Mechanisms of onset and termination of abnormal cardiac rhythm studied by constant monitoring

*Ernest W. Reynolds, Jr., M.D.**
Walter J. MacDonald, M.D.
Bruce M. Greenfield, M.D.
Alan A. Semion
Ann Arbor, Mich.

Knowledge of the events which take place at the onset and termination of the cardiac arrhythmias has been useful in understanding the mechanisms of the arrhythmias in experimental animals as shown by Moe, Harris, and Wiggers.[1] Information concerning the onset and termination of abnormal rhythm in man is scarce, being dependent on chance observations or recordings. Since such knowledge might throw light on the factors at the beginning or end of arrhythmias which could help either in understanding the underlying mechanism or in treatment, it was decided to obtain this information by constant monitoring of the electrocardiogram and computed heart rate with special attention to the sequences occurring at the onset and termination of attacks in man. The method is specially adaptable to a study of the paroxysmal arrhythmias and of rhythm disturbances that are terminated with drugs.

Methods

Facilities for monitoring consisted of a mobile, two-channel, magnetic tape recorder and a recording cardiotachometer, as shown in Fig. 1. The latter instrument permitted a 24 hour count of premature beats and proved a useful aid in searching the tape for conversion sequences. Patients were monitored while resting in bed or sitting in a chair. Wires were attached to the chest by snap fasteners† crimped to adhesive patches.‡ The exposed flat underside of the fastener served as the electrode and was smeared with a nonirritating electrode jelly.§ Two bipolar chest leads were used, of which one augmented P waves and reduced R-wave amplitude and the other produced a tall R wave to trigger the cardiotachometer. The first of these leads connected the left side of the manubrium to the fourth rib along the right sternal border; the second lead employed the same manubrial connection and a

From the University of Michigan Medical Center, Ann Arbor, Mich.
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*Address: Heart Station, University Hospital, University of Michigan Medical Center, Ann Arbor, Mich. 48104.
†Dot Products Supply Co., Newtonville, Mass.
‡Parke, Davis & Co., Detroit, Mich.
§Telemedics, Inc., Southampton, Pa.

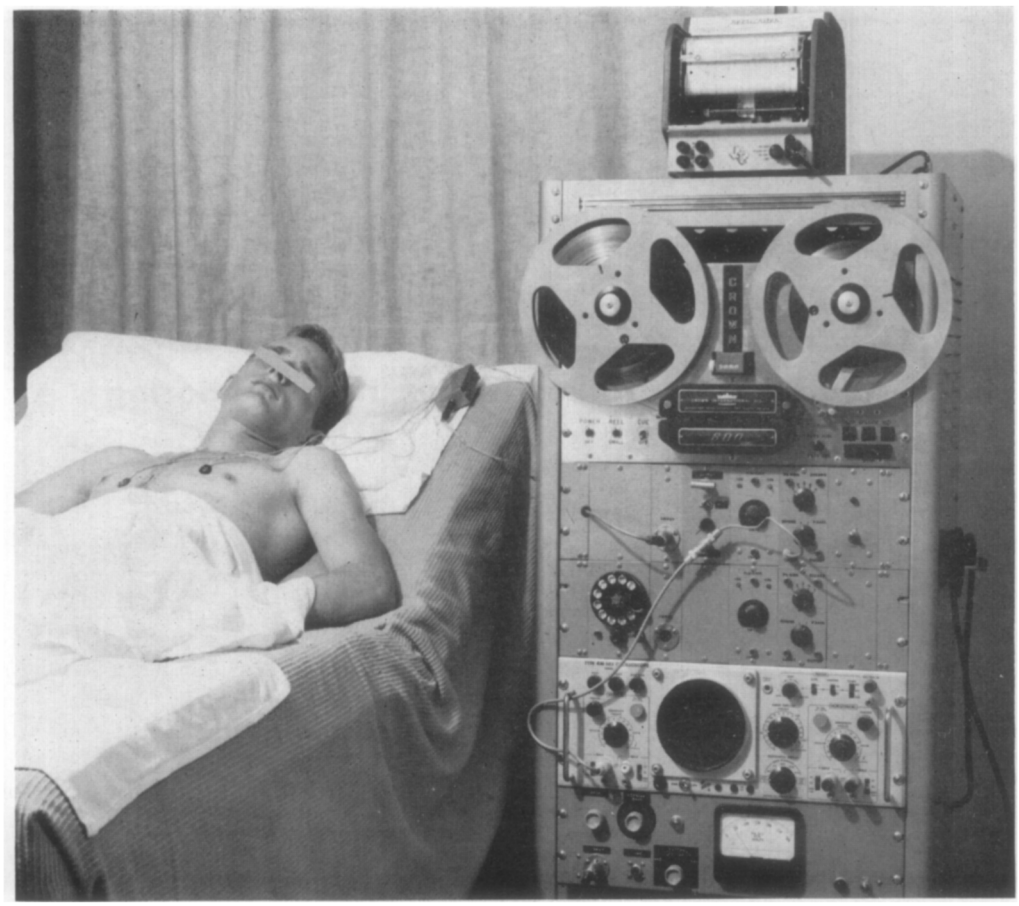

Fig. *1*. The two-channel, mobile tape recorder and recording cardiotachometer as used at the bedside. Using a recording speed of 15/16″/sec. provides 16 hours of uninterrupted recording on tape. The frequency of premature beats is recorded on the strip chart recorder continuously for a 28 hour period. The telephone dial permits coding the tape with patient's study number, time, and type of drug being used on the magnetic tape.

connection near the cardiac apex. A ground wire was attached over the ziphoid process.

Patients selected were those who gave a history of a paroxysmal arrhythmia or who were undergoing medical conversion of an arrhythmia. There were 137 patients monitored for periods generally of a week's duration, but only those providing useful data are reported here.

The results in 17 monitored patients with atrial flutter treated with digitalis are shown in Fig. 2. In the 10 patients who converted to atrial fibrillation, the atrial rate increased from a mean of 271.4 ± 11.4 (S.E.) to 300 ± 15.7 beats per minute. Four of these patients terminated with normal sinus rhythm. In the 7 patients who remained in atrial flutter after digitalis therapy, the atrial rate increased from a mean of 266.6 ± 9 to 279 ± 16.1 beats per minute. The mean increase in atrial rate in the patients terminating with atrial fibrillation was 24.6 ± 2.7 beats per minute, compared with 12.6 ± 10 beats per minute for those patients whose atrial flutter failed to terminate. Using the t test for paired observations, the atrial rate change in the successful terminations was significant ($P < 0.001$), and in the unsuccessful terminations was not significant ($P = 0.25$).

These results show that the conversion of atrial flutter to atrial fibrillation is correlated with the ability of digitalis to increase atrial rate. This desired action is dependent on the greater relative magnitude of the indirect vagal action of digi-

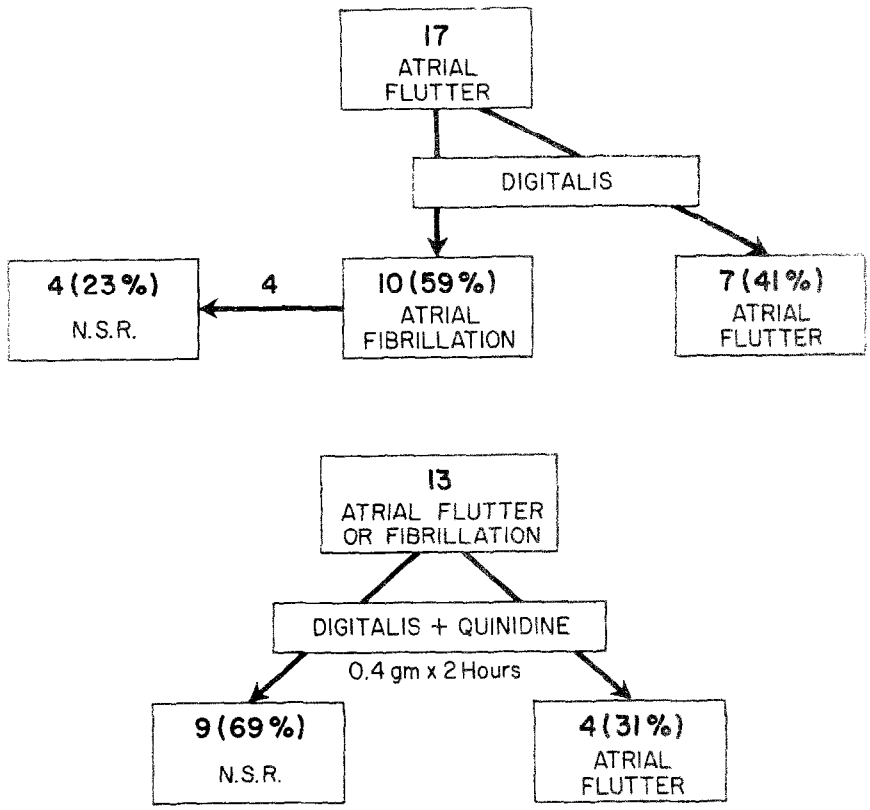

Fig. 2. Of 18 patients with atrial flutter or fibrillation, 14 (78 per cent) converted to N.S.R. with digitalis or the combination of digitalis and quinidine.

talis, as suggested by Farah and Loomis.[2] Thus, the present studies confirm that the over-riding effect of digitalis in man is vagal—except for 2 patients in whom the direct muscular effect of the drug caused a slowing of the atrial rate and in two patients in whom the drug caused no change in atrial rate. This tendency for the direct action of digitalis to occasionally override or balance the vagal action prevents effective use of the drug in terminating atrial flutter in many patients.

The transition from atrial flutter to atrial fibrillation was an uneventful, gradual increase in atrial rate until the atrial rhythm became irregular. It is of interest that postconversion interference dissociation was not observed in the 4 patients who terminated with normal rhythm, nor in 4 additional patients in whom atrial flutter terminated without drugs. In these studies postconversion interference dissociation was observed only after the combined use of digitalis and quinidine.

Combined use of digitalis and quinidine

The patients with atrial flutter who failed to convert to a normal sinus mechanism with digitalis were given quinidine, 0.4 Gm. every 2 hours for up to 8 doses. Quinidine in these doses caused a slowing in the atrial rate from a mean of 257 ± 4.4 to 199.1 ± 17.8 beats per minute in those instances where the rhythm terminated with normal sinus rhythm. When quinidine therapy was unsuccessful in terminating the rhythm, the atrial rate still slowed from a mean of 256.8 ± 14.6 to 201.8 ± 16.4 beats per minute. The mean decrease in atrial rate in the 7 successful instances was 57.9 ± 15 beats per minute, which was a significant change ($P < 0.01$), compared with 55 ± 21.5 beats per minute in the 4 unsuccessful cases. However, the magnitude of the quinidine-induced atrial slowing does not differ significantly in the successful compared to the unsuccessfully treated groups. This indicates the futility

of attempting to predict which patients will convert to normal sinus rhythm by monitoring atrial rate. It is also apparent that some other factor than mere atrial slowing accounts for the termination of atrial flutter by quinidine.

Since all patients in this group were fully digitalized in addition to receiving quinidine, it was not surprising to find more than one mechanism of termination. In 9 patients, the quinidine effect was predominant so that progressive slowing of the atrial rate occurred. When the atrial rate was reduced below 176, 2 patients exhibited asystole lasting 1.3 and 2.5 seconds respectively (as shown in Fig. 3), and 2 patients exhibited interference dissociation followed by normal sinus rhythm in each case. Three patients whose atrial rate declined but failed to fall below 176 remained in atrial flutter. In 4 patients, the atrial rate fell initially but remained between 214 to 273, or actually increased, suggesting an overriding digitalis effect; all developed atrial fibrillation, followed by normal sinus rhythm in three. Of the 7 atrial flutter patients terminating with normal sinus rhythm, 3 developed a post-conversion interference dissociation.

The spontaneous termination of atrial flutter occurred in circumstances that produced a slowing of the atrial rate followed by a short period of asystole in 3 patients. This was similar to the effects observed with the use of quinidine. The period of asystole lasted from 1 to 2.4 seconds before normal sinus rhythm was resumed, as shown in Fig. 3. Since quinidine slowed the atrial rate in flutter producing asystole, and a similar mechanism was observed in 3 patients during the spontaneous termination of atrial flutter, this suggests that a brief period of asystole is not a toxic effect of quinidine.

Two additional patients monitored during the spontaneous termination of atrial flutter showed no atrial slowing and developed atrial fibrillation instead of asystole followed by a normal sinus mechanism.

The opportunity to record the onset of atrial flutter is rare, and this event has been monitored in only 4 patients. One of these was a 2½ week old infant with paroxysmal atrial flutter and fibrillation, in whom 381 transient attacks of atrial fibrillation and 75 transient attacks of atrial flutter were monitored. In addition to studying the time of onset of each of these attacks, the time of appearance of 437 atrial premature beats was noted with respect to the onset of the last normal P wave. Tracings on this patient printed

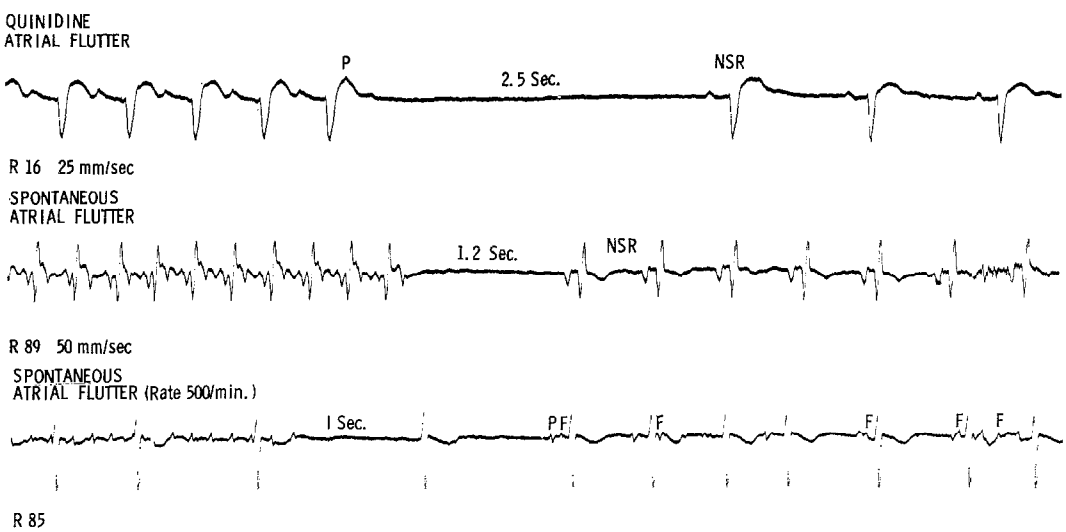

Fig. 3. Termination of atrial flutter (upper trace) with quinidine is followed by an electrical pause which is similar in magnitude to the pause occurring following spontaneous termination of atrial flutter (lower 2 traces) and has a variance of 1 to 2.5 sec. in both situations.

from magnetic tape are shown in Fig. 4. The frequency of attacks of both atrial fibrillation and atrial flutter, and atrial premature beats occurring at various times after the last normal P wave, are shown in Fig. 5. It was immediately apparent that the onset of neither atrial fibrillation, atrial flutter, nor atrial premature beats fell at random in the electrical cycle. The mean time of onset of atrial fibrillation occurred 159.9 ± 35 (S.D.) msec. after the last normal P wave, atrial flutter began 174.5 ± 39.4 msec. after the last normal P wave, and the mean time of onset of atrial premature beats was 221.3 ± 65 msec. after the last normal P wave. The difference

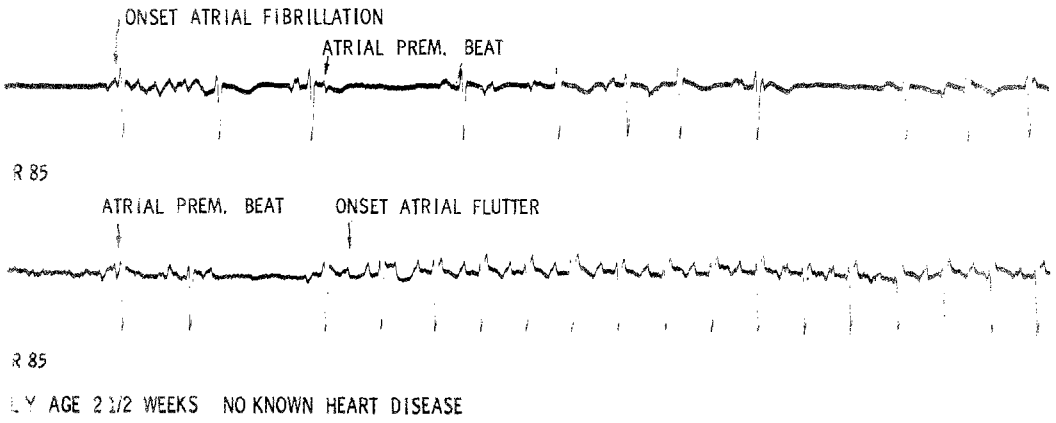

Fig. 4. The onset of atrial fibrillation is shown occurring in the P-S interval in the upper trace. The lower trace shows the onset of atrial flutter occurring in the S-T interval. Several atrial premature beats are shown.

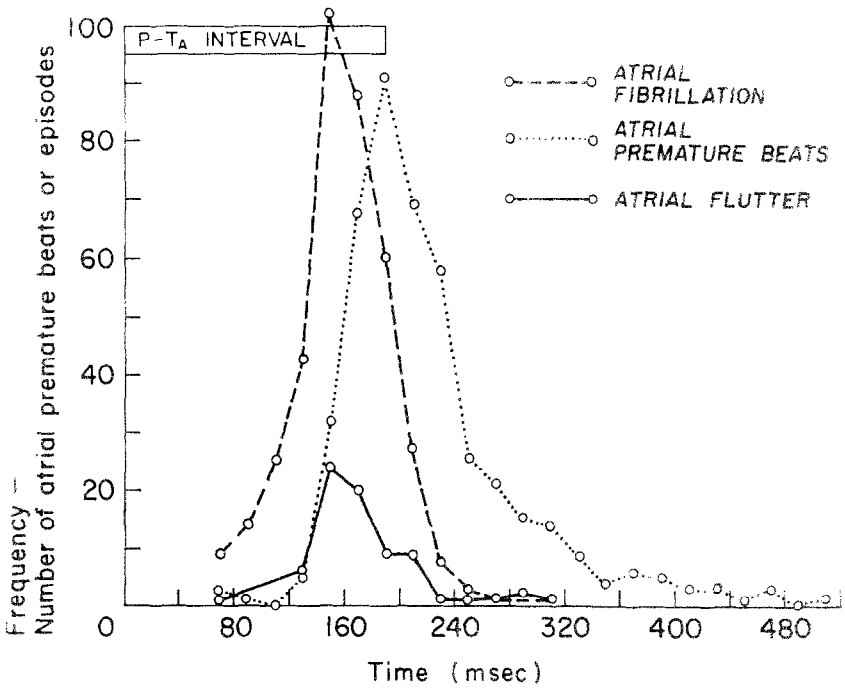

Fig. 5. The frequency of atrial premature beats, atrial flutter, and fibrillation are plotted according to the time of onset after the last normal P wave. Since large numbers of premature beats and episodes of arrhythmia were plotted, these were grouped and the midpoint of each group considered as the time of onset. Thus, the group plotted as 70 msec. corresponds to a time of onset from 60 to 80 msec. after the normal P wave.

between the mean time of onset of both atrial fibrillation and atrial flutter compared to the mean time of onset of atrial premature beats is significant ($p > 0.001$).

These observations suggest a coupling mechanism to the previous atrial cycle for atrial premature beats, atrial flutter, and fibrillation. Since the attacks of atrial flutter and fibrillation occurred earlier in the electrical cycle than did atrial premature beats, the duration of the atrial T wave was measured to see if this separation could be explained by incomplete atrial recovery favoring the development of either atrial flutter or atrial fibrillation. The duration of the atrial T wave was measured in blocked atrial premature beats where the atrial T wave could be seen separated from the QRS complex. The mean duration of the atrial $P\text{-}T_a$ interval was 190 msec., which meant that the majority of attacks of atrial flutter and fibrillation began before atrial recovery was complete, and the majority of atrial premature beats occurred after recovery was completed. The fact that the onset of atrial flutter and fibrillation favors a time in the electrical cycle when the atria are incompletely recovered would favor reentry as the underlying mechanism. Most investigators have stated, assumed, or implied that fibrillation results from early premature responses in partially or irregularly excitable tissues.[3] The significance of depression of conduction velocity in the initiation of fibrillation which occurs with propagation of electrical impulses in the relatively refractory period is specifically considered by Moe, Harris and Wiggers[1] and Moe and Méndez.[4] Moe and Abildskov[3] have reinvestigated the mechanisms of fibrillation and, although unwilling to attribute fibrillation to a single mechanism, these authors suggest that nonuniform recovery of atrial muscle with the accompanying slow conduction velocity in relatively refractory muscle favors formation of wavelets which lead to sustained atrial fibrillation.

Atrial premature beats occurring after atrial recovery is completed are simply propagated over the atrium, leaving no further pathway for reentry. Atrial premature beats were seen in all parts of the electrical cycle, but the greatest frequency occurred toward the end and immediately following the atrial T wave. The mechanism of this obvious tendency for atrial coupling is not explained by these studies, although a single reentrant path is the hypothesis favored by the data presented, rather than the random occurrence of ectopic beats. Wallace and Mignone[5] have explained ventricular coupling on the basis of a reentrant pathway produced artificially by local myocardial cooling, and the mechanism for atrial coupling is probably related to reentry also.

Atrial and nodal tachycardia

Paroxysmal atrial and nodal tachycardia began with one or more premature beats occurring in an irregular sequence. When more than one premature beat preceded the stable tachycardia, the ectopic rate either accelerated or decelerated, varying during the onset as much as 37 beats per minute before a stable rate was achieved. There was no constant relationship between the timing of the first premature beat and the previous cycle. Study of single attacks in 8 patients revealed that the initial premature beat fell after the previous T wave in 5, in the previous S-T interval in 2, and in the previous P-S interval in 1.

Examples recorded from three patients are shown in Fig. 6. The upper two tracings show decelerating ectopic rates before a stable tachycardia is achieved. In the second tracing, the first atrial premature beat appears at the apex of the previous T wave and in the subsequent cycles on the upstroke of the T wave.

When more than one attack could be recorded in the same patient, the same complex sequence of ectopic activity was occasionally observed during each subsequent attack. An example of this is shown in Fig. 6 (2 lower tracings) where 2 attacks of nodal tachycardia are preceded by trigeminal rhythm made up of a normal and 2 nodal ectopic beats with interference dissociation. Notice that in each attack the equivalent rate of the second pair of nodal beats is slower than the first pair. Following this a nodal beat falls on the previous T wave. Then there is an accelerating rate of nodal ectopic activity with retrograde conduction show-

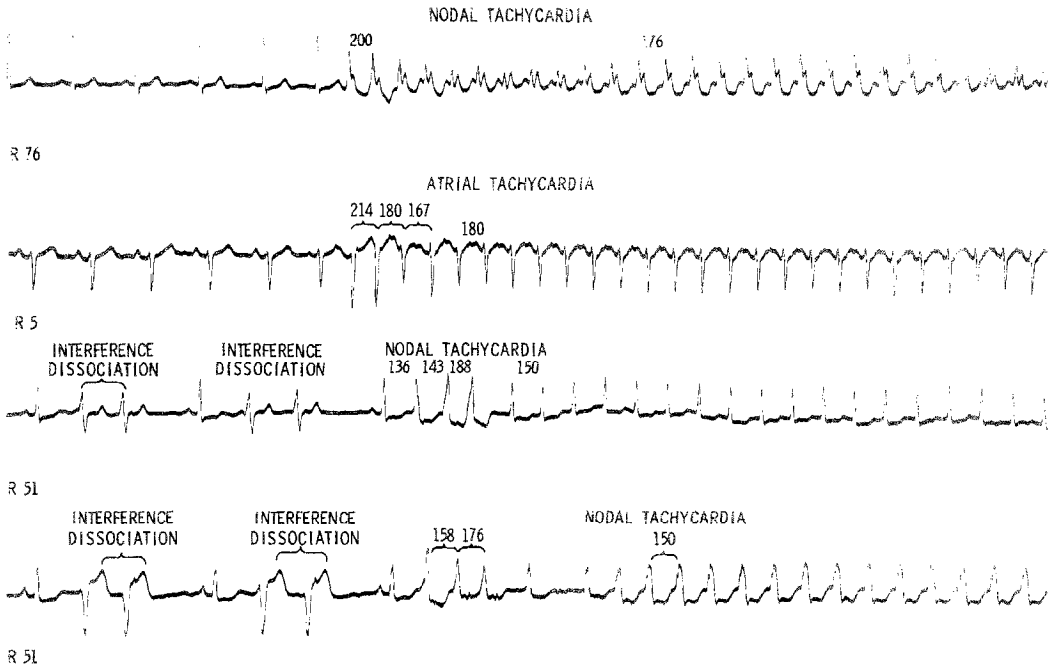

Fig. 6. Recordings of the onset of atrial and nodal tachycardia showing the decelerating rates of premature beat activity in the upper 2 traces. The lower two traces are from separate attacks in the same patient, showing remarkably similar and complex premature beat activity. See text for description.

ing progressive retrograde block. In the third tracing the attack begins with a stable rate of 150, while in the lower attack marked retrograde block occurs with the P wave falling after the T wave. The attack begins with normal conduction becoming progressively aberrant over the next 3 beats. A stable tachycardia of 150 per minute then ensues.

The period of most conspicuous variation in rate during atrial and nodal tachycardia was observed toward the end of attacks when the atrial rate slowed an average of 23 ± 3.3 beats per minute in 13 patients, as shown in Fig. 7. Two patients were excluded from this study: one had nodal tachycardia superimposed on atrial fibrillation, and in one the tape was accidentally erased. Two of the patients included in the analysis showed the characteristic abrupt termination which is considered the usual method of termination in textbooks. In these 2 patients the atrial rate slowed only 4 and 5 beats per minute, respectively, before the rhythm terminated. The data presented here suggest that gradual termination is the more usual method of termination.

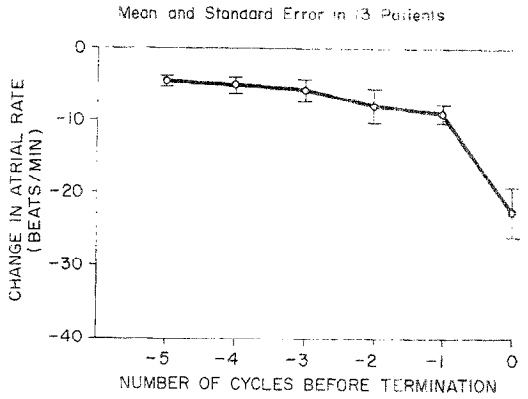

Fig. 7. The changes in rate between the last cycle of the tachycardia and the fifth cycle before termination is highly significant ($P < 0.00001$) and for the next to last and final cycle ($P < 0.001$).

Termination of the attack was followed by sinus pause lasting from 0.9 to 5.6 seconds in 9 of 14 patients, during which time ventricular escape in the form of single, multiple, or coupled ventricular beats was observed in 10 of 14 patients. The ventricular rate during this escape activity exceeded the attack rate by a

wide margin in 3 patients, as shown in Fig. 8. In the upper trace, after slowing of atrial rate occurs, the attack appears to be interrupted by two paired ventricular beats with an equivalent rate of 250 per minute, compared to the attack rate of 214 per minute. The 2 middle tracings are from patients with nodal tachycardia treated with a pressor agent. Short bursts resembling ventricular tachycardia occurred during the usual pause, and this was not observed with any other form of therapy. This result is attributed to raising pressure and not to the specific drug used. Similar effects have been reported for epinephrine by Levy[6] and Allen,[7] and for norepinephrine by Meek[8] and Conway.[9]

When atrial tachycardia with block is treated with digitalis, atrial slowing is observed[10] before termination occurs. This effect is, of course, the opposite to that expected in atrial flutter where, after digitalis, the atrial rate increases before terminating with atrial fibrillation. It is of interest that, in one patient monitored during the digitalis-induced termination of atrial tachycardia with block, atrial slowing was followed by several sudden increases in atrial rate until during one of these the rhythm terminated, as shown in Fig. 9. Thus, digitalis initially slows the atrial rate, but it is possible that as the dose of digitalis is raised a different mechanism similar to that seen in atrial flutter takes over.

Summary

Digitalis accelerated the rate in atrial flutter resulting in atrial fibrillation, whereas the addition of quinidine slowed the atrial rate producing either asystole or interference dissociation. In some patients receiving both digitalis and quinidine, the atrial rate showed less of a tendency to slow or actually increased, resulting in

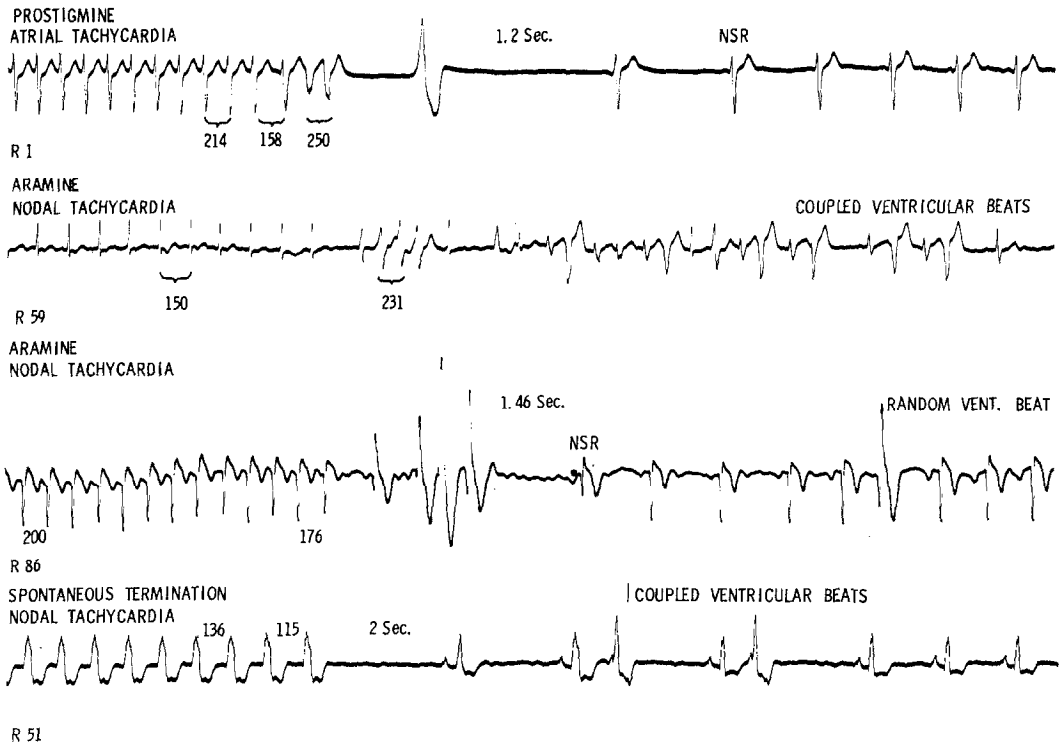

Fig. 8. The offset of atrial and nodal tachycardia recorded in 4 patients showing the 3 types of ventricular escape; *viz.*, paired beats (upper trace), short bursts of ventricular tachycardia (two middle traces), and coupled beats (lower trace). The characteristic slowing of the rate as the attack subsides is best seen in the lower trace; all attacks are followed by short periods of atrial arrest.

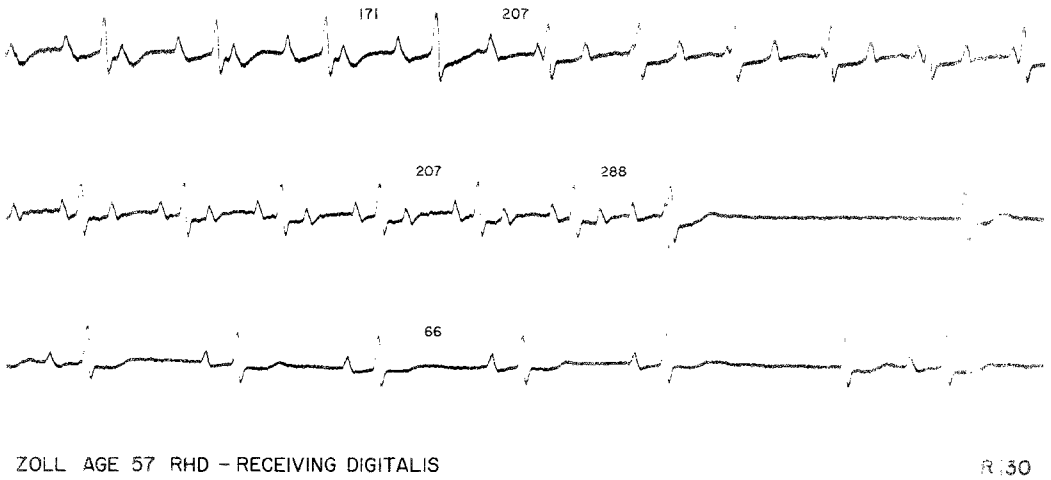

Fig. 9 The termination of atrial tachycardia with 2:1 block by digitalis is characterized by a progressive slowing of the atrial rate from 214 to 170 over a period of 4 days, followed by 3 abrupt increases in the atrial rate which terminated with a sinus pause, a nodal beat, and normal rhythm, as shown here.

atrial fibrillation followed by normal sinus rhythm. This suggests an overriding effect of digitalis.

Since the spontaneous termination of atrial flutter occurred in unknown circumstances that usually slowed the atrial rate and asystole was observed, this suggests that asystole is not a toxic effect of quinidine.

Atrial flutter, fibrillation, and atrial premature beats began more commonly in the P-T cycle than in the T-P cycle. Since atrial recovery is more likely incomplete during the P-T cycle, this favors reentry as the underlying mechanism in the patient studied.

Atrial and nodal tachycardia begin with an irregular sequence of premature beats before a stable tachycardia is established. There is usually a significant slowing of the rate prior to termination of the abnormal rhythm. Sinus arrest with ventricular escape is the usual method of termination, regardless of the form of therapy used. Bursts of rapid ventricular rhythm resembling ventricular tachycardia were seen only after the use of pressor agents.

Atrial tachycardia with block treated with digitalis shows an initial atrial slowing but, as the dose of digitalis was raised in one patient, abrupt increases in atrial rate occurred until the rhythm terminated. This is a mechanism similar to that seen in the digitalis-induced termination of atrial flutter.

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