THE MECHANISM OF THE ELECTROCARDIOGRAPHIC DISORDERS IN ANAPHYLACTIC SHOCK

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The essential participation of the sympathetic nervous system in the pathogenesis of anaphylactic shock has been proved by the work of several authors [15 and others].

In animal experiments, Yu. S. Tatarinov [15] found that the preliminary injection of adrenalin makes the course of the shock milder. After perfusion of the isolated heart of sensitized rabbit with adrenalin, N. P. Mordovskii [8] observed modification of the reaction to the subsequent injection of serum. S. M. Pavlenko [9] and I. Kh. Abdullaev [1] showed that atropine had a moderating action in shock in guinea pigs and rabbits. A. D. Ado[2] found that the effect of bilateral vagotomy depends on the period of sensitization. A. M. Bezredka [3], M. L. Garmasheva [4], A. N. Gordienko [6], V. S. Mats-Rossinskaya [7] and others have noted the action of anesthesia in preventing anaphylactic shock.

In the present investigation we studied the part played by the sympathetic nervous system in the changes in the activity of the heart during anaphylactic shock and the influence of ether anesthesia on these changes.

EXPERIMENTAL METHOD

The part played by the sympathetic nervous system in the disorders of cardiac activity in shock was investigated in 27 guinea pigs (males) weighing 300-350 g. The animals were sensitized by a single subcutaneous injection of 0.05 ml of normal horse serum, without preservative, 15-17 days before the assaulting injection of 1 ml of the same serum into the external jugular vein. In the first series of experiments the animals received injections of ephedrine in doses of 1-4 mg/kg into the jugular vein 5-10 min before the assaulting dose; in the second series nine guinea pigs received intravenous injections of atropine in doses of 0.1-5 mg/kg 5-25 min before the assaulting dose; in 12 animals in the third series of experiments, bilateral vagotomy was carried out 5-25 min before the assaulting injection. The action of anesthesia was studied in 28 guinea pigs sensitized in the manner described above. An assaulting dose (0.2-3.5 ml of the same serum) was injected into the jugular vein of the animals on the 15th-17th day of sensitization 5-10 min after the induction of deep ether anesthesia. In order to provide a comparison with the usual course of shock, the results of 56 experiments carried out earlier were used.

In the course of each experiment simultaneous recordings were made of the electrocardiogram in three standard leads and of the respiration by means of a 4-channel ink-recording apparatus of type 4-PFD-7. In some animals an effective sign of respiration—the movement of air in the trachea—was recorded by a photocell. Simultaneously, the respiratory movements, the blood pressure in the carotid artery (by means of a Hürthle manometer) and the general motor reaction were recorded on a kymograph.

EXPERIMENTAL RESULTS

In the experiments using ephedrine and atropine, and also after vagotomy, the injection of an assaulting dose of serum into the sensitized animals caused fatal anaphylactic shock. In the period of injection of the antigen, the changes in the blood pressure and the ECG (Fig. 1b) were the same as in ordinary sensitized guinea pigs. Those observed included a slowing of the rhythm, lengthening of the QT (more rarely, the PQ) interval, left axis deviation of the T wave and an increase in its amplitude with a less marked right axis deviation of the QRS (R), demonstrating that the disorder of function mainly affected the right ventricle [5]. Similar changes in the ECG were observed during stimulation of the vagus nerves with an alternating current. In all the experiments, during the development of the shock, the T wave was displaced to the right of the axis and inverted in the standard leads; right axis deviation of the T wave from 90° ($-T_1$) was noted in three cases, from + 150° ($-T_{1,2}$) in six and beyond −150°($-T_{1,2,3}$) in 17 cases. At the same time there was an increase in the amplitude of the T wave and a sloping negative displacement of the ST interval. These changes, reflecting a disturbance of the functions mainly of the left ventricle, were intensified in the period of respiratory-motor disturbances of shock. During the

development of shock in the sensitized animals, inversion of the T wave was observed, as a rule, in only one of the standard leads, but the magnitude of the T wave and of the discordant displacement of the ST interval was less strongly and less constantly altered.

Ventricular extrasystoles, which are customary in shock, were much reduced or absent in these particular experiments. Another characteristic feature was the acute development of terminal changes in the ECG, occurring simultaneously with the terminal disorders and cessation of the respiratory movements, but with no definite connection with the reduction of the effective sign of respiration (Fig. 1c). These changes took the form of an increasing widening of the PQ interval, an accelerated left axis deviation of the T wave and the vector of the deflection of the ST interval (with suc-

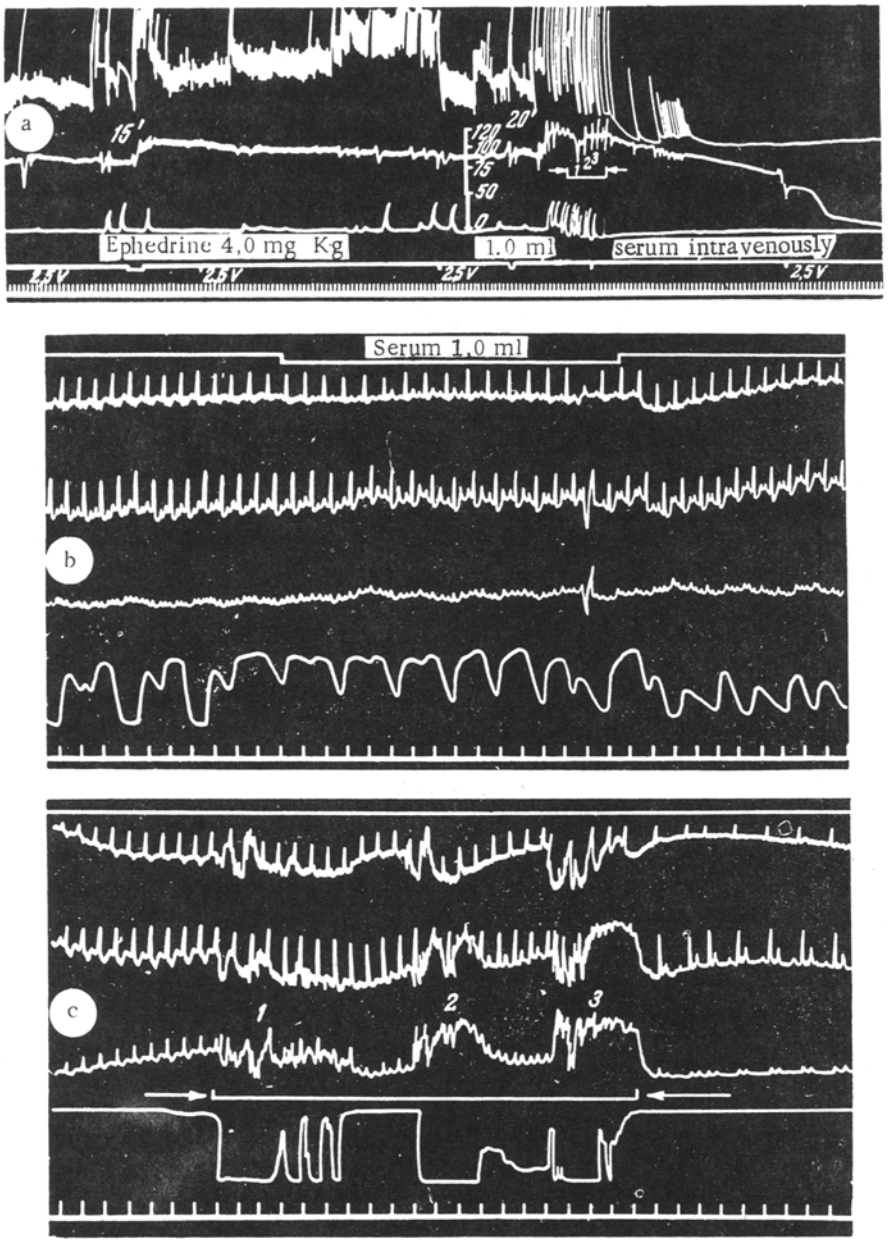

Fig. 1. Anaphylactic shock on a background of the action of ephedrine. Significance of the curves (from above, down): for a: Respiratory movements; arterial pressure; general motor reaction; marker of injection of drugs and stimulation of the peripheral end of the right vagus nerve; time marker (3 sec); for b and c: marker of injection of serum; I, II, III standard ECG leads; respiration (tracing from a piezoelectric pickup); time marker (0.25 sec). The signs ⟶⟵⟵ in Figs. a and c designate the same moments of the state of shock.

cessive positive transformation of T_3, $T_{2,3}$ and then $T_{1,2,3}$), and a decrease in the amplitude with analogous positive transformation of the ST deflection. Under these circumstances the ST deflection changed from concordant-negative to concordant-positive, which corresponded to the completion of the diametrical anticlockwise shift of the ST vector in the shock period. The positive transformation of the T wave was completed after the accelerated disorder of atrioventricular conduction, arising at first in the form of an incomplete, and then a complete, block. At the same time there was an increase in the amplitude of the positive T wave and of the deflection of the ST interval, and a widening of the QT interval was observed. The approximation of the electrical axes of R and T, observed in these conditions, was evidence of the disappearance of signs of a lesion predominantly of the left ventricle.

In ordinary shock the corresponding terminal changes in the ST–T complex develop less acutely This is due to the smaller divergence of the axes of the initial and terminal parts of the ventricular complex during the development of these disturbances. Disturbance of atrioventricular conduction under these circumstances takes place through a stage of dropping out of ventricular complexes, or Wenckebach-Samoilov periods.

The heart lesions in the experiments on sensitized guinea pigs using ephedrine, atropine and vagotomy were more severe than those in ordinary shock, as was shown in particular by the more profound changes in the ECG in the period before death. Furthermore, morphological investigations of the heart of a number of animals from all three series confirmed the great severity of the vascular and dystrophic lesions of the myocardium. The period between the arrest of respiration and the cessation of the working of the heart in five experiments using atropine, and in all 12 experiments with preliminary vagotomy was, on the average, shortened by half (its duration was approximately equal to 10 min). The ECG in the period before death in such cases was atypical in character; this took the form of a more pronounced slowing of the rhythm of the ventricles, a widening of the QT interval and a considerable divergence of the axes of the initial and terminal parts of the ventricular complex. The latter was connected with changes in the source of automatism and with disturbances of intraventricular conduction. The deflection of the ST interval was insignificant, and no merging of the elements of the ventricular complex into a monophasic curve took place. The ventricular complexes came to an end even when their amplitude was relatively high. The atrial rhythm was slower and irregular, and their activity ceased before or soon after disappearance of the ventricular complexes.

Of the 28 animals in which anaphylactic shock was produced on a background of deep ether anesthesia, 14 died, and no obvious relationship was observed between the outcome of the shock and the size of the assaulting dose of antigen.

The injection of serum against a background of anesthesia was accompanied by the same changes in the ECG as during the ordinary development of shock. Both external and electrocardiographic manifestations of anaphylactic shock were weakened, which is in agreement with the findings of Mikulicich [22] obtained in rabbits under nembutal anesthesia; in this case the ventricular extrasystoles were less marked or were absent altogether.

A moderate change in the size of the waves and a discordant deflection of the ST interval were observed, which developed more slowly and increased immediately before the cessation of respiration.

Terminal disorders of the ECG, similar to the same disorders in ordinary shock, developed at the same time as the cessation of the functions of the respiratory center. In this case we could find no relationship between the disorders of the ECG and the depth of the changes in blood pressure and effective respiration (Fig. 2a and b). The development of atrioventricular block was preceded by lengthening of the PQ interval; in some cases Wenckebach-Samoilov periods developed. After the arrest of respiration and the approximation of the blood pressure to the zero line, the usual signs of clinical death took place; disturbance of atrioventricular conduction, approximation of the axes of the R and T waves, increase in the amplitude of the positive ST–T complex and a reduction in the R wave, which corresponded to the formation of a monophasic curve.

In five experiments which terminated fatally, and four cases of nonfatal shock, reversal of the development of the terminal changes in the ECG took place. A minute or more after the arrest of respiration it recommenced, with a lower effective value of the respiratory movements. In the first few seconds after the first inspiration, regression of the terminal changes in the ECG and an increase in the blood pressure to (or slightly above) the initial level were observed (Fig. 2c). On the ECG, atrioventricular conduction was restored through a stage of lengthening of the PQ interval. At the same time there occurred a rapid reduction in the amplitude of the T wave and the deflection of the ST interval, and a shortening of the QT interval. Usually after 10-20 cycles, the principal disorders of the ECG were rectified. The rise in the arterial pressure was unstable; it quickly changed into a gradual fall to the zero line, but no obvious disturbances were observed in the ECG at this time. In fatal cases of shock repeated terminal disturbances of the ECG developed at the same time as the cessation of respiration. The sequence of changes in the ECG during the development and regression of the terminal disturbances was constant. Changes in the ST–T complex appeared earlier and disappeared later. Atrioventricular block and widening of the QT interval began later and disappeared sooner.

The rapid restoration of the functions of the heart simultaneously with the first, barely effective respiratory movements after prolonged and complete asphyxia and gross hemodynamic disorders can hardly be due to abolition of the myocardial anoxia. In the same way, the terminal disturbances in the ECG cannot be explained by the development of anoxia.

It must be mentioned that the idea of a direct reflex connection between the respiratory and cardiac centers had been put forward by Binet and Strumza [17]. M. I. Rafiki [13] also explains the coincidence of the terminal changes in the ECG and the cessation of respiration in shock in rabbits by disturbances of extracardial regulation.

As we have already stated above, in our experiments with vagotomy and atropinization, special changes were observed in the ECG of sensitized guinea pigs throughout the whole period of shock and death. This is evidence

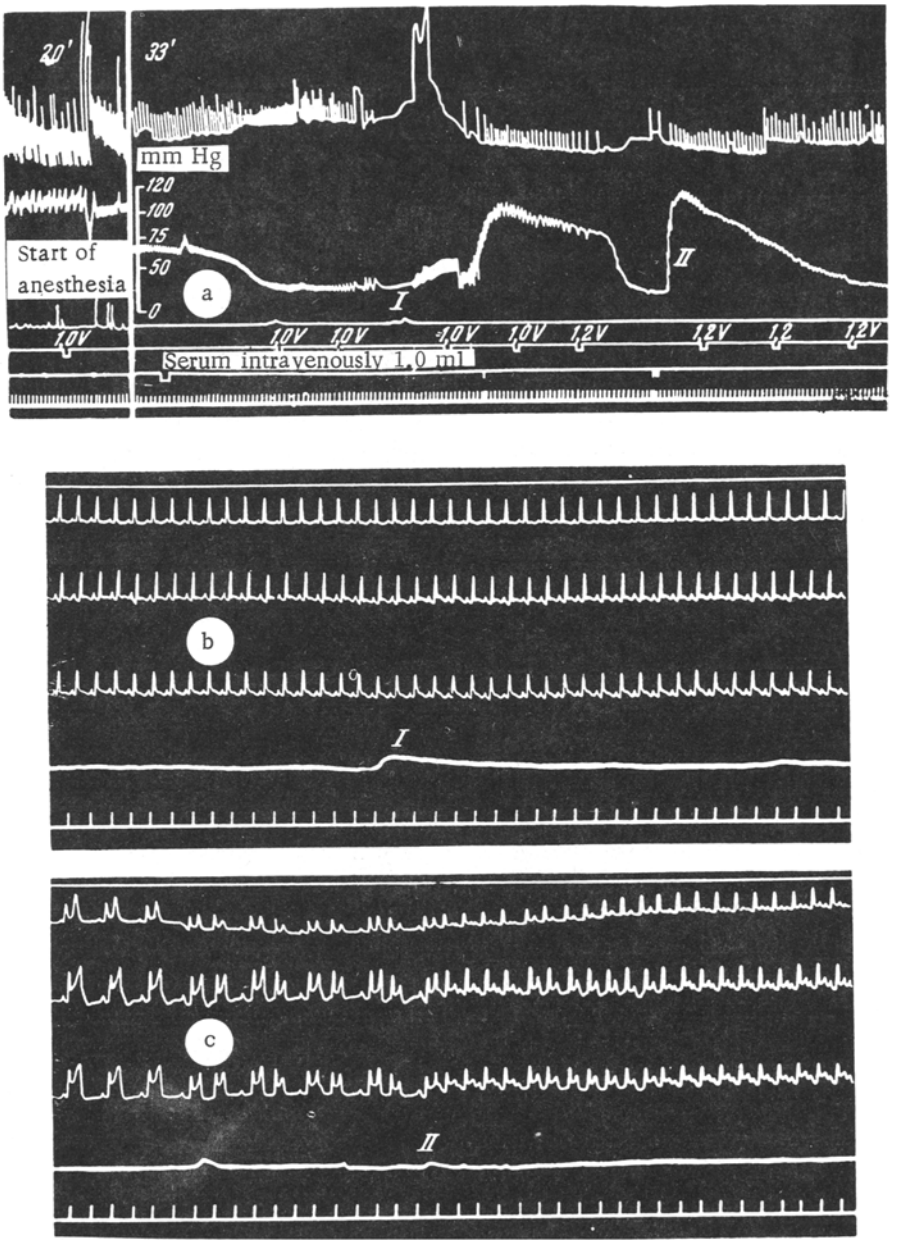

Fig. 2. Anaphylactic shock on a background of ether anesthesia. Significance of the curves (from above, down): for a: Respiratory movements; arterial pressure; general motor reaction; marker of stimulationof the right peripheral segment of the vagus nerve; marker of injection of assaulting dose of serum; time marker (3 sec); for b and c) marker of injection of serum; standard leads I, II, III of the ECG; effective respiration; time marker (0.25 sec). Points I and II on Figs. a, b, and c correspond to the same moment of the state of shock.

of the essential participation of the vagus nerves in the disorders of cardiac activity in anaphylactic shock, which is also in agreement with the findings of M. I. Rafiki [13], Criep [18] and others. The principal distinctions of the ECG in shock in these conditions (negative ST--T complex in standard leads) are a characteristic expression of sympathetic influences on the heart [12, 16, 19, 20, 21]. These disturbances may thus be attributed to the predominance in shock of sympathetic influences, intensifying the anoxia of the myocardium [11, 21].

Meanwhile, the experiments described justify the rejection of a direct role of the vagus nerves in the reflex mechanism of production of the terminal changes in the ECG, since both after atropinization and after vagotomy these disturbances develop in an even more acute and profound form. Our experimental results show that even with the most trivial changes in the rhythm of the heart and the level of the blood pressure in the course of terminal changes in the ECG, the first to disappear are the inversion of the T wave and the negative deflection of the ST interval, which are characteristic of the influence of the sympathetic nervous system.

In the course of regression of the terminal disorders, changes arise which are typical of the action of factors stimulating the sympathetic nerves: atrioventricular conduction is restored [11], systole is shortened [10, 16] and the T wave is inverted [21 and others], in conjunction with activation of respiration (Kamis-Krestovnikov phenomenon) and a rise in blood pressure. The development and regression of the terminal changes in the ECG may thus be regarded, in the first case as the expression of a fall, and in the second case of restoration, of the adaptational and trophic sympathetic influences on the heart, mainly reflex in character (ephedrine aggravates only the terminal changes in the ECG).

The greater severity of the functional and morphological lesions of the heart in animals with shock after vagotomy or administration of atropine and ephedrine is obviously the results of the predominance of sympathetic influences on the heart; this is in agreement with the findings of I. P. Pavlov [10] and Gaskell concerning the negative after-action of the accelerator nerves on the heart when nutrition is impaired.

The acute development of the terminal disturbances of the ECG in the experiments described may be explained by the considerable severity of the heart lesions arising in connection with the intensification of its work in the pathogenic conditions of anaphylactic shock. These lesions are responsible for disturbances of cardiac activity on account of a fall in the adaptational and trophic sympathetic influences on the heart.

SUMMARY

Participation of the sympathetic nervous system in the cardiac changes occurring in anaphylactic shock was studied on 27 guinea pigs, and the effect of ether anesthesia, on 28 animals. Simultaneous recordings of the 3 standard ECG leads were taken as well as of respiration, blood pressure and motor reaction. The prevalence of sympathetic effects during shock was created by the administration of ephedrine, or atropine, or vagotomy. Nonspecific ECG changes, similar to the vagus-stimulation effect occurring during the intravenous booster injection of the antigen, developed both in the vagotomized and in the atropinized animals. Ventricular extrasystoles diminished in both groups of experiments. The ST vector experienced consecutive shifts to the left during the shock. The terminal disturbances of the ECG in the form of increasing positive values with rising ST complex and T wave, widening of the QT interval and disturbances of atrioventricular transmission developed simultaneously with the arrest of respiration in both vagotomized and atropinized animals. This excludes the leading role of the vagus nerve in the appearance of such disturbances. In 9 cases of shock against the background of anesthesia, a spontaneous regression of the terminal disturbances of the ECG occurred simultaneously with the resotration of respiration. The terminal ECG disturbances are evidently reflex in origin and are connected with diminished adaptational and trophic effects of the sympathetic nervous system on the heart. The regression of the terminal changes is in keeping with the degree of restoration of these influences.

LITERATURE CITED

1. I. Kh. Abdullaev, Izvest. Akad. Nauk. Uzb. SSSR, Ser. Med. No. 3, 69 (1958).
2. A. D. Ado, Antigens as Extraordinary Stimuli of the Nervous System [in Russian] (Moscow, 1952).
3. A. M. Bezredka, Anaphylaxis and Antianaphylaxis [in Russian] (Moscow, 1928).
4. N. L. Garmasheva, Mechanism of Pathological Rections [in Russian] (Leningrad, 1947) Nos. 9-10, p. 29.
5. A. V. Gol'tsman, A New Method of Analysis of the Electrocardiogram--Axonometry--and its Importance in the Clinical Management of Diseases of the Myocardium (Candidate's dissertation) [in Russian] (Odessa, 1950).
6. A. N. Gordienko, The Nervous System and Immunity [in Russian] (Krasnodar, 1949).
7. V. S. Mats--Rossinskaya, Role of the Central Nervous System in the Mechanism of Anaphylaxis (Candidate's dissertation) [in Russian] (Stalino, 1955).
8. N. P. Mordovskii, Med. Byull. Irkutsk. Med. Inst. No. 5, 18 (1942).
9. S. M. Pavlenko, Problems of Rheumatism [in Russian] (Moscow-Leningrad, 1936) Nos. 9-10, pp. 23-31.
10. I. P. Pavlov, Complete Collected Works, 1 [in Russian] (Moscow-Leningrad, 1951), p. 419.

11. V. Raab, Progress in Cardiology [in Russian] (Moscow, 1959), p. 67.
12. M. E. Raiskina, Klin. Med. No. 9, 57 (1955).
13. M. I. Rafiki, Uchenye Zapiski LGU, Ser. Biol. No. 176, 203 (1954).
14. N. N. Sirotinin, Fundamentals and Achievements of Modern Medicine 2, [in Russian] (Kharkov, 1934) p. 28.
15. Yu. S. Tatarinov, Trudy Astrakhansk. Med. Inst. 11, 191 (1954).
16. L. I. Fogel'son, Clinical Electrocardiography [in Russian] (Moscow, 1957).
17. L. Binet and M. V. Strumza, Compt. rend. Soc. biol. 141, 251 (1947).
18. Z. H. Criep, Arch. Intern. Med. 48, 1098 (1931).
19. E. Goldberger, Unipolar Lead Electrocardiography and Vectorcardiography (Philadelphia, 1954).
20. A. Grishman, and L. Scherlis, Spatial Vectorcardiography (Philadelphia, 1952).
21. E. Lepeschkin, Modern Electrocardiography (Baltimore, 1951).
22. G. Mikulicich, J. Allergy 22, 249 (1951).