THE EFFECTS OF DIGITALIS ON THE HYPOTHERMIC HEART

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In view of the frequent use of hypothermia in certain surgical procedures, the pharmacological behaviour of the hypothermic heart assumes practical significance. The present paper is concerned with some aspects of digitalis action in the hypothermic animal.

RESULTS

Digitalis and the Heart at Normal Body Temperature. A previous study from our department (Szekely and Wynne, 1951) and further unpublished experimental data show that (1) the intravenous average lethal dose of tincture of digitalis in the cat is 1 ml. per kg. and (2) cardiac arrhythmias occur very frequently with ventricular fibrillation as the usual terminal event. These findings are in agreement with the original work of Robinson and Wilson (1918). A characteristic sequence of events is shown in Fig. 1.

Digitalis in Hypothermia. Hypothermia was induced in 24 cats by the method described in a previous communication (Wynne *et al.*, 1960). At various temperatures ranging from 21° C. to 32° C. one-third of the average lethal dose of tincture of digitalis, calculated as for cats at normal body temperature, was injected at five-minute intervals until death of the animal.

The average lethal dose of digitalis was found to be larger in hypothermia than in animals at normal body temperature. The lower the temperature, the larger the average lethal dose appeared to be. This relationship is shown in Table I.

TABLE I
DIGITALIS IN CATS AT NORMAL BODY TEMPERATURE AND DURING HYPOTHERMIA

Temperature	Average lethal dose of tincture of digitalis, ml. per kg.	Incidence of ventricular fibrillation, percentage
Normal	1	90
29° C.-32° C.	1.5	62.5
25° C.-28° C.	2.5	37.5
21° C.-24° C.	3	12.5

Ventricular fibrillation as a result of digitalis action was encountered much less frequently than was the case in animals at normal body temperature, and its incidence diminished with falling temperature (Table I). The electrocardiogram reproduced in Fig. 2 is representative of the changes observed following the administration of digitalis in hypothermia. Other cardiac arrhythmias

FIG. 1.—Cat, weight 2 kg., lead II. Normal temperature. (A) Initial tracing. (B–E) After a total amount of 1 ml. per kg. of tincture of digitalis. Ventricular extrasystoles followed by ventricular tachycardia and ventricular fibrillation.

such as extrasystoles and ventricular tachycardia were also much less common than in the control group.

The elevated S–T segment produced by hypothermia as well as the T waves were lowered by digitalis in several experiments (Fig. 3). However, this digitalis effect became less noticeable at lower temperatures. The prolonged Q–T_c interval was not significantly altered by digitalis.

DISCUSSION

The present investigations show that myocardial sensitivity to digitalis is reduced in hypothermic cats. The average lethal dose of digitalis is larger and digitalis-induced cardiac arrhythmias, including ventricular fibrillation, are less frequent in hypothermia than at normal body temperature. Satoskar and Trivedi (1956) also found in cats that the amount of digitalis needed to produce cardiac arrest at 25° C.–26° C. was significantly larger than the dose that produced similar effects in animals at 37° C: in their experience ventricular fibrillation following the administration of digitalis was also less common in hypothermia than at normal body temperature. Crismon and Elliott (1947) reported that hypothermic rats which received lanatoside C developed cardiac arrhythmias less frequently than the controls. Angelakos *et al.* (1958) observed a diminished susceptibility of the hypothermic dog heart to ouabain-induced arrhythmias, as compared with animals at normal body temperature. They found that the amount that produced cardiac arrhythmias at normal body temperature was only one-fifth of that required at 27° C. Lombardo *et al.* (1957) stated that hypothermic animals subjected to venous inflow occlusion and open cardiectomy were less likely to develop ventricular fibrillation, if they received acetyl strophanthidin.

All the available data suggest that hypothermia protects the animal to some extent against digitalis-induced cardiac arrhythmias. This antagonistic effect of digitalis and hypothermia cannot be satisfactorily explained on the basis of electrolyte changes. Potassium and digitalis are believed

FIG. 2.—Cat, weight 1.7 kg., lead II. (A) Sinus rhythm. Hypothermia deflection at the junction of QRS complex and S-T segment at 24° C. (B–E) 22° C.–24° C. After a total amount of 3.33 ml. per kg. of tincture of digitalis. Slow ventricular rate throughout until cardiac arrest. Note absence of ventricular fibrillation.

to be antagonistic in their action, but there is no conclusive evidence of an increase in intracellular potassium in hypothermia. It is known that the effect of cold is opposite to that of digitalis on the refractory period of the myocardium and this may be responsible for the behaviour of the digitalized heart (Angelakos *et al.*, 1958).

According to current concepts the toxic manifestations of digitalis are but an extension of the therapeutic effects at the cellular level and the therapeutic-toxic ratio remains essentially unchanged (Lown and Levine, 1955). This point was experimentally investigated by Taeschler and Weidmann (1957) and by Taeschler *et al.* (1958) in relation to hypothermia. They found that digitalis had no positive inotropic effect on the isolated guinea pig atrium, when the perfusing fluid was cooled to 18°–19° C.: toxic effects were also absent even after very large doses. On rewarming the fluid to 30° C. digitalis produced a positive inotropic effect again and further amounts led to toxic changes.

It is reasonable to assume that, if the hypothermic human heart also shows a decreased sensitivity to digitalis toxicity, then its responsiveness to therapeutic doses of digitalis is likely to be also diminished. In this case larger amounts of digitalis would be required to achieve therapeutic effects during hypothermia than at normal body temperature.

FIG. 3.—Cat, weight 1.7 kg., lead II. (A) Initial tracing at 36° C. (B) Elevation of S-T segment at 28° C. (C) After 0.66 ml. per kg. of tincture of digitalis at 28° C. Note lowering of S-T segment and T wave.

SUMMARY

The average lethal dose of digitalis was found to be significantly larger in hypothermic cats than in controls at normal body temperature. Digitalis-induced cardiac arrhythmias also occurred much less frequently in hypothermia than at normal body temperature.

The significance of these findings is discussed.

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