Ventricular Fibrillation Due to Digitalis Preparations

A Review and Report of Two Cases following Intravenous Administration of Acetyl Strophanthidin

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Contrary to expectations, there are very few substantiated clinical case reports of ventricular fibrillation attributable to digitalis preparations. Two cases, one of them fatal, are here described. The nature of ventricular fibrillation due to digitalis is different from that due to other agents. Hence it may not respond to present methods of treatment in the rare cases when opportunity for treatment exists. It is vital therefore to prevent ventricular fibrillation by the avoidance of digitalis when certain premonitory signs are present.

It is universally taught that the ultimate danger of digitalis poisoning is ventricular fibrillation, yet a careful search of the literature discloses very few clinical cases with electrocardiographic proof. In this communication the subject will be briefly reviewed, and 2 additional cases will be described. Both of our cases were attributable to acetyl strophanthidin, a synthetic ester of the cardiac aglycone strophanthidin. This new drug acts with unusual speed after intravenous administration, producing early effects in a very few minutes and peak effects within a quarter hour; the duration of action being less than four hours.

Review of the Literature

Since 1894 ventricular fibrillation has been known to be the cause of death in animals poisoned with digitalis. This arrhythmia is reputed to be the chief cause of death in patients with digitalis poisoning. Nevertheless we have been able to find only 4 cases with graphic proof reported in the literature.

Reid, in several publications, described a case which occurred in a patient with auricular fibrillation who received excessive amounts of tincture of digitalis. Sudden regularization of the rhythm was shown electrocardiographically to be due to bidirectional ventricular tachycardia, which abruptly changed to ventricular fibrillation as death ensued. The fibrillatory oscillations gradually diminished in amplitude and frequency prior to final standstill. Eggleston, in discussing this case, described a similar one; but the records have not been published to our knowledge.

Penati reported a case in which 0.125 mg. of strophanthin was given six days after digitalis bigeminy had been noted. Several hours later the electrocardiogram showed ventricular tachycardia followed by fatal ventricular fibrillation. The delayed onset is unusual, since most strophanthin deaths occur within an hour or two after administration of the drug.

Zwillinger's case was one of toxicity due to digitalis and strophanthin, and exhibited paroxysms of ventricular tachycardia and fibrillation with imperceptible merging of the two arrhythmias. The fibrillatory curves display the same waxing and waning of amplitude and rate as seen in experimental animals. The paroxysms were abolished by intracardiac and intravenous injections of magnesium sulfate, but the patient died some hours later.

Tandowsky, Anderson and Vandeventer have published a short strip of electrocardiogram showing small irregular ventricular fibrillatory oscillations which occurred in association with sudden death. The patient had one minute earlier received an injection of ouabain, the dose of which is not stated. The control electrocardiogram showed regular sinus rhythm with right bundle branch block and ventricular extrasystoles.

From New York Polyclinic Medical School and Hospital, and Montefiore Hospital, New York, N. Y.
Schwartz and Jezer have described 3 patients with complete heart block and episodes of ventricular fibrillation. The latter arrhythmia could be provoked in these persons by the intravenous administration of 0.25 mg. of ouabain or 0.5 cc. Digifolin. They reproduced only one record, however, which shows very short bouts of three or four complexes resembling the first (undulatory) phase which precedes actual fibrillation of the ventricles.

Two other published cases may be considered as instances of ventricular fibrillation probably or possibly due to digitalis bodies. In one instance, during routine electrocardiography the patient suddenly collapsed and died, the records showing sinus tachycardia with frequent multifocal ventricular extrasystoles succeeded by ventricular fibrillation. This patient had been taking undisclosed amounts of digitalis daily. Another case, reported as an illustration of successful electric defibrillation during surgery, can be interpreted as an instance of digitalis-induced fibrillation, since it followed the administration of 1.6 mg. of lanatoside C. The drug had been given because of a tachycardia occurring during induction of anesthesia.

Many instances of sudden death ascribable to digitalis preparations have been described or mentioned. The patients generally had advanced heart disease and the deaths occurred at the expected time of action of the preparations used. However, since no graphic proof is available in these cases, the implication of ventricular fibrillation in these deaths is only presumptive. It is known that patients with advanced heart disease are liable to sudden death by virtue of the disease per se.

In some reports the presumption of ventricular fibrillation is better founded because bidirectional ventricular tachycardia was demonstrated shortly before death. This type of ventricular tachycardia is considered a forerunner of ventricular fibrillation clinically as well as experimentally. Nevertheless, death may be due solely to ventricular tachycardia which may cause vascular collapse or end in standstill. Indeed, the latter may be as common an event as fibrillation at the termination of ventricular tachycardia.

It is interesting to note that some cases of sudden death following digitalis preparations occurred in association with profuse diuresis. Most strophanthin deaths are said to be due to overdosage or to profuse diuresis. Whether the diuresis is accompanied by recirculating digitalis bodies or by a possibly profound depletion of potassium which alters the response of the myocardium to digitalis, it remains clear that severe diuretic action is involved in some cases of grave digitalis intoxication.

**Case Reports**

*Case 1.* A 70 year old man was admitted to New York Polyclinic Hospital in a state of advanced congestive heart failure, due to arteriosclerotic and thyrotoxic heart disease. Although he had noticed progressively increasing shortness of breath, swelling of the legs and weakness for six months, he sought no medical aid until the day of admission. Five days previously he had experienced moderately severe epigastric pain followed by vomiting.

Physical examination disclosed marked orthopenia, bulging neck veins, diffuse lung rales, moderate enlargement and tenderness of the liver, and edema of the legs. There was marked exophthalmos and a soft, diffusely enlarged thyroid gland. The heart rate was 136, the rhythm regular, and the apex beat displaced about 3 cm. to the left of the midclavicular line in the fifth intercostal space. There was a systolic blowing murmur of moderate intensity over the precordium.

Laboratory data indicated a mild anemia, moderate azotemia, normal blood sugar and chlorides, and slight proteinuria accompanied by a few red and white blood cells in the urine. Chest x-ray films showed left ventricular and generalized cardiac enlargement. The lung fields were hazy, and there was some fluid at both bases. The admission electrocardiogram (fig. 1A) showed auricular flutter with 2:1 A-V block, the ventricular rate being 136. Flutter waves were best seen in leads II, III and aVF, and sharp auricular deflections were obtained in CF2. The ventricular complexes were marked by a small Q in lead I and a QR configuration in CF3 associated with upward bowing of the S-T segment and terminal negativity of T, indicative of recent myocardial infarction.

Within three hours of admission, despite the use of oxygen and aminophylline, the dyspnea became worse. It was clear that reduction of the ventricular rate or abolition of the flutter mechanism was vitally necessary. For this purpose acetyl strophanthidin was selected. Electrocardiograms were made just prior to administration of the drug and at short intervals thereafter. Later, when the records were
developed, it was seen that just before the injection of 1.2 mg. of acetyl strophanthidin intravenously frequent ventricular extrasystoles were present (fig. 1B, C, D). Two minutes after the injection, a paroxysm of ventricular tachycardia at least seven complexes long occurred, followed by extrasystoles from the same focus (fig. 1E). The three-minute record showed that the flutter mechanism had been replaced by a supraventricular tachycardia at a rate of 150 without A-V block (fig. 2A). The form of the ventricular complex was altered and there were occasional slightly premature (fusion) beats. Two minutes later the premature beats increased in frequency and arose from several foci (fig. 2B). About five and three-fourths minutes after the injection the patient suddenly cried out unintelligibly and fell back in collapse. He became strikingly pale, his eyes rolled up and he made two convulsive gasping respirations, then ceased to breathe. At this point, about six minutes after the acetyl strophanthidin, no heart sounds could be heard and the records showed a low amplitude ventricular fibrillation at a rate of about 220 (fig. 2C). Artificial respiration, including manual pressure on the bag of the oxygen apparatus, was started at once and continued for 20 minutes. About four minutes after the collapse intracardiac needle puncture was made, but to no avail. Electrocardiograms made almost continuously showed that the fibrillation remained unchanged for about 10 minutes (fig. 2D). Then the rate began to slow and the amplitude of oscillations gradually diminished (fig. 2E). About 17 minutes after the onset of fibrillation all electrical activity ceased (fig. 2E).

Autopsy examination revealed chronic congestive heart failure, left ventricular hypertrophy and dilatation, and recent infarction of the left ventricle involving anterior and posterior portions of the interventricular septum. The coronary arteries were narrowed, irregular and calcified but not occluded. Microscopic examination of the thyroid showed marked hyperplasia.

Comment. In view of the history it is probable that the myocardial infarction had occurred five days before admission. It is generally felt.
that there is a liability to ventricular fibrillation after myocardial infarction, particularly when ventricular extrasystoles are present, or when ventricular tachycardia occurs. However, not all cases of ventricular fibrillation after myocardial infarction are fatal. Neither can it be said that all cases of sudden death in myocardial infarction complicated by ventricular tachycardia are due to fibrillation, sympathoadrenal discharges. The last-named could have operated in our case, since thyrotoxicosis was present.

The danger of a full dose of an intravenous digitalis preparation in recent myocardial infarction is recognized, for it may provoke ventricular fibrillation. Hence small doses are advised when such preparations are used. Experimental evidence indicates that the tolerance to digitalis does not change until some days after myocardial infarction, so that in three weeks ectopic rhythms are produced by about three-fourths of the dose effective in intact animals. The general clinical impression is that diminished tolerance occurs earlier. In a recent case sudden death occurred one minute after 0.8 mg. of digitoxin was injected intravenously in a patient eight days after myocardial infarction. In our case, the time interval was probably five days.

While it is conceivable that in our case the fatality was due only to the underlying disease, the sequence of events makes this assumption untenable. The increase in frequency of ventricular extrasystoles, the appearance of transient ventricular tachycardia, and the final development of fibrillation all occurred during the expected time of action of acetyl strophanthinid. In this case, had the character of the electrocardiogram just prior to administration of the drug been known, it might have been possible to avoid the fatality. The ventricular extrasystoles constituted a distinct contraindication to rapid digitalization.

Case 2. A 56 year old man was admitted to Montefiore Hospital because of intractable heart failure. He had suffered many attacks of angina pectoris and protracted chest pain in the preceding eight years. In the half year before admission he had increasing dyspnea and orthopnea, and generalized edema. For the past five months he was unable to take digitalis preparations because of nausea and vomiting after moderate or small doses, and mercurial diuretics had lost their effectiveness.

Physical findings on admission were striking. There was severe cyanosis, extreme distention of neck veins, profound orthopnea, a hacking cough, massive edema of the legs, some ascites, a moderately enlarged liver, and a right hydrothorax. The heart rate and rhythm were normal; the apex displaced to the anterior axillary line; and a systolic murmur of moderate intensity was heard at the apex.

Fig. 2. Case 1. CR1, in third intercostal space. See text.
Venous pressure was 200 mm. H₂O, rising to 250 mm. during pressure on the right upper abdomen. Decholin circulation time was 45 seconds, and ether time 22 seconds. In leads I and II, QRS duration was 0.12 second, P-R interval 0.20 second. Precordial leads showed QS and rS deflections to the right of the transitional zone, and qr deflections in the left lateral positions.

Laboratory examinations showed moderate proteinuria and cylindruria; slight azotemia; normal serum proteins; normal serum sodium and low chloride concentrations; serum potassium concentrations varied from 5.1 to 6.1 mEq. per liter; serum bilirubin, 1.7 mg. per 100 cc.; cephalin flocculation and alkaline phosphatase normal. The admission electrocardiogram showed low voltage of QRS groups in standard leads, with Q predominant in leads I and II. These findings were interpreted as evidence of anterior myocardial infarction with defective intraventricular conduction.

During the first three hospital days there was slight improvement under a low sodium regime supplemented by diuretics, sedation, and almost continual oxygen inhalation. On the fourth day, 1.2 mg. of acetyl strophanthidin was given intravenously. Just before the injection, lead V₁
showed normal rhythm, a rate of 66, P-R interval 0.21 second, and QRS interval 0.14 second. The first change occurred five minutes after the drug, when a single ventricular extrasystole appeared (fig. 3, line 1). Following this the P-R intervals grew progressively shorter until they appeared to vanish (fig. 3, line 2), and later to emerge again (fig. 3, line 3). From the ninth minute on, the rhythm became irregular due to changes in both the sinus pacemaker and the lower (nodal?) center. In 10 minutes, ventricular aberration appeared and increased as the rate and irregularity increased (fig. 3, lines 4, 5). At this time the patient had severe precordial pain and a sense of great terror, wearing off as the rate suddenly slowed (fig. 3, line 7), then speeded up (fig. 3, line 9). In the next five minutes the sinus rate rose and the P waves diminished. Inspection of the 15-minute tracing shows a ven-

Fig. 4. Case 2. V, throughout. Response to 1.2 mg. acetyl strophanthidin, continued. See text.
stupor, breathing irregularly, and his heart sounds became inaudible. An oxygen mask was applied, and before other measures could be attempted coordinated heart beats returned, at first slow and irregular (fig. 4, line 5), then faster and more regular (fig. 4, line 7), the patient meanwhile rapidly recovering. For some time afterwards, there were occasional irregularities due to incomplete A-V block and sinus arrests (fig. 4, line 8). Forty-five minutes after the drug, all effects disappeared and the patient seemed no worse for the experience.

Two days later, the patient having improved further, his response to half the dose of the drug was observed. After a control observation (fig. 5, line 1), 0.6 mg. of acetyl strophanthidin was given intravenously. Again the latent period was five minutes, at which time a pair of ventricular extrasystoles appeared, followed by a nodal escape (fig. 5, line 2). Then the phenomenon formerly noted reoccurred; the P-R intervals seemed to diminish to the vanishing point and then reappear (fig. 5, lines 3, 4, 5, 6). Several groups of ventricular extrasystoles arose, but the disturbance did not progress to a fibrillatory state (fig. 5, lines 4, 5, 6). In 17 minutes all electrocardiographic effects disappeared. During this trial, the patient experienced only slight substernal oppression of a few minutes duration.

The patient continued to improve for a few more
days. Toward the end of the second week, there was a sudden episode of intensification of cyanosis and dyspnea culminating in shock. Despite continuous oxygen therapy and plasma infusion, recovery was transient. On the fifteenth hospital day he died.

Autopsy examination revealed extreme general passive congestion and anasarca. The heart weighed 500 Gm. and was flabby and dilated. There were old and recent thrombi in the right atrium and its auricular appendage, and many infarcts of varying age in the lungs. The left ventricle was scarred by a huge area of old infarction involving both anterior and posterior walls, and there were scattered discrete scars in other parts of the left ventricle. The coronary arteries were calcified, irregular, and completely occluded in many places.

Comment. This case demonstrates the ease with which serious digitalis intoxication can occur in a patient with far advanced heart disease. It will be remembered that on many previous occasions this patient had toxic responses to oral digitalis preparations, even in reduced dosage. In animals it is known that ectopic rhythms appear after one-half to two-thirds the minimum lethal dose of digitalis, ouabain or strophanthin have been given.\textsuperscript{42-45} In man, however, it has long been recognized that ectopic beats may occur when less than half the lethal dose has been given.\textsuperscript{18} Cases are occasionally encountered where patients have continued or even increased their doses for long periods of time after toxic extrasystoles have appeared, yet did not succumb.

The onset of ventricular fibrillation in case 2 resembled in many respects the pattern of development of the arrhythmia in experimental animals, as discussed below. However, in addition to the ventricular ectopic activity, there was also a complex interplay between sinus and lower pacemakers. It has been noted that the development of ventricular fibrillation does not always follow the same pattern except in a general way.\textsuperscript{48}

In the second trial, half the former dose of acetyl strophanthin evoked a prefrillatory state. A similar response occurred in a case reported by Robinson and Bredeck.\textsuperscript{47} Their patient received 1 mg. of strophanthin one day after a paroxysm of ventricular fibrillation. Ten minutes later there were groups of rapid, irregular ectopic ventricular beats; two hours later, partial A-V block and frequent ventricular extrasystoles; and nine hours later, the patient died suddenly, presumably because of ventricular fibrillation.

DISCUSSION

The Mechanism of Digitalis-Induced Ventricular Fibrillation. In cats continuously infused with digitalis the heart rate gradually slows. Before the auricular rate reaches its greatest decline, A-V dissociation appears with the ventricles beating faster than the auricles.\textsuperscript{42} Initially the ventricular rate may be only slightly higher than the auricular.\textsuperscript{18} This has also been noted after two-stage coronary ligation in undigitalized animals.\textsuperscript{22} This phenomenon may explain the apparent progressive shortening of P-R intervals and disappearance of P waves in our case 2 (figs. 3, 5).

As the infusion in cats is continued after A-V dissociation has occurred, rapid and irregular beats arise from many ventricular foci. These increase in rate and aberrancy until finally fibrillation ensues.\textsuperscript{42} At this point, the mechanical activity of the ventricles deteriorates in the fashion described so graphically by Lewis\textsuperscript{46} and by Wiggers.\textsuperscript{48} Cardiac dilatation accompanies the late stages.\textsuperscript{49}

It is probable that the nature of ventricular fibrillation caused by digitalis differs from that due to other agents. The fibrillation threshold determined by electric shocks in digitalized animals is not lowered, as it is after coronary ligation.\textsuperscript{50} Furthermore, the type of fibrillation induced in digitalized animals is different in that the oscillations are slower, more regular and more uniform. Still different is spontaneous ventricular fibrillation due to digitalis, in which various degrees of A-V block appear early, and progressive widening and deformity of ventricular complexes occurs; a pattern similar to that following toxic doses of potassium.\textsuperscript{50} The unique nature of digitalis-induced ventricular fibrillation is also suggested by the following observations: sympatholytic agents, procaine, and quinidine protect against fibrillation provoked by electric shocks, but are ineffective in preventing ventricular fibrillation after digitalis.\textsuperscript{51}

Despite the popular notion that ventricular
fibrillation implies heightened irritability, the disorder is most apt to occur in conditions of depression as in poisoning with digitalis, quinidine and other substances. Under these conditions the heart no longer follows the "all or none law," and some parts develop local blocks which favor re-entry. The depressive action of digitalis is well known; for example, it reduces the responsiveness of the myocardium to electric stimulation. This has also been demonstrated after toxic doses of strophanthin. The occurrence of depressed conduction preceding ventricular fibrillation has already been mentioned. Indeed, the occurrence of A-V block emphasizes the difference between ventricular fibrillation caused by digitalis (as well as by potassium, procaine, papaverine and quinidine), and that caused by hydrocarbons and epinephrine, electric current, and coronary ligation. The additive depressant effects of digitalis and quinidine may make fibrillation more likely in some cases.

The Prefibrillatory State. By analogy with the development of experimental ventricular fibrillation it is possible to recognize clinically a prodromal state which could well go on to fibrillation. This was stressed by Schwensen in his report of a sudden death attributed to digitalis. Just prior to death, the electrocardiogram showed bidirectional ventricular tachycardia closely resembling tracings obtained in cats under chloroform anesthesia just before the ventricles began to fibrillate. Hence the tachycardia was considered to be prefibrillatory. Similarly, clinical cases have been observed which resembled digitalis toxicity in cats in the stage preceding ventricular fibrillation. The usual progression of digitalis poisoning consists of the following in increasing order of severity: ventricular premature beats, coupling, polymorphism of abnormal and normal beats, salvos of premature beats, and ventricular tachycardia in paroxysms of varying length. All of these have been considered as manifestations of the prefibrillatory state. As a rule these disturbances are noted only in persons with organic heart disease. Digitalis, even in apparently nontoxic doses, may be capable of unmasking or aggravating the prefibrillatory state in patients with advanced organic heart disease, as in our case 2.

In the recognition of this dangerous condition in its early stages it is important to note the association of conduction disturbances with ventricular bigeminy or multiple ectopic centers. Fortunately the presence of ventricular tachycardia does not always portend fibrillation, as indicated by clinical experience as well as experimental evidence. It has been stated that transient ventricular fibrillation in man has never been observed without characteristic signs of a premonitory nature. This statement may well be extended to apply to fibrillation due to digitalis, hence the importance of recognition of the prefibrillatory state.

Treatment. Except for the case described by Zwilinger, in which intracardiac injection of magnesium sulfate abolished ventricular fibrillation, we are unaware of any successful result in a case due to digitalis. If the case of Beck, Pritchard and Feil is considered as one due to digitalis (lanatoside C), then it can be said that electric defibrillation might restore a digitalis-poisoned heart.

Prevention. Since it is not feasible to treat this grave arrhythmia except by drastic methods of doubtful value (intracardiac injection of antifibrillatory drugs, surgical exposure followed by manual massage and electric defibrillation), ventricular fibrillation must be prevented at all costs. The recognition, or even suspicion, of a state of digitalis intoxication must automatically call for the immediate cessation of further digitalis therapy. If it is feared that a prefibrillatory state is present, recourse may be had to potassium or procaine amide. Induction of diuresis at such times should be avoided or tempered by the use of small doses of diuretic agents.

Summary and Conclusion

1. The literature on ventricular fibrillation caused by digitalis preparations was reviewed. Only 4 cases with electrocardiographic proof were found in man.

2. Two additional cases, following intravenous administration of acetyl strophanthidin, were herein reported.
3. The characteristics of digitalis-induced ventricular fibrillation were reviewed.

4. The general features of the prefibrillatory state were described. These are identical with many of the common signs of digitalis intoxication.

5. Since there is no feasible method of treatment of ventricular fibrillation due to digitalis, it must be prevented by the early recognition of the prefibrillatory state and appreciation of its ominous nature. In such cases digitalis, particularly rapidly-acting preparations, must not be used.

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Circulation. 1951;3:647-657
doi: 10.1161/01.CIR.3.5.647

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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