. Chloroform was studied mainly in cats whereas cyclopropane has been studied almost exclusively in dogs. Embley has noted the dog to be relatively insensitive to spontaneous arrhythmias under chloroform (22) and Meek et al. have demonstrated the sensitivity of the dog to chloroform-adrenaline arrhythmias to increase with the depth of anaesthesia (11). Under cyclopropane anaesthesia, the cat is said to be more sensitive to spontaneous arrhythmias than is the dog, and the dog to be more sensitive to adrenaline-induced arrhythmias (17,18).

2. The Roles of Hypoxia and Hypercarbia

Spontaneous or adrenaline-induced arrhythmias are produced less readily in the chloroform-anaesthetized cat (7) or dog (23) under artificial respiration than when the animal is breathing spontaneously. Several authors (9,10,18,21,24) have demonstrated that spontaneous arrhythmias in cats or dogs anaesthetized with cyclopropane occur at the point of respiratory arrest and that institution of artificial respiration abolishes these arrhythmias (9,10,24). The appearance of such arrhythmias appeared to be related to the retention of carbon dioxide (24) rather than to hypoxia (18). However, hypercarbia is not essential for the development of spontaneous arrhythmias since they will occur in animals receiving artificial respiration if the cyclopropane concentration is sufficiently high (9,10,24). Lurie et al. demonstrated that spontan-

eous arrhythmias occur at normal end-expiratory carbon dioxide tensions in patients under cyclopropane anaesthesia, but that administration of carbon dioxide increases the incidence of such arrhythmias (25).

The mechanism of the carbon dioxide effect has not been defined adequately. It is well known that carbon dioxide may stimulate the vasomotor centre and increase the activity of the sympathetic nervous system. Price et al. demonstrated increased plasma levels of catecholamines following administration of carbon dioxide to patients anaesthetized with cyclopropane and related increased sympathetic activity to the occurrence of arrhythmias (26). Because the level of catecholamines at which arrhythmias occurred was much lower than the levels required when exogenous adrenaline was administered, this group inferred that the circulating catecholamines reflected release at sympathetic nerve endings. They also observed that bilateral infiltration of the stellate ganglia with local anaesthetics increased the threshold of carbon dioxide required for arrhythmias. Although local anaesthetics are antiarrhythmic agents, it is unlikely that sufficient systemic absorption would occur to influence this observation.

Levy reported that asphyxia protected against chloroform arrhythmias (27). Several other reports indicate that hypercarbia induced by the administration of carbon dioxide or by decreasing alveolar ventilation protects against cyclopropane-adrenaline arrhythmias (16,28,29). It is apparent from the values given for arterial pH, pCO_2, pO_2, or percent carbon dioxide administered that these animals were in severe respiratory acidosis. Price and Helrich have demonstrated cardiac depression to be produced by metabolic or respiratory acid-

osis (30).

It would appear that the superficially conflicting reports on the effects of carbon dioxide can be reconciled. The data indicate that moderate retention of carbon dioxide sensitizes to arrhythmias by stimulation of the sympathetic nervous system, and that more gross disturbances inhibit the production of arrhythmias through a cardiac depressant effect. In this context it is interesting to note that spontaneous arrhythmias have been reported to occur when elevated arterial carbon dioxide tensions are reduced suddenly (21,25,26,29).

3. The Role of the Nervous System

a. The Sympathetic Nervous System

The spontaneous arrhythmias which occur in the sensitized preparation probably require an intact autonomic nervous system. Levy noted that sudden deaths occurred more frequently during induction of chloroform anaesthesia or during recovery from this agent and was able to demonstrate that sensory stimulation of the lightly anaesthetized cat produced ventricular rhythms and even ventricular fibrillation (7, 27). This observation was confirmed by Brow et al. (31).

Although endogenous catecholamine release probably is involved in the response, it is difficult to quantitiate the relative importance of the sympathetic innervation of the heart and of circulating neurohumours in the genesis of such arrhythmias. It has been demonstrated that stimulation of either the right stellate ganglion (7,27,31) or of the splanchnic nerves (27) produces arrhythmias. Because spontaneous chloroform arrhythmias occurred in animals subjected to bilateral stellate ganglionectomy, Levy considered release of catecholamines from the adre-

nal medulla to be of primary importance (7). Although he was unable to abolish such arrhythmias by bilateral adrenalectomy, he attributed this failure to the presence of residual chromaffin tissue. Nahum and Hoff demonstrated that neither bilateral adrenalectomy nor bilateral stellate ganglionectomy protected against spontaneous arrhythmias in the benzol-sensitized cat, but that protection was complete when these surgical procedures were combined (32). It has been reported, however, that spontaneous arrhythmias occurring in the cyclopropane-sensitized cat are prevented if removal of the thoracic sympathetic chain as far as T6 is combined with bilateral stellate ganglionectomy (24,33).

Many authors have sought to implicate the sympathetic nervous system in the genesis of adrenaline-induced arrhythmias in the sensitized preparation. Although Levy demonstrated that chloroform-adrenaline ventricular rhythms and ventricular fibrillation occurred following cardiac denervation and pithing of the spinal cord (7), Bouckaert and Heymans claimed that carotid sinus denervation protected dogs against chloroform-adrenaline "syncope" (ventricular fibrillation) (34). This was confirmed in vagotomized dogs sensitized with benzol (35). These authors suggested that carotid sinus denervation allowed continued release of neurohumours at the heart during the pressor response to adrenaline, and that this prevented the cardiac dilatation which appears to precede ventricular fibrillation. Although these results suggest that sympathetic innervation of the heart may be important in the genesis of fibrillation, it is of interest that less severe arrhythmias were not prevented by carotid sinus denervation (35).

Extensive removal of lumbar sympathetic chains and plexuses has

been stated to protect against chloroform-adrenaline ventricular fibrillation (36). Allen et al. (37) and Stutzman et al. (38,39) have shown that many surgical procedures including abdominal evisceration, extensive lumbar sympathectomy, section of the spinal cord, decerebration or stellate ganglionectomy, protect against cyclopropane-adrenaline arrhythmias. They suggested that cyclopropane acted on receptors in the region of the mesentery and postulated a reflex reaching a midbrain level. The efferent impulses of the arc were stated to reach the heart by the cardiac sympathethic nerves, and to there "sensitize" the myocardium to exogenous adrenaline. Although these results are quoted widely in the anaesthetic literature, their validity is in serious doubt. Rennick et al. have demonstrated conclusively that extensive cardiac sympathectomy does not protect against cyclopropane-adrenaline arrhythmias (40). In these experiments functional removal of all postganglionic fibres was ensured by the concomitant use of tetraethylammonium, a ganglionic blocking agent.

b. The Parasympathetic Nervous System

Section of the vagi (41,42,43) or the administration of atropine (43,44) protects in large measure against adrenaline-induced arrythmias in the nonsensitized preparation although arrhythmias may still be obtained if sufficiently large doses are employed (43,45). Riker et al. suggest that adrenaline stimulates all centres of automaticity including the sinoatrial node, the atrioventricular node and potential ventricular pacemakers, the lower centres manifesting their activity only when the SA node is depressed by vagal activity (43). Dresel has demonstrated, however, that the vagal effect on conduction through the

atrioventricular node is of sufficient magnitude that artificial maintenance of the atrial rate does not change the threshold dose of adrenaline necessary to induce cardiac arrhythmias. He has shown AV-nodal block to precede initiation of arrhythmia both in the presence and in the absence of atrial drive (46). These authors agree that a brief period of ventricular slowing is required for the emergence of the ventricular pacemaker in the nonsensitized preparation.

Vagotomy or the injection of atropine does not protect against ventricular arrhythmias produced by adrenaline in the sensitized preparation (11,34,43,47-50). On the contrary, severance of the vagi, or administration of atropine in the lightly-chloroformed cat may produce cardiac irregularities (17,27). It has been claimed that intravenous atropine produces bigeminal rhythm in cyclopropane-anaesthetized man (51).

Stimulation of the vagus (42,52,53) or injection of acetylcholine (42) will produce ventricular rhythms in the nonsensitized animal in the presence of subeffective doses of adrenaline. In contrast, vagal stimulation during chloroform or cyclopropane anaesthesia will abolish or prevent arrhythmias (7,31,54) other than ventricular fibrillation (54,55).

4. The Role of the Systemic Blood Pressure

Levy initially speculated that the adrenaline-induced increase in the systemic blood pressure might be a factor in the production of arrhythmias in the sensitized preparation (5) but later rejected this possibility (27). He found that ventricular fibrillation produced by strychnine in the sensitized cat was prevented by bilateral

stellate ganglionectomy although this procedure did not modify the pressor response to the drug. He also demonstrated that tetrahydroxypapaveroline, which is cardioactive and produces a depressor response, nevertheless induced ventricular fibrillation in this situation. He concluded that neither multifocal nor fibrillatory rhythm was related to blood pressure (27). This conclusion was predicated on his view that multifocal and fibrillatory rhythms of the ventricle were the same basic phenomenon, differing only in degree.

Other authors have sought to implicate the pressor response to adrenaline in the production of ventricular fibrillation. Shen demonstrated that adrenergic blocking agents such as yohimbine and the benzodioxanes F993 and F883 protected in large measure against chloroform-adrenaline ventricular fibrillation (35,56). He contended that an increase in systemic blood pressure was important in the genesis of this arrhythmia, the rate of rise of the pressure being considered of greater importance than the absolute pressure achieved. VanDongen showed, however, that F993 raised the threshold for electrically-induced fibrillation of the heart and that it still protected if administered simultaneously with adrenaline to the sensitized preparation (57). He concluded that these agents protected against ventricular fibrillation by a direct action on the heart and not by preventing the pressor response to adrenaline. Neither of these authors concerned themselves with arrhythmias other than ventricular fibrillation. Brockman and Huggins have reported that preliminary haemorrhage to 50 mm. Hg reduced the pressor response to 10 µg./kg. of adrenaline and protected against ventricular fibrillation in cyclopropane-sensitized dogs (58). How-

ever, since the animals employed in their investigation were only ventilated "when necessary" the possibility exists of severe myocardial depression due to the combined effects of anaemic and anoxic hypoxia.

Although the possibility cannot be excluded that the pressor response to sympathomimetic amines is important in the production of ventricular fibrillation in the sensitized preparation, it is certainly not requisite for the development of this arrhythmia. Several authors have demonstrated ventricular fibrillation to occur in response to isoproterenol in the sensitized preparation (48,59,60).

The role of the systemic blood pressure in the production of ventricular arrhythmias other than fibrillation has been studied more adequately. Although Levy did not consider the pressor response to adrenaline to be of importance, he demonstrated that ventricular beats could be produced by elevation of the systemic blood pressure, and that spontaneous chloroform arrhythmias could be abolished by procedures lowering the blood pressure (27). He interpreted the latter phenomenon to be due to decreased blood supply to the heart, and suggested that the protection afforded by this manoeuver was analagous to that provided by asphyxia.

Much of the interest in the role of blood pressure in the genesis of such adrenaline-induced ventricular rhythms in the sensitized preparation has stemmed from the observation that such arrhythmias are prevented by pretreatment with α-adrenergic blocking agents, which do not block any other measurable cardiac action of the sympathomimetic amines (61). It is interesting that the protection afforded by appropriate doses of these agents is virtually complete and is of a