The Effect of Intravenous Trypsin Administration on the Electrocardiogram of the Rabbit

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The intravenous injection of trypsin into rabbits resulted in marked changes in the rhythm and alteration in the P, QRS, S-T and T deflections of the electrocardiogram.

In the course of animal experimentation, it was noticed in our own laboratory and elsewhere that the intravenous administration of solutions of trypsin was frequently followed by death of the experimental animal. Autopsies revealed the presence of large adherent thrombi in the pulmonary artery and right heart of these animals. The detailed pathologic studies of Kellner and Robertson point to an effect of trypsin, as well as other proteolytic enzymes, directly on the myocardial cells. In view of these findings it seemed desirable to determine whether intravenous trypsin would produce significant alterations in the electrocardiogram of a suitable experimental animal.

Method

Market-bought rabbits, weighing between 3 and 5 Kg., of both sexes, were maintained on a standard laboratory diet. They were anesthetized with pentobarbital, using between 0.5 and 1.0 cc. of pentobarbital sodium, 50 mg. per cubic centimeter, intravenously. The animals were fastened to a narrow animal board, with the four paws extended. The trunks were wrapped with an elastic bandage in order to minimize any change in the position of the animal which might produce changes in the form of the electrocardiogram. Electrical contact was established by passing metal pin electrodes through the soft tissues of each paw. These were then connected to the appropriate leads of a Sanborn Twin-Viso electrocardiograph, and the bipolar leads of the frontal plane were recorded at frequent intervals, at a paper speed of 50 mm. per second. All records were standardized at 1.7 cm. per millivolt.

A fresh solution of trypsin was prepared for each infusion. Enzar* was used in a concentration of 1 mg. per cubic centimeter and was infused into an ear vein of the anesthetized rabbit at a rate of 0.2 to 1.0 cc. per minute. The rate of infusion was limited by the occurrence of thrombosis at the site of injection at low rates, and sudden death with rapid rates. In many experiments, electrocardiographic observations were continued after the completion of the infusion, if the animal lived.

Thrombin was prepared in a fresh solution of 50 or 100 mg. per cubic centimeter and infused at a comparable rate.

Normal saline solutions were utilized as a control, and were infused by similar technics, at approximately the same rates of infusion. The same electrocardiographic observations were made.

Results

The form of the initial electrocardiogram resembled that described by Levine. The usual rate was approximately 300 per minute, with T waves upright and of significant voltage in leads II and III, generally upright but of low voltage in lead I. There was usually rightward deviation of the electrical axis, and the T waves were generally found to be upright in all three leads, with leads II and III being greater than lead I. Deviation of the S-T segment from isoelectricity was not observed to exceed 0.1 millivolt. Except for runs of coupled rhythm, which appeared shortly after the animals were pinned to the board, and generally disappeared within 5 or 10 minutes, no arrhythmias were observed in the resting electrocardiograms.

In six rabbits, electrocardiograms were taken before and after the usual dosage of pento-

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Marked reduction in obviously extracardiac muscular activity and stabilization of the baseline were seen after the animals had been suitably narcotized. In no case did the anesthesia have a lethal effect, nor was the administration of this drug followed by any significant change in the form of the electrocardiogram, other than the suppression of the ectopic focus which had previously produced the coupled rhythm.

Ten animals received infusions of normal saline by the same technic and rate of administration as that used in experimental runs. In one of the animals, a slight leftward deviation of the electrical axis of the P wave was observed. Otherwise, there was no discernible effect on the rhythm, or in the form of the electrocardiogram. QRS, S-T and T waves were unchanged.

Approximately 50 rabbits received intravenous trypsin. A number of the experiments were terminated prematurely by local thrombosis or sudden death of the animal. Of 24 successful infusions into individual animals, four showed no significant alterations in the electrical activity of the heart. One showed no changes until a point so close to death that the changes were considered terminal. The remaining 19 showed significant alterations during or following the intravenous administration of this proteolytic enzyme.

Twelve of the animals showed significant alteration in their P waves. The most frequent occurrence was rightward deviation of the electrical axis of P, usually with an increase in the magnitude of the electrical vector. This can be seen in figure 1. This occurred in six animals; six more evolved various nonspecific alterations (fig. 3). These changes often continued to evolve after the infusion had been completed.

Ten rabbits evolved definite changes in the intrinsic structure of the QRS complexes in the frontal plane. In seven, these continued during the period of observation, and frequently consisted of a change in the direction and magnitude of the initial component of the complex, such as the appearance of the R1 shown in figure 3. Three other rabbits developed marked alterations in the form of the QRS (figs. 2, 4), which did not persist throughout the period of observation, but reverted to a form generally similar to that of the control. These were presumed to represent intraventricular conduction defects and usually were followed by persistent ST-T alterations.
Fig. 3. Administration of 6.5 mg. of Enzar produced marked downward displacement of the pacemaker, with relative bradycardia and alteration of the intrinsic form of the QRS. The lower strips were taken 2 and 10 minutes after the infusion was terminated, at a time when reflexes and respirations were observed. Fifteen minutes after end of infusion, the animal was clinically dead. In lead II one complex of each strip has been overlined for reproduction.

Sixteen of the animals developed clear-cut changes in the ST-T deflections. These could not be explained on the basis of altered position of the heart in the chest. The usual change was the development of a marked S-T vector, of variable direction, with definite bowing of the S-T, with concavity frequently directed toward the baseline as in figures 3 and 4. Although the direction of this new vector varied from animal to animal, and sometimes from time to time in the same animal, in general the most common finding was a depression of the S-T segment in lead I, with variation in leads II and III. The T waves showed marked and unpredictable variation in their height, direction, and shape. The Q-T interval was in general limited by the appearance of the P wave of the following beat, but the general impression gained from inspecting these records is that the Q-T interval was frequently prolonged. Figure 1 illustrates a complex of alterations which occurred in variable amount in a number of the animals. The T wave assumed the form of a straight, oblique line, which rose during the inscription of the complex, until finally it fused imperceptibly with the P wave of the following complex.

The rate usually remained unchanged during and after the administration of the enzyme. In a number of instances, relative bradycardia with persistence of the sinus mechanism was recorded; figure 2, however, illustrates the appearance of a brief run of relative tachycardia. Shift of the pacemaker is shown in figure 3, while figure 4 showed the appearance of an electrical syndrome resembling the Wolff-Parkinson-White syndrome.

Fig. 4. After 25 mg. of Enzar, there were transient conduction defects, followed by the development of an R wave in lead I, and S-T depression in leads I and II, with T wave inversion in lead II. The lower strips were recorded 2 and 10 minutes after termination of the infusion. The animal lived.

Fig. 5. Administration of 150 units of thrombin produced alteration in the intrinsic structure of the QRS complex with T-wave reversals. The last strip was recorded 37 minutes after the termination of the infusion. The animal lived.
A number of the animals either actively convulsed, or emitted several loud cries. At this time they ceased to breathe, and corneal and other reflexes, previously obtainable, were no longer elicited. At this time, there abruptly appeared a rather characteristic electrocardiogram. There was marked bradycardia, with extreme prolongation of the P-R, QRS and Q-T intervals. Marked conduction defects were frequently present, and there was often either complete A-V dissociation, or marked downward shift of the pacemaker. In every one of these animals, the changes persisted with the beats becoming less frequent and of persistently lower voltage, until finally no electrical activity was elicited. These characteristic signs were clearly distinct from the previously described alterations. They are similar to terminal electrocardiograms in the human, as described by Turner.4

Four rabbits were given infusions of thrombin. Three of them died after convulsions, and terminal records similar to those described in the preceding paragraph were obtained in two. Earlier in the course of the administration, changes in the intrinsic form of the QRS and S-T displacements were recorded in two of the four animals, which were clearly distinguishable from the A-V dissociation, marked bradycardia and idioventricular rhythm of the preterminal records (fig. 5).

**DISCUSSION**

These data suggest that the administration of intravenous trypsin in the dosage described is usually accompanied by alterations in the electrical activity of the rabbit’s heart. These are much greater than the spontaneous variations reported by Levine.4 There can be little doubt that administration at these levels is accompanied by some intravascular thrombosis, and it would appear likely that some emboli reach the heart or lungs and are responsible for some of the electrocardiographic abnormalities. However, administration of thrombin in doses which were sometimes sufficient to
render the blood completely incoagulable in a small group of animals, appeared capable of producing only a part of the electrocardiographic changes which the proteolytic enzyme produced. This suggests that some action, other than the known thrombus-producing one, is involved. The work of Kellner and Robertson casts considerable light on this problem. They showed that the intravenous infusion of trypsin or of papain produced “focal areas of necrosis of muscle fiber, distributed throughout both ventricles, and having no relationship to blood vessels.” (See plate I.) A small group of heparinized animals in their series appeared to give a similar response.

In the data reported here, a number of dramatic and precipitous electrocardiographic changes are shown. Some of them are short-lived. This would suggest that limited episodes of impaired intracellular metabolism or of local thrombosis might produce transient functional blocks in the Purkinje system which would account for both the appearance of conduction defects in the usual sense, and the appearance, in several of the rabbits, of a complex compatible with the Wolff-Parkinson-White syndrome. The implication that “accelerated conduction” has appeared, is worthy of consideration in these records. The T-wave alterations are compatible with random myocardial damage, and the marked S-T displacements indicate that certain randomly distributed areas of epicardium have been severely injured. The P-wave alterations suggest diffuse damage of the auricular myocardium.

It would appear, therefore, that the intravenous administration of trypsin produced changes in the electrocardiogram of the rabbit, which may be due to a direct effect on intracellular metabolism, or the thrombogenic activity of trypsin, or to both.

**Summary**

An aqueous solution of trypsin was infused into anesthetized rabbits. It produced marked changes in the rhythm, and alteration in the P, QRS, S-T and T deflections of the electrocardiogram. These were distinct from the characteristic changes in the electrocardiogram of the dying animal. Changes which were generally similar, but of a much less marked degree, were produced in a small number of animals which received intravenous thrombin.

**Sumario Español**

Una solución aquosa de tripsina fue administrada a conejos anestesiados. Produjo marcados cambios en el ritmo y alteraciones en la P, QRS, S-T y deflexiones T del electrocardiograma. Estos fueron distintos a los cambios característicos en el electrocardiograma de un animal moribundo. Cambios que generalmente fueron similares, pero de mucho menor grado, fueron producidos en un número reducido de animales que recibieron trombina intravenosa.

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