Changes in the acetylcholine content of the heart after arrhythmogenic and anti-arrhythmic drugs have recently been reported(1–5). The present work was undertaken in order to determine acetylcholine concentration in the heart during occurrence of various atrial and ventricular arrhythmias and consequently to reversion by quinidine.

Methods: Experiments were performed on mongrel dogs of both sexes weighing 7–10 kg and anaesthetized with pentobarbitone sodium (30 mg/kg i.v.). Lead II of the electrocardiogram was recorded. Cardiac arrhythmias were induced in different groups of animals by the following methods:

1) Aconitine-induced atrial arrhythmia (6): a cotton pledget soaked in 0.05% solution of aconitine nitrate was applied to the right atrium.

2) Injury-stimulation-induced atrial flutter (7): the right atrium around the crushed intervenae caval bridge was stimulated electrically for 5–10 sec with square waves (duration 1 msec, frequency 20 Hz and 10–20 V).

3) Coronary ligation-induced ventricular arrhythmia (8): the anterior descending branch of the left coronary artery was ligated 0.5 mm from the origin.

The acetylcholine concentrations of both the atria and the apex of the ventricle were determined. The procedure for extraction of acetylcholine was essentially the same as that of Nachmansohn as described by Anand (9). Acetylcholine was assayed rectus abdominis muscle of frogs by the technique described by Richter and Crossland (10).

The atrial and ventricular arrhythmias were induced 30 min after induction of anaesthesia and the hearts were then removed for acetylcholine estimation 15 min later. In the treated group, quinidine sulphate (10 mg/kg i.v.) was administered 15 min after induction of the arrhythmia. This reverted the various arrhythmias to normal sinus rhythm within 10 min and the hearts were then immediately utilized for acetylcholine analysis. In some animals when arrhythmia could not be produced, quinidine sulphate (10 mg/kg i.v.) was injected 15 min after the chest had been opened. Five to ten min after the injection, hearts were excised for acetylcholine estimation.

In the control group, hearts were removed for acetylcholine estimation 15 min after the chest had been opened.
Results: In the control group, the mean acetylcholine content of the right atrium, left atrium and ventricle was 5.3 µg/g, 4.3 µg/g and 1.9 µg/g respectively. Quinidine, 10 mg/kg i.v., caused a reduction of acetylcholine concentration in the normally beating heart (Table 1). Acetylcholine concentration was significantly decreased both in the atria and the ventricles during atrial arrhythmias produced by aconitine and injury-stimulation and ventricular arrhythmias resulting from coronary occlusion.

Treatment with quinidine produced an inconsistent pattern of changes in these effects of various arrhythmias. Quinidine did not produce any significant change in the coronary ligation group. There was insignificant reduction in the concentration of right atrial but significant increase in the left atrial and ventricular acetylcholine in the injury-stimulation group. In the aconitine group there was a significant increase in the right atrial, insignificant decrease in the left atrial and no change in ventricular acetylcholine concentration after administration of quinidine.

Table 1. Acetylcholine concentration (µg/g) of the myocardium during different arrhythmogenic procedures with and without treatment with quinidine in dogs.

| Group               | n   | Right atrium Mean±SE | Left atrium Mean±SE | Ventricle Mean±SE | Infact ventricle Mean±SE |
|---------------------|-----|----------------------|----------------------|-------------------|-------------------------|
| Control             | 12  | 5.3±0.6              | 4.3±0.7              | 1.9±0.4           |                         |
| Aconitine           | 8   | 0.5±0.06             | 0.5±0.08             | 0.5±0.14          |                         |
| Injury-stimulation  | 8   | 2.5±0.48             | 0.6±0.06             | 0.3±0.04          |                         |
| Coronary ligation   | 6   | 1.9±0.5              | 0.8±0.12             | 0.6±0.09          | 0.6±0.17               |
| Quinidine sulphate  | 8   | 2.4±0.5              | 1.7±0.3              | 0.7±0.08          |                         |
| Aconitine + quinidine sulphate | 8 | 1.0±0.1     | 0.4±0.06             | 0.5±0.02          |                         |
| Injury stimulation + quinidine sulphate | 10 | 1.6±0.19 | 0.9±0.06             | 0.8±0.07          |                         |
| Coronary ligation + quinidine sulphate | 5 | 1.5±0.4     | 0.7±0.1             | 0.5±0.1          | 0.5±0.04               |

Mean value of groups 2-5 was compared with group 1; that of group 6 with 2; that of group 7 with 3 and that of group 8 with 4. Significance differences were assessed by student's 't' test.

Discussion: The present results indicate that acetylcholine concentrations in the heart are reduced during various cardiac arrhythmias. These findings are at variance with an earlier observation, that in arrhythmias produced by aconitine, barium and digitalis in the isolated rabbit's atria, acetylcholine concentration of the atria was increased (4). These divergent results may represent differences in the in vitro and in vivo studies and in the species and techniques for the production of arrhythmias. In another recent study also, divergent changes in cardiac content of acetylcholine during various arrhythmias were reported (1). While there was an increase in the acetylcholine concentration of the atria without any change in that of the ventricles in arrhythmias produced by digitalis
and petroleum-adrenaline, acetylcholine content of both atria and ventricles declined in arrhythmias produced by injury-stimulation and coronary occlusion. Thus there is either no direct correlation between arrhythmias per se and acetylcholine concentration of the heart or the role of acetylcholine is not the same in arrhythmias produced by different techniques.

Since acetylcholine decreases the resistance of cardiac cell membrane to the outward flux of potassium resulting in electrophysiological changes conductive to the development of arrhythmias and since quinidine depresses this cationic efflux, it has been postulated by Holland (11) that interference with the acetylcholine system in the heart may be the essential biochemical mechanism underlying the antiarrhythmic action of quinidine. Decrease in the acetylcholine concentration of the normally beating heart in vivo by quinidine was taken as corroborative evidence for this postulate (5). Divergent changes such as increase or decrease or no significant change in the acetylcholine concentration of the heart on successful treatment of various arrhythmias by quinidine, as observed in this study, do not lend support to the viewpoint that acetylcholine is involved in mediating the antiarrhythmic action of quinidine.

Summary: Acetylcholine concentration of the right and left atria of dogs and the ventricles were significantly decreased in atrial arrhythmias induced by aconitine and injury-stimulation as well as in ventricular arrhythmias resulting from coronary occlusion. Since divergent changes in the acetylcholine content of the heart during various arrhythmias were reported previously, no obvious correlation appears to exist between arrhythmias per se and acetylcholine concentrations. Further, evidence has been presented that the acetylcholine system in the heart is not involved in mediating the antiarrhythmic action of quinidine.

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