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# SUPPRESSION OF OUABAIN-INDUCED ATRIAL ARRHYTHMIAS BY CAROTID SINUS STIMULATION

BY

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In dogs anaesthetized with chloralose ectopic atrial arrhythmias were produced by subepicardial injection of ouabain. Stimulation of the right carotid sinus abruptly suppressed the ectopic arrhythmias. They returned on cessation of stimulation and sometimes already during the period of stimulation. It is suggested that in view of its response to carotid sinus stimulation the ouabain-induced arrhythmia resembles paroxysmal atrial tachycardia and that it is distinct from the aconitine-induced arrhythmia which on account of its response to vagal stimulation has been classified as atrial flutter.

It is well known to clinicians that attacks of atrial paroxysmal tachycardia can often be terminated by carotid sinus pressure whereas this procedure is ineffective in atrial flutter. It is equally well known that different types of atrial arrhythmias can be produced in animals by local application of various drugs to the epicardial surface of the heart (Scherf, 1944, 1947; Kisch, 1944; Scherf & Chick, 1951; Prinzmetal, Corday, Brill, Oblath & Kruger, 1952; Scherf, Blumenfeld, Taner & Yildiz, 1960), but it has never been shown that any of these resemble paroxysmal atrial tachycardia in man by the crucial test of being consistently suppressible by means of carotid sinus stimulation. It has now been found that the arrhythmia produced by subepicardial injection of ouabain is regularly susceptible to carotid sinus stimulation.

## METHODS

Dogs weighing between 9 and 14 kg were premedicated with morphine, 1 mg/kg injected subcutaneously, and anaesthetized with chloralose, 0.1 g/kg injected intravenously. The blood pressure was recorded from a femoral artery and a cannula was inserted into the trachea.

In all experiments stimulation of the carotid sinus was carried out on the right side with both sinus and aortic nerves intact in order to approximate the effects obtained in man, where pressure on the right carotid sinus is more frequently effective in terminating attacks of atrial paroxysmal tachycardia (Scherf & Schott, 1953). The right carotid sinus was exposed, and stimulating shielded platinum electrodes were applied to the dissected sinus nerve and connected to a transistor stimulator (Joslin, 1959). Stimulation was carried out with impulses of 15 V, 1 msec, 100/sec. In a few experiments the innervated right carotid sinus was isolated, according to the method of Moissejeff (1927), making possible its distension by introducing liquid into it, and at the same time recording the intrasinusal pressure.

After dissection of the carotid sinus, the sternum was split, the chest opened in the midline to expose the heart, while artificial respiration was given with a Starling ("Ideal") pump.

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Lead 2 of the electrocardiogram was recorded on a direct-writing electrocardiograph of the Cambridge Instrument Co. ("Electrite"). In this lead ectopic beats originating from the site of an ouabain injection were characterized by inverted P waves and were easily distinguishable from normal sinus beats which had upright P waves.

Ouabain (Burroughs Wellcome & Co.), 0.1 ml. of a 0.1% solution in either 70% alcohol, 0.9% sodium chloride solution, or distilled water, was injected subepicardially at the posterior surface of the heart between the inferior vena cava and a pulmonary vein. Unless otherwise stated, the ouabain solution was freshly prepared, as advised by Scherf (1944), in order to obtain arrhythmia consistently.

## RESULTS

Seven experiments were carried out with subepicardial injection of freshly prepared ouabain solution. In four experiments, arrhythmias with inverted P waves were produced; in two, the arrhythmia was doubtful because the P waves closely resembled the normal sinus P waves, and in one atrial fibrillation occurred after a period of ventricular arrhythmia. In three different experiments, two subepicardial injections of 0.1 ml. of distilled water, four of 70% alcohol and one injection of 10% sodium chloride solution did not produce any ectopic arrhythmia.

In the four experiments in which the ouabain produced ectopic arrhythmia with inverted P waves, the arrhythmia was temporarily abolished by stimulation of the right carotid sinus nerve. The stimulation caused each time a prompt and appreciable fall in arterial blood pressure. The arrhythmia returned either during the period of stimulation or after its cessation, in which case it was usually preceded by a few sec of undisturbed sinus rhythm. When the sinus nerve was stimulated again, the arrhythmia was again temporarily suppressed. This occurred twice in one, and four, seven and ten times in the other three experiments.

One of the four experiments is illustrated in Fig. 1. The tracing (a) shows the effect of sinus nerve stimulation before the injection of ouabain. Stimulation produced a gradual slowing of the heart; the rate also returned gradually after the end of stimulation. These gradual changes are characteristic of the effect of sinus stimulation on the normal rhythm, and contrast with the abrupt changes brought about during ectopic arrhythmia produced by ouabain, as shown in (b). The ectopic arrhythmia was fully developed 4 min after the ouabain injection. When the sinus nerve was stimulated for periods of about 20 sec the ectopic rhythm was temporarily suppressed. Such stimulation was carried out seven times. The tracing (b) shows the effect of the third period of stimulation. At the beginning of Fig. 1 (b) the ectopic atrial arrhythmia has cycle lengths varying between 0.24 and 0.32 sec (rate 188 to 250). The ventricular complexes have a pattern which suggests injury, presumably because ouabain leaked into the ventricular myocardium. There was in addition alternation in cycle length, a phenomenon previously observed in atrial arrhythmia elicited by aconitine and in ventricular tachycardia precipitated by ouabain (Scherf, 1944; Scherf & Terranova, 1949). Stimulation of the carotid sinus nerve abruptly suppressed the ectopic arrhythmia and a slow sinus rhythm appeared. The third beat after the onset of stimulation was no longer ectopic, its P wave being upright. The onset of stimulation was recorded manually and with appreciable error. Therefore the length of the interval between onset of stimulation, as indicated on the record, and suppression of the ectopic arrhythmia cannot

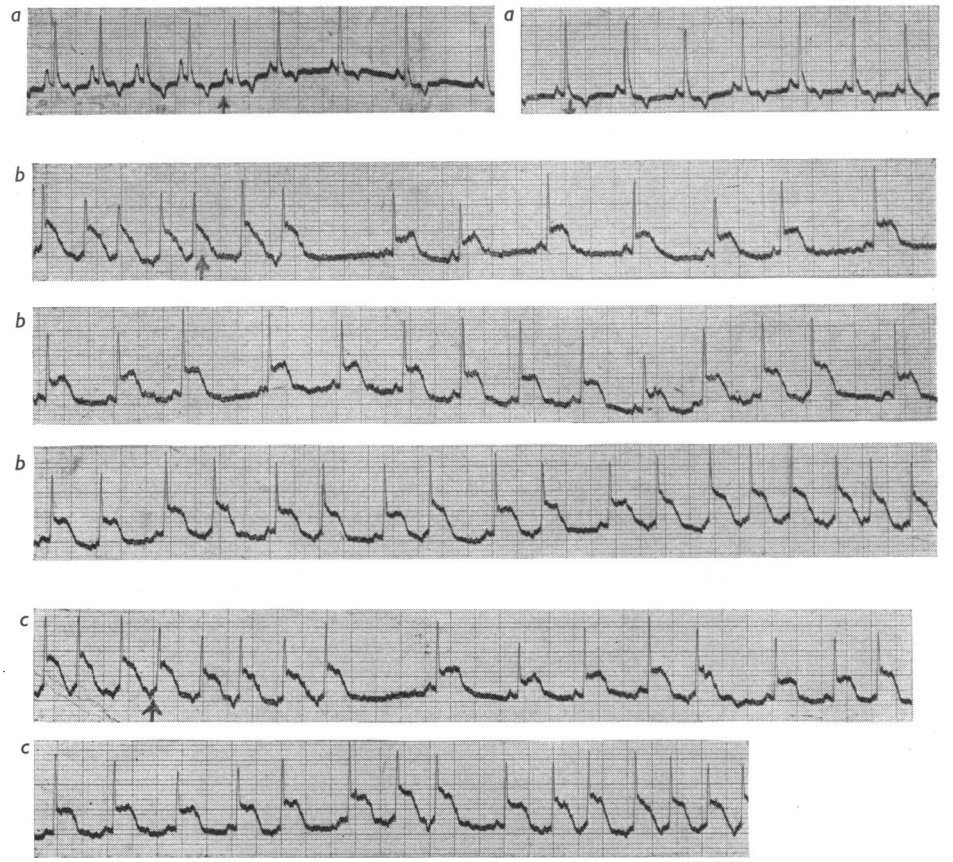


Fig. 1. Electrocardiogram of a dog anaesthetized with chloralose 100 mg/kg after premedication with morphine 1 mg/kg. Lead 2. (a) Stimulation of the right carotid sinus nerve between the arrows. The interval between the two sections of the record was 10 beats. (b) About 5 min after a subepicardial injection of 0.1 ml. of a 0.1% solution of ouabain. The three sections of the record are continuous. From the arrow until the end of the record the right carotid sinus nerve was stimulated. (c) About half a min after (b). The two sections of (c) are continuous. From the arrow until the end of the record renewed stimulation of the right carotid sinus nerve. Time base 0.2 sec between the thick vertical lines.

be regarded as accurate. In this experiment the atrial arrhythmia returned during the period of stimulation. The first signs were single atrial extrasystoles. The first extrasystole, which occurred after 19 sinus beats, is reproduced as the penultimate beat in the middle strip; it is characterized by its prematurity and inverted P wave. The beginning of the bottom strip of (b) shows that each of the first five sinus beats was followed by one atrial extrasystole (atrial bigeminy). The interval between each extrasystole and its preceding sinus beat was constant (0.38 sec), that is, the extrasystoles had fixed coupling. The end of the bottom strip illustrates the reappearance of the atrial arrhythmia 17.5 sec after the beginning of stimulation. Fig. 1 (c) shows the effect of the fourth period of stimulation to demonstrate the renewed suppression of the atrial arrhythmia, but this time the effect was unusually

transient. The first single atrial extrasystole appeared already after four sinus beats, the shortest duration of converted undisturbed sinus rhythm during stimulation found in any experiment. Further single atrial extrasystoles with fixed coupling occurred after two and four sinus beats, then two extrasystoles followed the next sinus beat. Finally, about 10 sec after the beginning of stimulation, the ectopic atrial arrhythmia recurred, as shown at the end of the figure. After the seventh stimulation of the carotid sinus nerve the right vagus was cut. Stimulation of its peripheral end for 24 sec resulted in cardiac standstill with ventricular escape beats, followed after the end of stimulation by sinus rhythm. A second injection of ouabain produced again ectopic atrial arrhythmia ; five consecutive stimulations of the carotid sinus nerve had no effect on the ectopic arrhythmia, whereas subsequent stimulation of the peripheral end of the right vagus again precipitated cardiac standstill with escape beats.

Fig. 2 illustrates the experiment in which ten consecutive stimulations of the right carotid sinus nerve suppressed atrial ectopic arrhythmias throughout the period of stimulation which lasted for 8 to 14 sec. The tracing (a) taken before the

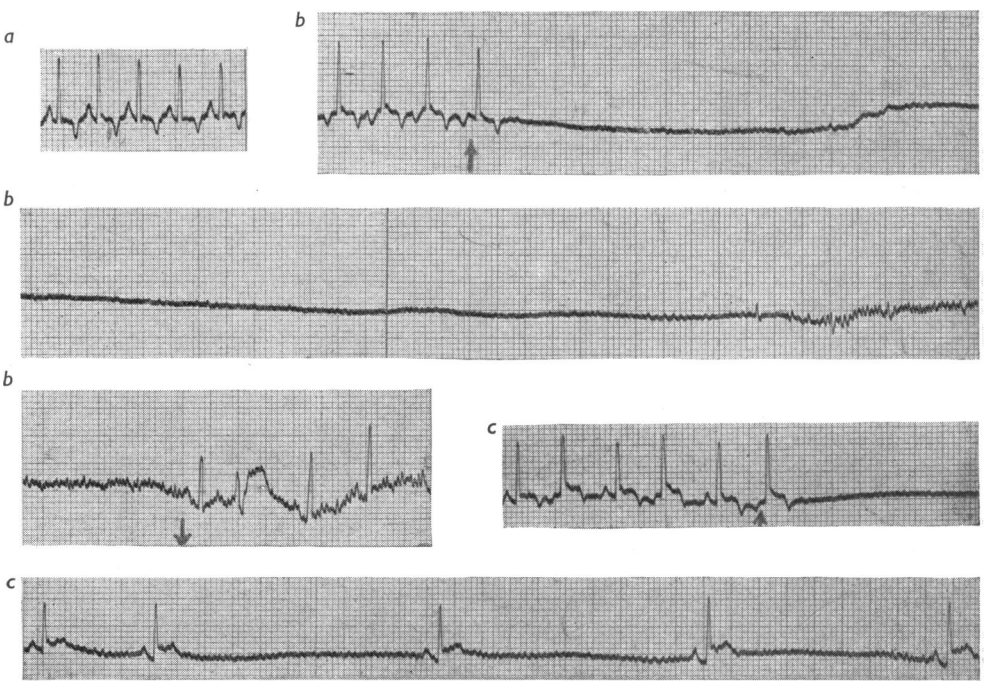


Fig. 2. Electrocardiogram of a dog anaesthetized with chloralose 100 mg/kg after premedication with morphine 1 mg/kg. Lead 2. (a) Before, (b) 4 min after subepicardial injection of 0.1 ml. of a 0.1% solution of ouabain. Between the arrows first stimulation of the right carotid sinus nerve. The three sections of (b) are continuous. (c) 10 min after the ouabain injection. From the arrow till the end of the record stimulation of the right carotid sinus nerve (seventh period of stimulation). The two sections of (c) are continuous. Time base 0.2 sec between the thick vertical lines.

ouabain injection shows sinus rhythm of a rate of about 214/min. Half a minute after the injection single atrial extrasystoles occurred. This was unusually early, since according to Scherf (1944) it takes as a rule several min for subepicardially injected digitalis glycosides to produce ectopic arrhythmia. Two min after the injection, periods of ectopic atrial arrhythmia of increasing length started to alternate with periods of sinus rhythm, both at first at a rate of about 150. Four min after the injection the ectopic atrial arrhythmia was fully developed and its rate had increased. After a series of 21 consecutive atrial ectopic beats with cycle lengths of 0.32 to 0.35 sec (rate 171 to 187) the carotid sinus nerve was stimulated. This produced cardiac standstill throughout the 12 sec period of stimulation. The beginning of tracing (b) shows the last four ectopic atrial beats with deeply inverted P waves before the onset of stimulation which resulted in the cardiac standstill. On cessation of stimulation there was return of sinus rhythm, the first sinus beat being followed by a ventricular extrasystole. The sinus rhythm had about the same rate as the previous ectopic arrhythmia. Such similarity of rates between sinus and an ectopic rhythm has previously been observed in ectopic ventricular arrhythmias elicited by the subepicardial injection of veratrine, sodium oxalate, citrate and chloride (Scherf, Blumenfeld, Golbey, Ladopoulos & Roth, 1954). The period of sinus rhythm lasted for 41 beats. It was followed by ectopic atrial arrhythmia, which was again abruptly suppressed with renewed carotid sinus nerve stimulation, and throughout its duration (11.5 sec) the ectopic arrhythmia was replaced by a slow sinus rhythm of a rate of 34 to 37/min (not shown in Fig. 2).

Essentially the same sequence of events was observed during all subsequent periods of stimulation. There was each time abrupt suppression of the ectopic rhythm during stimulation, followed either by cardiac standstill with or without an occasional idioventricular escape beat, or by a slow sinus rhythm (sinus escape), and after cessation of stimulation the ectopic arrhythmia returned, preceded by a period of undisturbed sinus rhythm. This ectopic arrhythmia consisted exclusively of ectopic beats as illustrated in Fig. 2b, or was an atrial bigeminy, as illustrated in Fig. 2c, which reproduces the effect of the seventh stimulation carried out 10 min after the ouabain injection. The beginning of Fig. 2c shows three sinus beats each followed by an atrial extrasystole. On stimulation this arrhythmia was immediately replaced by a slow sinus rhythm.

In a few experiments the ouabain solution used for subepicardial injection was not freshly prepared, but a stock solution about a year old containing 0.8 mg anhydrous ouabain in 1 ml. of 70% alcohol was used. In only one of them did the injection result in ectopic atrial arrhythmia. In this experiment, instead of stimulating the right carotid sinus nerve, the isolated innervated right carotid sinus was distended to a pressure of 200 mm Hg for periods varying between 13 and 43 sec. Each of nine successive distensions resulted in abrupt suppression of the atrial ectopic arrhythmia ; in six of these, single atrial extrasystoles appeared during the period of distension, but again only after an initial undisturbed sinus rhythm. As in the experiment of Fig. 1 the extrasystoles had fixed coupling. Fig. 3a illustrates the effect of the fifth period of distension. The first atrial extrasystole during the distension occurred after ten sinus beats, and the coupling of the three extrasystoles at the end of the tracing was 0.28 sec. This tracing also illustrates the strong vagal

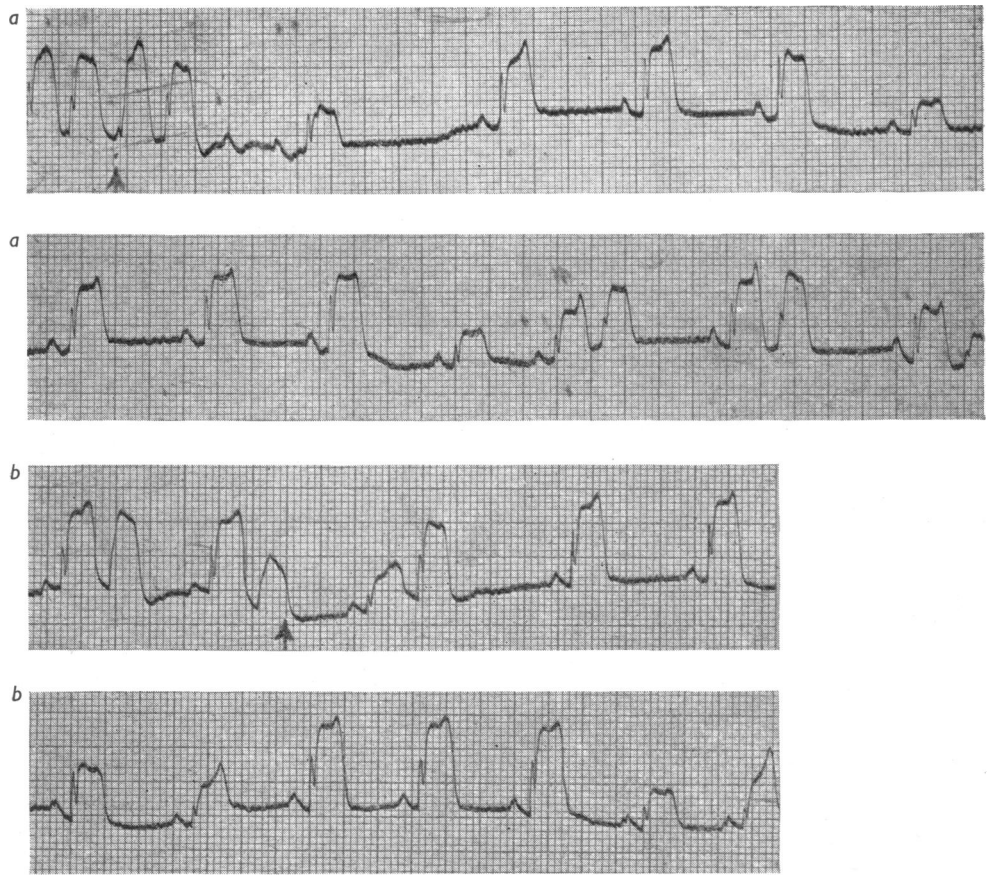


Fig. 3. Electrocardiogram of a dog anaesthetized with chloralose 100 mg/kg after premedication with morphine 1 mg/kg after subepicardial injection of 0.1 ml. of a 0.1% solution of ouabain. Lead 2. In both (a) and (b), which are both continuous records, the innervated right carotid sinus was distended to a pressure of 200 mm Hg from the arrow until the end of the record; (a) fifth and (b) sixth period of distension 5 and 6 min respectively after the injection. Time base 0.2 sec between the thick vertical lines.

effect on atrio-ventricular conduction immediately on suppression of the ectopic arrhythmia, as shown by the fact that the first sinus P wave was not followed by a ventricular complex and the second only after a prolonged P-R interval of 0.18 sec compared with 0.12 to 0.14 sec, the lengths of the P-R intervals of the subsequent sinus beats. After the distension the rhythm became that of atrial bigeminy, and renewed distension again selectively suppressed the extrasystoles. This is shown in tracing (b), in which the two sinus beats before and the first sinus beat after the onset of distension were each followed by an atrial extrasystole with a fixed coupling of 0.28 sec. The subsequent undisturbed sinus rhythm had a rate of about 94/min. At the end of distension atrial bigeminy returned. Selective suppression of the extrasystoles was again obtained during the two subsequent periods of renewed distension. It is interesting in this connexion to recall a similar observation of

Scherf (1944) made on arrhythmias induced by topical application of digitalis glycosides. He found a temporary suppression of atrial extrasystoles in atrial bigeminy by stimulation of the right vagus.

## DISCUSSION

The finding that the atrial ectopic arrhythmia and atrial extrasystoles elicited by subepicardial injection of ouabain were consistently and abruptly suppressed by right carotid sinus nerve stimulation or by distension of the isolated innervated right carotid sinus is relevant to the problem of the relation between atrial flutter and paroxysmal atrial tachycardia. These two forms of arrhythmia are now generally regarded as being due to rapid stimuli originating in an ectopic atrial centre, whereas formerly atrial flutter was attributed to a circus movement of the excitation wave in the atria, in accordance with Lewis's theory. This change in view about the origin of flutter results from the observation that the atrial arrhythmia elicited in dogs by the topical application of aconitine to the atrial surface responded to vagal stimulation by an increase in atrial rate and occasional conversion into atrial fibrillation (Scherf, 1947 ; Scherf, Romano & Terranova, 1948 ; Scherf, Schaffer & Blumenfeld, 1953). Many years earlier the same vagal response was obtained during atrial flutter produced by faradization (Rothberger & Winterberg, 1914). Suppression of the atrial arrhythmia by vagus stimulation in the two conditions was only infrequently obtained (Lewis, Drury & Bulger, 1921 ; Scherf & Terranova, 1949 ; Scherf, Blumenfeld, Mueller & Beinfield, 1953). It was on the basis of these observations that the aconitine-induced arrhythmia was classified as atrial flutter as distinct from paroxysmal tachycardia. The concept of a focal origin has also been applied to atrial flutter in man (Puech, 1956). The mode of origin of atrial arrhythmias, a subject which is still controversial (see Rosenblueth & Garcia Ramos, 1947 ; Brown & Acheson, 1952 ; Lanari, Lambertini & Ravin, 1956), has been reviewed by Scherf & Schott (1953), Spang (1957), Holzmann (1960), and Katz & Pick (1960).

The assumption that both arrhythmias, atrial flutter and paroxysmal tachycardia, are due to rapid stimulus formation in an ectopic centre presupposes a closely allied mode of origin. In fact, Prinzmetal *et al.* (1952) tentatively suggested a unitary nature of the two arrhythmias. However, there are serious objections to such a view. Atrial tachycardia is often found in subjects with otherwise normal hearts, whereas the reverse is true of atrial flutter. Pressure on the carotid sinus often abruptly terminates an attack of paroxysmal atrial tachycardia, but this does not occur in patients with atrial flutter.

The abrupt suppression by carotid sinus stimulation of the atrial ectopic arrhythmias induced in dogs by subepicardial injection of ouabain resembles the abrupt termination by carotid sinus pressure of paroxysmal atrial tachycardia in man. But, in contrast to the permanent suppression usually obtained in man, the effect on the ouabain arrhythmia in dogs was transient. This is perhaps not surprising, owing to the persistence of the arrhythmogenic agent ouabain. The transient effect of vagus stimulation on the flutter induced by topical application of aconitine has been similarly explained (Scherf, Schaffer & Blumenfeld, 1953).

The fact that the ouabain-induced arrhythmia was suppressed by carotid sinus stimulation whereas the arrhythmia induced by aconitine responds differently, that is, by an increase in atrial rate and occasionally by conversion into atrial fibrillation, suggests a difference in nature of these two arrhythmias. This conclusion rests on the assumption that the efferent pathway of the carotid sinus reflex to the heart is the vagus and that extravagal components play no or only an insignificant part in the anti-arrhythmic effect of carotid sinus stimulation. The findings of Winder (1938) that in dogs, with the major secondary factors controlled, the maximum extravagal component of carotid pressoreceptive slowing of normal rhythm was only approximately 8% may be relevant in this connexion. On account of its response to carotid sinus stimulation the ouabain-induced arrhythmia should be considered as resembling paroxysmal atrial tachycardia, as distinct from the aconitine-induced arrhythmia whose response to vagal stimulation characterized it as atrial flutter.

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