CARDIAC ARRHYTHMIAS OF CENTRAL NERVOUS SYSTEM ORIGIN: POSSIBLE MECHANISM AND SUPPRESSION

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CARDIAC ARRHYTHMIAS of central nervous system (CNS) origin remain controversial.¹ Many authors have described experimental techniques for the production of cardiac arrhythmias utilizing a variety of electrical and chemical stimuli applied to brainstem and diencephalic structures.²⁻⁹

Cardiac arrhythmias have been seen in association with CNS pathology and electro-convulsive therapy (ECT) and possible mechanisms have been proposed.^{10,11}

A wide variety of arrhythmias have been produced, defying simple classification, but the majority appear to be of a ventricular ectopic nature or variants thereof. A Wolf-Parkinson-White picture has also been reported following central stimulation.⁹

These arrhythmias have been successfully blocked or partially suppressed by vagotomy,^{2,8} adrenalectomy,² splanchnic resection,² stellate ganglionectomy,^{2,8} cord section,² and various drugs including alpha and beta blockers,² reserpine,² mebutamate,⁵ pentobarbital,^{7,12} chlorpromazine,⁴ morphine,⁴ and l-hyosciamine.¹³ Attempts to define a common mechanism have been hampered by difficulties in obtaining a reproducible arrhythmia from any one site. Most studies have utilized anaesthetized dogs and cats with no reported control of blood gases. A wide variety of agents which may interfere with the study of arrhythmias have been used, including thiamylal,⁹ pentobarbital,² ether and gallamine,¹² gallamine alone,¹⁴ α -chloralose,^{1,8} morphine and chloralose.¹⁵ It would appear that elucidation of a mechanism for the production of CNS induced cardiac arrhythmias would require elimination of interfering pharmacological agents plus maintenance of proper physiological control of the animal.

METHODS

In this series, production of CNS induced cardiac arrhythmias was studied in cats intubated and ventilated with air on a Palmer pump. Normal blood gases were maintained by adjusting tidal volume according to measured blood gases (Radiometer). The spring loaded pop-off of a Sierra valve inserted into the circuit allowed the tidal volume adjustment.

The cats were chronic preparations with permanently implanted cortical screw

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electrodes for EEG recordings and four subcortical chemitrodes for regional stimulation and/or chemical injection according to a modification of the method of Yamaguchi *et al.*¹⁶ A David Kopf stereotaxic instrument was used in conjunction with the co-ordinate system of Jasper and Ajmone-Marsan.¹⁷ A recovery period of two weeks was allowed before experimentation was begun. Accuracy of subcortical placement was verified histologically when possible. Stimulation was achieved with a Grass Model S6 stimulator using a square wave pulse of 1.8 msec duration and a frequency of 100 cps as verified on a Telequipment oscilloscope. Total duration of the stimulus was always 20 seconds. Voltage was varied as required to produce the arrhythmias, up to a maximum of 18 volts, which is that required to produce a convulsive pattern on the EEG in most cats. This stimulus was comparable to that required by other workers.^{1,5,7} The EEG and lead III of the EKG were recorded on a Grass Model 6 electroencephalograph. Blood pressure studies were carried out using the femoral artery and recorded with a Grass Model 7 polygraph. Lidocaine infiltration was used to establish the femoral artery cannulation and one hour was allowed to elapse before experimentation began. The cats appeared drowsy for one day following the experiment but thereafter showed no ill-effects.

A number of subcortical sites were studied: anterior, lateral and posterior hypothalamus, amygdaloid nucleus, caudate nucleus, hippocampus, globus pallidus, brainstem reticular formation and posterior ventrolateral nucleus of the thalamus. For each subcortical site, the minimum voltage required to produce the arrhythmia was determined and that voltage was considered to be the threshold voltage in that site, for that cat, on that day. Reproduceability was to within 0.5 volt. The effect on threshold voltage of a parenterally administered agent or one applied directly to the stimulation site was assessed. The drugs studied and doses utilized were:

diazepam:	50 μ g in 10 μ l solvent locally 0.5 mg/kg IV
lidocaine:	200 μ g in 10 μ l locally 2 mg/kg IV
diphenyl hydantoin:	500 μ g in 10 μ l locally 2 mg/kg IV

The threshold voltages were redetermined 15 minutes after local injection or 10 minutes after intravenous injection. An elevation of the threshold voltage by at least one volt was considered to be evidence of positive suppression of the arrhythmogenic action of the electrical stimulation. Reproduceability of the new threshold was also to within 0.5 volt following a three-minute rest period after each arrhythmia. A change in threshold has been used by others in their experimental models as evidence of the effectiveness of their techniques for suppressing CNS induced cardiac arrhythmias.⁸ There was no evidence of permanent myocardial damage on the EKG. The effects on the arrhythmias of propranolol (0.1 mg/kg IV), phenoxylbenzamine (2 mg/kg IV) and atropine (0.02 mg/kg IV) were determined.

TABLE I
INCIDENCE OF CNS INDUCED CARDIAC ARRHYTHMIAS
PRODUCED BY VARIOUS SITES

Site Stimulated	Incidence of Arrhythmias
Anterior hypothalamus (A.H.)	86% (6/7)
Posterior hypothalamus (P.H.)	86% (6/7)
Lateral hypothalamus (L.H.)	100% (3/3)
Amygdaloid Nucleus (Am.N.)	100% (5/5)
Hippocampus (Hp.)	100% (4/4)
Brainstem Reticular Formation (BSRF)	100% (6/6)
Caudate Nucleus (C.N.)	50% (3/6)
Globus Pallidus (G.P.)	60% (3/5)
Posterior Ventrolateral Nucleus of Thalamus (PVL of Thalamus)	0% (0/3)

RESULTS

There was some variation in the ease with which stimulation of the various sites produced cardiac arrhythmias. The most consistent were those sites involved with the limbic system (Table I).

The globus pallidus, caudate nucleus and posterior ventrolateral nucleus of the thalamus produced a much lower incidence of arrhythmias than the other sites. The VPL nucleus of the thalamus was rejected for further study but the other sites were retained.

The arrhythmias produced were surprisingly constant in nature (Figure 1).

Two to five seconds following initiation of stimulation, a "U" wave appeared and heart rate increased by approximately 20 to 40 beats per minute. Just prior to or within 10 seconds after discontinuing stimulation, the sinus tachycardia reverted to a sinus bradycardia followed immediately by a ventricular escape phenomenon lasting up to 25 seconds. Inconstant variations in this pattern included a tall peaked or inverted T wave, an elevation or a depression of the ST segment. A summary of the EKG changes appears in Table II.

Stimulation of the globus pallidus and the caudate nucleus did not usually produce the "U" wave or the initial sinus tachycardia. It should be noted that these areas also produce a lower incidence of arrhythmias than the sites with the standard EKG changes.

An example of the ability of one of the three drugs investigated to suppress CNS induced cardiac arrhythmias is demonstrated in Figure 2.

The overall effectiveness of the systemically administered agents is demonstrated in Table III.

Systemic diazepam proved to be superior to both lidocaine and diphenylhydantoin in suppression of the arrhythmias, being effective in 84 per cent of all sites in all cats tested. Moreover, in 40 per cent of these the cardiac arrhythmias could be abolished entirely at any voltage up to convulsive levels. Lidocaine, on the other hand, suppressed the arrhythmias in 55 per cent of cases and totally abolished them

CNS INDUCED CARDIAC ARRHYTHMIAS

FIGURE 1

TABLE II
EKG CHANGES FOLLOWING STIMULATION
OF CNS SITES

(A) Consistent:
(1) "U" wave.
(2) Sinus tachycardia
(3) Post-stimulation bradycardia
(4) Idioventricular rhythm
(B) Variations:
(1) Tall peaked T wave
(2) Inverted T wave
(3) Elevated or depressed ST segment

in 31 per cent. Diphenylhydantoin suppressed 32 per cent and abolished only 21 per cent.

When diazepam was administered systemically, each site except the brainstem reticular formation was suppressed in at least two-thirds of the cats stimulated. Lidocaine did not demonstrate such universal success with individual sites. Diphenylhydantoin did not suppress the formation of arrhythmias in two-thirds of the cats with stimulation at any one site.

The results obtained following local injection of the three drugs into the central sites being stimulated are given in Table IV.

Lidocaine proved slightly more successful in suppression of the arrhythmias in

DIAZEPAM SUPPRESSION OF CNS INDUCED ARRHYTHMIAS

FIGURE 2

TABLE III
INCIDENCE OF SUCCESSFUL SUPPRESSION OF CNS
INDUCED CARDIAC ARRHYTHMIAS BY SYSTEMIC
ADMINISTRATION OF AGENTS

	Diazepam 0.5 mg/kg	Lidocaine 2 mg/kg	Diphenylhydantoin 2 mg/kg
A.H.	3/3	2/3	0/2
L.H.	3/3	2/3	1/3
P.H.	3/3	2/3	1/3
Am.N.	2/3	2/3	1/3
C.N.	2/3	2/2	1/1
Hp.	3/3	1/3	1/3
G.P.	3/3	1/2	0/1
BSRF	2/4	0/3	1/3
Total	84% (21/25)	55% (12/22)	32% (6/19)

Sites which are suppressed in at least two-thirds of all cats tested are boxed.

this model (64 per cent vs 55 per cent). The sites in which at least two-thirds of the cats tested would demonstrate suppression were the same as those demonstrated for systemic lidocaine. Diazepam applied locally was not as effective *in toto* or in as wide a range of sites as when given systemically (56 per cent vs 84 per

TABLE IV
INCIDENCE OF SUCCESSFUL SUPPRESSION OF CNS INDUCED
CARDIAC ARRHYTHMIAS BY AGENTS APPLIED TO
STIMULATION SITES

	Diazepam 50 µg	Lidocaine 200 µg	Diphenylhydantoin 500 µg
A.H.	2/3	3/3	0/2
L.H.	2/3	3/3	3/3
P.H.	1/3	2/2	2/3
Am.N.	1/3	3/3	2/3
C.N.	2/3	2/3	1/1
Hp.	2/3	0/3	2/3
G.P.	3/3	0/2	0/1
BSRF	1/4	1/3	1/3
Total	56% (14/25)	64% (14/22)	58% (11/19)

Sites which are suppressed in at least two-thirds of all cats tested are boxed.

cent). Diphenylhydantoin was more effective locally in both total percent (58 per cent vs 32 per cent), and in the number of sites demonstrating a high success rate. Local injection of solvents for each of the drugs produced no effect on the threshold voltage.

Combined blood pressure and EKG studies were used to help elucidate the mechanism of the arrhythmia. It was found that blood pressure rose instantaneously (approximately 60 mmHg) with initiation of the stimulus and was sustained at an elevated level for approximately one minute. An example of effect of prior adrenergic blockade on both the blood pressure and the EKG are shown in Figure 3.

Prior administration of phenoxybenzamine delayed the rise in blood pressure by five to ten seconds but did not significantly affect the degree of rise or the overall duration. The initial sinus tachycardia and the post-stimulation bradycardia were unaffected. The arrhythmias were not blocked. Propranolol reduced the degree of blood pressure rise, prevented the initial sinus tachycardia but did not affect the post-stimulation bradycardia. The arrhythmia was successfully blocked.

Cholinergic muscarinic blockade using atropine was found to prevent the post-stimulation bradycardia and to abolish the arrhythmias (Figure 4).

Diazepam markedly reduced the acute hypertensive phase of the stimulation, largely prevented the post-stimulation bradycardia, and abolished the arrhythmia following stimulation of those sites which previously produced an arrhythmia. When locally applied diazepam successfully suppressed an arrhythmia, the hypertension and initial sinus tachycardia were unaffected but no post-stimulation bradycardia occurred (Figure 5).

DISCUSSION

The electrocardiographic sequence reported in our series is similar to one of the patterns described by other workers using CNS stimulation.^{1,2,7,8,12,18} It is possible that the removal of all interfering pharmacological agents and maintenance of

EFFECTS OF ADRENERGIC BLOCKADE

FIGURE 3

proper blood gas levels were responsible for the more consistent electrocardiographic abnormalities obtained in our series. It has been suggested that simultaneous parasympathetic and sympathetic over-activity are required to produce the arrhythmia.^{8,11} Manning¹¹ suggested that the increase of circulating catecholamines resulting from sympathetic activity may increase ventricular excitability while vagal overactivity will suppress the SA node. The conditions would then be set for the development of an idioventricular rhythm. Our work supports Manning's theory¹¹ in that either beta adrenergic blockade or cholinergic muscarinic blockade prevented the arrhythmia. There is no evidence to suggest that the high vagal cardiac activity would have to be primary as in direct CNS stimulation, rather than secondary (a reflex response to increased blood pressure). The role of the hypertension itself in the arrhythmogenic sequence is unsettled. One could postulate that it may simply be a reflection of massive sympathetic discharge, with no function in the genesis of the arrhythmia. It may, however, increase cardiac work by an in-

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EFFECTS OF CHOLINERGIC MUSCARINIC BLOCKADE

FIGURE 4

EFFECTS OF DIAZEPAM ON
CNS INDUCED BLOOD PRESSURE CHANGES

FIGURE 5

crease in afterload and thereby contribute to the development of the abnormal rhythm, or may cause reflex bradycardia.

Our results of drug suppression using diazepam, lidocaine, and diphenylhydantoin allow some tentative conclusions. Given systemically, diazepam raised the threshold stimulus required to produce arrhythmia in a significantly greater number of sites more consistently than either of the other two agents. That this is a central rather than a myocardial effect is suggested by the following:

- (1) Arrhythmias can be suppressed in one of the susceptible sites by administration of the drugs but the same arrhythmia can be produced by stimulating a resistant site (e.g. BSRF) in the same cat at its original threshold.
- (2) All of the drugs were successful in suppressing the arrhythmias to some extent when given locally.
- (3) Hockman¹⁹ has nicely shown that diazepam centrally suppresses reflex vagal bradycardia but has no effect on the myocardial response to direct vagal stimulation.

The diminished efficiency of lidocaine when given systemically rather than locally may reflect a short duration of action by this route, an insufficient tissue level achieved at the dose used, or a lack of specificity for the structures involved in the arrhythmogenic mechanism. The latter two points may also explain the similar results seen for diphenylhydantoin. The marked superiority of diazepam over the other two drugs may reflect a longer duration of action and a specificity of action on the central structures involved in the arrhythmogenic mechanism. Hockman's work^{19,20} suggests the latter in that he demonstrated that the depression of reflex vagal activity by diazepam occurred at a limbic level. Others have shown electrical activity in the hippocampus and amygdaloid nucleus to be altered following diazepam²¹ while Chai²² has shown that diazepam is capable of altering cardiovascular control mechanisms especially through actions on the hypothalamus. Our results confirm these impressions. Given systemically, suppression of both parasympathetic and sympathetic responses occurred. Given locally, however, if the arrhythmia could be successfully suppressed, only the post-stimulation bradycardia was abolished; but this was sufficient to eliminate the arrhythmia.

CLINICAL IMPLICATIONS

Cardiac arrhythmias of a nature similar to those described here have been seen in patients with cerebrovascular accidents and no known heart disease.¹⁰ Fentz has reported 69 cases of cerebrovascular accidents in which EKG abnormalities were detected in 71 per cent of those with haemorrhage and 15 per cent of those with infarction. It is postulated that the mechanism involved may be local hypoxia or mechanical stimulation of vital CNS structures. Although "silent" infarction may be difficult to exclude in individual cases, it would seem unlikely that such large numbers would develop this malady. Pitts²³ stated that the chief cause of mortality in electroconvulsive therapy for affective disorders is cardiovascular complications, and that although deaths are rare (0.02 per cent), they increase in frequency with drug modification. Kauntze²⁴ describes EKG changes similar to those described in our series occurring in patients receiving ECT prior to the days of administration

of modifying drugs. All but seven of the 63 reported developed marked post-stimulation bradycardia. In only 8 per cent, however, were multifocal premature ventricular beats recorded. It should be noted that there was an undefined delay in establishing the post-stimulation EKG due to the muscle activity of the convulsion. As our figures indicate that the vast majority of arrhythmias terminate within 30 seconds, it is conceivable that this figure should be higher. Pitts claimed that thiopentone increased the incidence of arrhythmias during ECT over that observed in an unmedicated group while methohexitone produced an incidence about the same as in the unmedicated group. Cardiovascular disease increased the incidence in both groups. In view of these and our own findings, it would appear that a clinical appraisal of diazepam for use during ECT is in order.

Van Loon²⁵ has reported a patient arriving at hospital in ventricular fibrillation and successfully resuscitated but who later developed recurrent episodes of multifocal premature ventricular beats. These proved resistant to lidocaine, procaine amide, diphenylhydantoin, and antazoline but were suppressed by diazepam 20 mg intravenously on each occasion. Although the mechanism of the arrhythmia was probably multifactorial, the case does serve to illustrate that diazepam has been clinically effective in treating ventricular arrhythmias. Based on our information, it would seem more likely to be effective in patients who have experienced some type of cerebral insult, not an unlikely possibility in the aforementioned patient.

It would appear that any situation in which widespread generalized sympathetic discharge is combined with high vagal tone (reflex or primary), an arrhythmogenic situation of the type previously discussed is created. This could occur with situations such as cerebrovascular accidents, cerebral hypoxia, increased intracranial pressure, neurosurgical operations, ECT, the administration of cholinomimetics during light anaesthesia, or the administration of analeptics. Our results suggest that diazepam may prove to be useful in the suppression of some of these arrhythmias through a CNS depressant mechanism.

SUMMARY

- (1) A consistent type of ventricular arrhythmia can be produced by elective stimulation of brainstem and diencephalic structures of the unanaesthetized cat.
- (2) The EKG patterns are similar to those seen in some human CNS pathology and in ECT therapy.
- (3) This arrhythmia apparently requires simultaneous parasympathetic and sympathetic activity.
- (4) Systemic diazepam appears to be of value in suppressing these arrhythmias.

RÉSUMÉ

Nous avons étudié sur des chats les arythmies cardiaques provoquées par l'intermédiaire du système nerveux central (SNC). Les vingt-quatre chats soumis à l'étude étaient tous des préparations chroniques; chacun était porteur d'une électrode permanente corticale droite et gauche et de quatre chemitrodes souscorticales.

Nous avons choisi pour étude huit sites dans la substance cérébrale et dans le diencéphale.

Pour chacun des sites souscorticaux, nous avons déterminé le voltage minimum nécessaire pour produire l'arythmie (jusqu'à un maximum de 18 volts); nous avons estimé que cela était le voltage seuil pour le site donné, ce jour-là. La reproductibilité était en deçà de 0.5 volt.

Nous avons évalué l'effet sur le voltage seuil d'un médicament donné par voie parentérale ou appliqué directement au site de stimulation. Les médicaments étudiés ont été le diazepam, la lidocaïne et le diphenylhydantoin.

Nous avons convenu qu'une élévation du seuil d'au moins un volt constituait une évidence positive de suppression de l'arythmie.

Les arythmies obtenues nous ont semblé être d'un type de base avec des variations mineures. En deçà de deux à quatre secondes après la stimulation génératrice, une tachycardie sinusale est apparue et une onde U s'est montrée. Peu de temps avant ou en deçà de cinq secondes de l'arrêt de la stimulation, une bradycardie sinusale est apparue suivie par un phénomène de disparition ventriculaire ou de rythme idioventriculaire.

Nous avons observé que le diazepam supprimait les arythmies dans environ 85 pour cent du total des 25 sites étudiés. Dans 40 pour cent, nous ne pouvions plus provoquer l'arythmie du tout même avec des voltages sousconvulsivants. Par contre, avec la lidocaïne, nous avons réussi dans 60 pour cent et, avec le diphenylhydantoin, dans seulement 33 pour cent.

En application locale, le diazepam a supprimé la production de l'arythmie dans 65 pour cent de tous les sites, la lidocaïne, dans 60 pour cent et le diphenylhydantoin, dans 50 pour cent. Les solvants utilisés dans chacun de ces médicaments, employés en application locale à des volumes identiques, n'ont pas réussi à élever le voltage seuil. Bien plus, du fait que les arythmies sont bloquées par le propranolol et/ou par l'atropine et non par la phénoxybenzamine, il serait permis de penser alors à un mécanisme β -adrénergique et cholinergique muscarinique.

Nous avons fait une revue des implications anesthésiques cliniques de ces résultats.

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