

THE EFFECT OF DIGITALIS ON THE VENTRICULAR RATE IN MAN *

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Of the various cardiac irregularities produced experimentally by digitalis, the earliest to appear in most instances is an occasional omission of ventricular contractions, owing to an interruption of the stimulus between the auricles and ventricles. Somewhat later, or even immediately after this, the heart may assume a most peculiar rhythm in which the auricles and ventricles are beating quite independently of each other.^{1, 2} This irregularity differs from the ordinary rhythm of complete heart-block in that the ventricular rate is not slow, but approaches and, indeed, usually exceeds the auricular rate; so that, for example, one may count sixteen ventricular to fifteen auricular contractions. This rhythm is so common in carefully graded digitalis poisoning in dogs that it has become a regular portion of the pharmacologic demonstrations given by Dr. Edmonds to the University of Michigan students and by Professor Hatcher to the Cornell University students. So far as we know, this form of irregularity has never been described in man. Its probable occurrence in the patient whose history follows has led us to report the case and to discuss briefly the effect of digitalis on the ventricular rate in man.

CASE 1.—Patient.—A teamster, 27 years old, entered the first medical division of Bellevue Hospital, New York, on June 27, 1908, complaining of cough and dyspnea. His family history was negative. He had had acute articular rheumatism at 12 years, a suspicious venereal sore at 22, and had been a heavy drinker up to five months before admission. For two years he had been troubled with shortness of breath on moderate exertion, but in the past two months this had become much more severe and was often paroxysmal in character. He had a loose cough and at times slight fever. No edema.

Examination.—This showed a well-nourished young man suffering from dyspnea. The cardiac dulness was not enlarged; the heart-sounds were clear and of

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1. Cushny, A. R.: The Action of Substances of the Digitalis Series on the Circulation in Mammals. *Jour. Exper. Med.*, 1897, ii, 233.

2. Tabora: Ueber die experimentelle Erzeugung von Kammersystolenausfall und Dissociation durch Digitalis. *Ztschr. f. exper. Path. u. Therap.*, 1906, iii, 549.

normal intensity. The lungs showed a diffuse bronchitis, and, in addition, the left lower axilla showed dulness, diminished breath-sounds, diminished fremitus, and numerous crackling râles. The liver was palpable at the level of the umbilicus. The urine showed a heavy cloud of albumin with a specific gravity of 1,020 and many hyalin and granular casts. He was discharged on July 10 considerably improved.

Course of Disease.—On Aug. 3, 1908, he was readmitted to the second medical division of Bellevue Hospital complaining of dyspnea. His heart was now distinctly enlarged, the apex-beat being in the sixth intercostal space, 15 cm. from the mid-line, with the right border 2 cm. beyond the sternal margin. There was a soft systolic murmur at the apex transmitted to the axilla and back. The second pulmonic sound was accentuated. The pulse was weak, of small volume, and occasionally irregular. The urine was at times negative; at other times it showed traces of albumin. The feet were swollen. During this stay in the hospital he ran a slight but continuous fever, occasionally reaching 100.5, and toward the end 102. His blood showed a mild anemia, with 9,000 to 11,000 white blood corpuscles. Blood cultures were negative. He died on September 5. There was no autopsy. The clinical diagnosis was chronic myocardial insufficiency with dilatation.

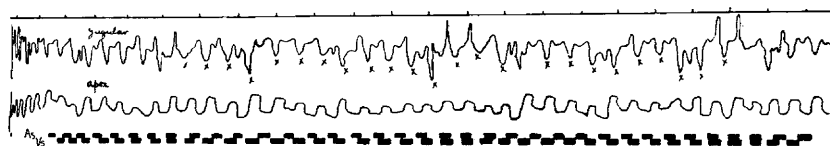


Fig. 1.—Jugular and apex tracing with chart showing the relation of auricular and ventricular systoles, 1/15 second being allowed for the venous waves to reach the neck.



Fig. 2.—Same as Figure 1, except that the apex tracing was too indistinct for reproduction.

During the earlier part of the patient's second stay in the hospital, his venous pulse was of the usual negative type, the well-marked *a* waves indicating normal auricular contractions. On Sept. 4, 1908, one day before he died, the patient's general condition had become much more serious and his edema and dyspnea more severe. At times gallop rhythm was heard over the precordia. The venous tracings taken on this day were remarkable in that they showed a regularly recurring cycle of changes (Figs. 1 and 2). Each cycle required about seven seconds for its completion, and included about fourteen ventricular contractions. At certain portions of the cycle a single, sharp, positive wave occurred in the jugular pulse just after the onset of ventricular systole. Midway between

these groups of sharp waves, each ventricular systole was represented on the venous pulse by two waves of almost equal height connected by a more or less distinct plateau. It was evident from the duration of these cycles (seven seconds) that they were independent of the respiration, for the respiratory rate was constantly about 30 per minute.

In our opinion, the explanation of these cycles is to be sought in the interference of two systems of waves which were independent of one another and not quite synchronous. The one system is best represented on our venous tracings by the negative waves marked *x*, which recur regularly and nearly always distinctly. The other is represented by the apex-beats. A comparison between these two shows that the former recur at a slightly slower rate than do the latter, so that, for example, thirteen *x* waves correspond to fourteen apex-beats. There was evident, therefore, a lack of synchronism between the apex-beats representing the systoles of the left ventricle and the portion of the heart which caused the *x* waves. Several reasons can be advanced against the view that these latter were due to the contractions of the right ventricle. In the first place a dissociation of this character between the two ventricles is unknown experimentally and would be highly improbable on theoretical grounds. In the second place, such a dissociation ought to cause recurring variations in the shape of the apex-beat which were not present in our tracings. Finally, it is difficult to explain the rhythmical changes in the venous pulse on this hypothesis.

It is much more probable that the negative *x* waves were due to auricular diastoles and that the cyclic variations in the venous pulse were caused by a lack of synchronism between the auricles and ventricles of such a nature that for thirteen auricular there were fourteen ventricular contractions. On this assumption these cycles in the venous pulse become clear. The positive wave, which can usually be distinguished just before the *x* wave, was in each case due to the auricular contraction, the other waves were caused by the contractions of the right ventricle, and the changing character of the venous pulse was due to the complicated interference of the two systems of waves. Unfortunately, it is not always possible to identify the individual waves on the venous tracings. Yet one thing comes out clearly when a diagram is constructed to show the relation of auricular and ventricular contractions according to this hypothesis (Figs. 1 and 2). This is the fact that the single high waves on the venous pulse occurred when the onset of ventricular systole coincided with that of auricular systole. Such single high waves are common in those extrasystoles where premature ventricular contractions coincide

with auricular systoles,³ and their occurrence in our tracings just where one would theoretically expect them strengthens our hypothesis.

Through the kindness of Dr. C. W. Edmonds, tracings were obtained from the internal jugular vein of a dog during digitalis poisoning, at the stage where the ventricular contractions were slightly more rapid than the auricular (Fig. 3). This venous tracing, though not precisely similar to those obtained from our patient, resembles them in the prominence of the x waves due to auricular diastoles and in the occurrence of single waves when the onset of ventricular systole coincided with that of auricular systole. In these particulars, therefore, it supports our interpretation of the tracing obtained from man.

We have already stated that this peculiar rhythm is frequently observed in the later stages of experimental digitalis poisoning. On inquiry it was found that the patient from whom our tracings were

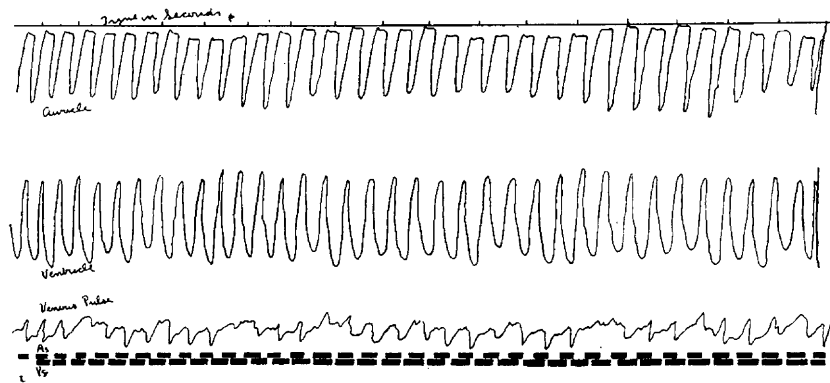


Fig. 3.—Dissociation of auricles and ventricles produced experimentally by digitalis, with auricular, ventricular and venous tracings. The main negative waves of the venous pulse coincide with auricular diastoles and the single positive waves with the simultaneous onset of auricular and ventricular systoles.

obtained had been taking drugs of the digitalis series in considerable quantities over a long period of time. From August 8 to August 16 he took daily one dram of the tincture of strophanthus, from August 18 to August 28 one-half dram daily of the tincture of digitalis, on August 29 six minims of the fluidextract of digitalis, on August 30 two minims of the fluidextract of digitalis. From August 31 to September 2 he took fifteen minims of the tincture of digitalis and thirty minims of the fluidextract of apocynum daily, on September 3, 4 and 5 thirty minims of the

3. Hewlett, A. W.: The Interpretation of the Positive Venous Pulse. *Jour. Med. Research*, 1907, xvii, 119.

fluidextract of apocynum, and in addition on September 4 and 5 eighteen minims of the fluidextract of digitalis. During all this time his heart failure was gradually becoming worse and he died on September 5. Although the daily amount of digitalis and its allies did not seem excessive, especially from August 16 up to September 4, nevertheless in view of the fact that the type of arrhythmia corresponded to that seen in experimental digitalis poisoning, it seems probable to us that the irregularity was due to a cumulative action of the drug. If this be true, it illustrates how difficult it may be to ascertain when enough digitalis has been given, for at no time was marked slowing of the pulse observed.

This peculiar irregularity is believed to be due to the action of digitalis in increasing the spontaneous ventricular rate. Ordinarily these chambers take their rhythm from the auricles and their tendency to contract spontaneously is held in abeyance. Should stimuli from the auricles fail to reach them, however, sufficient time may elapse for the ventricles to develop their inherent rhythm. In complete heart-block, for example, they contract spontaneously and regularly at a rate of about thirty per minute. Tabora² has shown that this spontaneous ventricular rhythm, induced experimentally by section of the His bundle, may be doubled by the administration of digitalis, and, furthermore, that during the pauses of a partial heart-block the ventricles may give one or more spontaneous contractions at a rate which shows that their inherent rhythm has been increased. Erlanger⁴ has also noted the increased ventricular rate produced by digitalis during complete experimental heart-block.

We have endeavored to find in the literature similar examples of digitalis action on man. Several instances have been recorded where the ventricles contracted spontaneously during a partial heart-block and it seemed of interest to see if these spontaneous contractions showed a ventricular rate greater than the normal and also to note their relation to the administration of digitalis. Rihl's patient had a partial heart-block, which was apparently due to the administration of digitalis.⁵ In the long pauses which occurred during the blocks the ventricles at times contracted spontaneously. These spontaneous contractions occurred 1.8 to 2 seconds after the normal ventricular contractions, thus corresponding to a spontaneous rate of thirty to thirty-three per minute. Apparently, therefore, although the digitalis produced a partial heart-block in this patient,

4. Erlanger, J.: Ueber den Grad der Vaguswirkung auf die Kammern des Hundeherzens. *Arch. f. d. ges. Physiol.*, 1909, cxxvi, 77.

5. Rihl: Klinischer Beitrag zur Kenntnis der Ueberleitungsstörungen von der Bildungsstätte der Ursprungsreize zum Vorhof. *Deutsch. Arch. f. klin. Med.*, 1908, xciv, 286.

it did not increase the automatic ventricular rate. In a similar case report by Mackenzie⁶ the ventricular pause of two seconds corresponded to a rate of thirty. No statement was made as to whether this patient was under the influence of digitalis. Joachim's⁷ patient had taken digitalis, though the amount is not stated. His tracings admit of an interpretation similar to those just cited and this would make the ventricular pauses in his patient about 1.3 seconds and the ventricular rate about 46. Finally, in the case reported by Wenckebach,⁸ spontaneous ventricular systoles occurred during partial heart-block at intervals of 1.3 seconds corresponding to a spontaneous rate of forty-six per minute. Wenckebach states that his patient had been taking the tincture of strophanthus, but he does not express an opinion as to any possible relation between the drug and the spontaneous ventricular contractions. In these last two cases the ventricular rate was distinctly faster than normal. So far as we may judge from the literature, therefore, spontaneous ventricular contractions are not common in man during partial heart-block caused by digitalis, and when they do occur they may or may not show an increased ventricular rate.

Of particular interest in this regard is the effect of digitalis on the ventricular rhythm in complete heart-block. Clinicians are not agreed as to its therapeutic value in this condition, some favoring its use in certain cases,⁹ others advising caution in its administration.¹⁰ Its deleterious action in producing or increasing a partial block has no bearing on its value when the block is complete. Neither is the slow heart-rate a contraindication to its use, for, so far as we know, digitalis does not slow the automatically beating ventricles either in animals or man. On the other hand, one might conceive that digitalis would be beneficial to patients with complete heart-block by increasing the force of the ventricular contractions or by increasing the automatic ventricular rate; or that the latter might serve as a therapeutic indicator of the effect of the drug. So far as we know, this possibility has not been considered by clinicians, and a definite increase of ventricular rate has not been observed during the therapeutic administration of digitalis to patients with complete heart-

6. Mackenzie, J.: The Cause of Heart Irregularity in Influenza. *Brit. Med. Jour.*, 1902, ii, 1411.

7. Joachim, G.: Ein atypischer Fall von Störung der Reizleitung im Herzmuskel. *Berl. klin. Wehnschr.*, 1908, xiv, 911.

8. Wenckebach, K. F.: Beiträge zur Kenntnis der menschlichen Herztätigkeit, III Teil, *Arch. f. Anat. u. Physiol. Physiol. Abteil.*, 1908 (Suppl.), 53.

9. Gibson, G. A.: Bradycardia. *Edinburgh Med. Jour.*, 1905, xliii, 9.

10. Osler, W.: The So-called Stokes-Adams Disease. *Lancet*, 1903, ii, 516.

block. Bachmann,¹¹ for example, found that, while strophanthus moderately slowed the auricles of his patient, it did not influence the ventricles.

In view of the meager clinical data on this point, we shall report a case of complete heart-block in which active preparations of digitalis were given in fairly large doses over a considerable period.

CASE 2.—Patient.—A laborer, 60 years old, was admitted to the second medical division of Bellevue Hospital on Nov. 27, 1908, having been picked up in the street during a period of unconsciousness. He had used alcohol regularly and at times to excess, and had had no infectious diseases except gonorrhea and a venereal sore.

Examination.—This showed an enlarged heart with an accentuated second aortic sound and a blowing systolic murmur over the apex region. The radial arteries were markedly thickened, and the pulse-rate was usually about 33 per minute.

Course of Disease.—While in the hospital he had a number of typical convulsive attacks. Of the many venous tracings taken during his stay the great

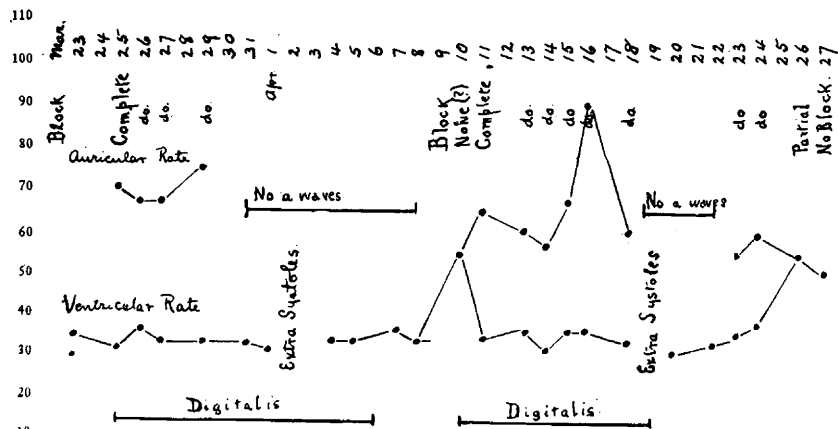


Fig. 4.—Chart showing effect of digitalis on the auricular and ventricular contractions of a patient with heart-block.

majority showed a complete heart-block, although at times there was a partial heart-block or none at all. The first course of digitalis, consisting of one-half ounce of the infusion four times a day was begun on March 18, 1908, and terminated on April 6. Venous tracings were taken almost daily and the auricular and ventricular rates as calculated from these are shown on the accompanying chart (Fig. 4). The auricular waves, which were easily recognized on the earlier jugular tracings disappeared on March 31 and did not reappear until April 10 or 11. On April 2 the apex tracings showed a ventricular arrhythmia which was due to a regular recurrence of normal and slightly premature beats.

The second course of digitalis (15 minims of the tincture four times daily) began April 10 and was terminated on April 19. On the latter day the auricular

11. In a later case Bachmann (*THE ARCHIVES INT. MED.*, 1909, iv, 238) obtained a slight acceleration of the ventricles, under strophanthus, and a marked improvement in his patient's condition.

waves again disappeared and did not return until April 23. On the 19th also the ventricles assumed a bigeminal rhythm, similar to that observed on April 2 except that the premature beats came earlier. At times this bigeminy was continuous (Fig. 5); at other times the premature contractions occurred after every other long interval (Fig. 6).

A study of the latter tracing shows that the premature contraction occurred 0.66 second after the normal, that the next interval was about 1.66 second, while the final interval was about 1.83 second. The intervals following the extrasystoles were always slightly shorter than those separating the normal beats. It is usually stated that ventricular extrasystoles occurring during complete heart-block are followed by the same intermission as occurs between normal beats, there being no compensatory pause. However, a slightly shortened period such as we observed on our apex tracings has been noted by others on radial tracings.^{12, 18} Their explanation, viz., that the extra systole is delayed in its transmission to the wrist, could not be applied to our patient.



Fig. 5.—Bigeminal rhythm during digitalis administration to a patient with complete heart-block.

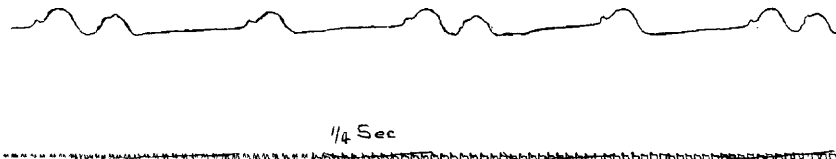


Fig. 6.—Extrasystoles after every other normal beat in same patient.

Shortly after the second course of digitalis, possibly also after the first, the heart-block was diminished, for, on the 26th, there was a definite partial block and on the 27th no block at all. It is possible that the diminution of the block bore some relation to the administration of digitalis.

No increase in the regular rate of the ventricles occurred during our administration of digitalis to this patient; and yet it seems probable that his heart showed some effects from the drug. The disappearance of the *a* waves from the jugular was at first regarded as a defect in technic, but their second disappearance from the apex tracings during the second

12. Wenckebach, K. F.: Kenntnis der menschlichen Herztätigkeit. Arch. f. Anat. u. Physiol., Physiol. Abteil, 1906, 297.

13. Gossage, A. M.: Complete Heart Block. Quart. Jour. Med., 1908, ii, 19.

course of the drug suggested that this may have been due to a toxic weakening of the auricular contractions. The appearance of the extra systoles on each occasion also suggested a digitalis effect. It is impossible, of course, to draw conclusions from this single experience, though it indicates that moderately large doses of an active preparation of digitalis may fail to increase the ventricular rate in patients with complete heart-block and that, therefore, one cannot rely on such an increase as a guard against an overdose of the drug in these patients.

In conclusion, we wish to thank Professors W. Gilman Thompson and C. L. Dana, in whose services at Bellevue Hospital these patients were observed and by whose permission their histories are reported.