

## ELECTROCARDIOGRAPHIC CHANGES IN EXPERIMENTAL MYOCARDITIS AND ARTHRITIS IN NEONATALLY THYMECTOMIZED RATS

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By now the etiological role of streptococci in rheumatism is beyond any doubt but its pathogenesis notwithstanding the intense experimental studies in course remains as yet unclarified. According to Bibikova and co-workers (1965) and Borisova (1967) allergy of the delayed (cellular) type is more characteristic of rheumatism than that of the early (rapid) form of allergy, under which heading it is classified by Cripe and assoc. (1966).

Arnasan and assoc. (1962 a, b; 1964), Jankovic and assoc. (1962) and Waksman and assoc. (1964) have demonstrated that neonatal thymectomy inhibits the reactions of hypersensitivity of delayed (cellular) type. According to Paul Kallos (1963) the study of the thymus is of interest not only for immunobiology in the strict sense of the word, but also for the better understanding of allergic and autoimmune phenomena. This gives us sufficient ground to assume that the thymus as an immune reactivity organ is related also to the pathogenesis of rheumatism. Neonatal thymectomy which inhibits the reactions of hypersensitivity of delayed (cellular) type would suppress the development of allergy of delayed type in rheumatism.

It is known that the course run by rheumatism in humans and also experimental myocarditis in animals, is accompanied in most of the cases by a change in electrocardiographic data. Hence the ECG study appears to be one of the reliable indices for the activity of experimentally induced myocarditis.

The purpose of the present study is to carry out a comparative ECG investigation on neonatally thymectomized and intact white rats with experimentally induced myocarditis.

### Material and Method

The experiments were carried out on white rats Wistar breed of both sexes divided into two groups: a control one composed of 28 animals and experimental one — thirty one.

In the animals of the control group thymectomy through aspiration was performed 24—48 hours after the birth.

Experimental myocarditis was produced in both groups of animals upon completing of the age of three months according to the method developed at the Chair of Pathophysiology — VMI, Varna. Intravenous inject-

ions were made three times at two-week intervals of 0,2 ml 1000 million suspension per ml of 24-hour culture  $\beta$ -hemolytic streptococci group A.

The initial electrocardiograms were made three days prior to the first administration of streptococci. In order to follow-up the dynamic process the subsequent ECG investigations were made on the fifth day after each streptococcus suspension injection. The rats were fixed in prone position over a wooden rack isolated by rubber padding. The electrocardiographic recordings were made on unanesthetized animals according to a method adopted in the Chair of Pathophysiology — Higher Medical Institute (VMI), Varna (*Z. Kemileva and assoc.*, 1963). Electrocardiograph PST 3 S300 Schwarzer was employed at amplification 1 mV/cm and velocity of paper 100 mm/sec which enabled the obtaining of a clearcut recording of the P wave the interval ST and the T wave. The upper right and left limbs were recorded electrocardiographically on the first channel, the upper right and lower left — on the second channel and the upper left and lower left limbs — on the third channel.

### Results and Discussion

The initial electrocardiograms of both animal groups — not thymectomized and thymectomized — reveal the following characteristic features. The average heart rate is 510 beats per minute (from 450 to 631) in not thymectomized and 512 beat/min (from 459 to 599) in the thymectomized animals. The P wave in most of the cases of both groups is isoelectric or hardly discernible in the first lead. In the remaining two leads it is invariably positive and tapered with average duration in the non-thymectomized animals 0,013 sec and in the thymectomized — 0,0126 seconds. The average  $P_2$  height in the non-thymectomized rats is 1,74 mm and  $P_3$  — 1,14 mm. In the thymectomized the average height of  $P_2$  and  $P_3$  is 1,41 mm and 1,02 mm respectively. The PQ interval for the non-thymectomized animals averages 0,037 sec, and for the thymectomized 0,036 seconds (shorter than the interval value given by *Kemileva and Vasilev* — 0,045 sec, and by *Boshkov and co-workers* — 0,04 sec). The Q wave in all three leads in most cases was not recorded and that is why its starting values are not reported in the paper. The QRS complex averaged 0,0165 sec in the non-thymectomized rats and 0,0173 sec in the thymectomized group (according to *Kemileva and Vasilev*, the average duration is 0,019 sec). The average duration of the R wave in the non-thymectomized rats is as follows:  $R_1$  — 0,0095 sec,  $R_2$  — 0,0094 sec and  $R_3$  — 0,0096 sec. In the thymectomized animals the data obtained show 0,0097 sec for  $R_1$ , 0,0096 sec — for  $R_2$  and 0,0097 sec — for  $R_3$ . The height of the same wave in the group of unoperated rats averages 5,10 mm for  $R_1$ , 8,40 mm for  $R_2$  and 4,50 mm for  $R_3$  whereas in the thymectomized, the height of  $R_1$  averages 3,62 mm,  $R_2$  — 6,72 mm and  $R_3$  — 3,40 mm. The figures just cited are higher than those reported by *Kemileva and Vasilev* ( $R_1$  — 2,51 mm,  $R_2$  — 5,9 mm and  $R_3$  — 4,9 mm) and by *Lepeshin* ( $R_2$  — 4,6 mm). The duration of the S wave in the non-thymectomized animals is on the average 0,0067 sec for  $S_1$ , 0,0063 sec for  $S_2$  and 0,0058 sec for  $S_3$ . In the thymectomized animals the average duration of the S wave in the three leads is respectively 0,0075, 0,0074 and 0,0074 seconds. The

depth of this same wave averaged 2,14 mm for  $S_1$ , 3,24 mm for  $S_2$  and 2,66 for  $S_3$  and for the thymectomized animals respectively — 2,06 mm, 4,32 mm and 2,40 mm for the first, second and third leads. The terminal part of the electrocardiographic complex is set on a wide base with average duration in the intact rats 0,056 sec and in the thymectomized rats — 0,058 seconds. The T wave is rounded. Its average duration in non-thymectomized rats is 0,049 sec, and in the thymectomized — 0,051 seconds. The height of the same wave in the first lead in both animal groups is either isoelectric or hard to detect. In the second and third lead in the group of non-thymectomized animals it is accordingly 2,01 mm for  $T_2$  and 1,51 mm  $T_3$  and in the thymectomized — 1,48 mm for  $T_2$  and 0,88 mm for  $T_3$ .

The results of the ECG investigation after each single injection of  $\beta$ -hemolytic streptococci, group A, are presented in Table 1. The pathologic changes are classified in two degrees: first and second. The first degree includes slighter deviations from the normal value — decrease of P, R and T wave to 40% of the starting level, slight elongation of PQ without other pathological alternations. The second degree electrocardiograms display a decrease of the T wave exceeding with 50% the starting level, substantial fall of the P and R waves, manifested by changes in both leads and conductivity impairment.

Table 1

Streptococci injection	ECG	CONTROLS %	THYMECTOMIZED %
After the first	unchanged	19,00	41,17
	I degree	57,14	52,94
	II degree	23,86	5,81
After the second	unchanged	7,14	41,17
	I degree	50,00	52,94
	II degree	42,86	5,81
After the third	unchanged	—	20,00
	I degree	23,81	40,00
	II degree	76,19	40,00

It is evident from the table that the ECG changes in the thymectomized animals show interesting dynamics as compared to that of non-thymectomized control rats. Following the first injection of streptococci 19% of the non-thymectomized rats show no deviations whatsoever from the initial electrocardiograms the same percentage for the thymectomized being 41,17, i. e. twice as higher. The percentage of changes of I degree is approximately equal whereas the percentage of II degree changes in non-thymectomized animals is 23,86 and in thymectomized — only 5,81. Following the secondary streptococci introduction this percentage in the non-thymectomized rats augments up to 42,86 whilst in the thymectomized it is maintained unaltered — 5,81. After the third injection all non-thymectomized animals disclose ECG data characteristic of myocardial impairment. In

20% of the thymectomized animals there were no changes whatsoever. The pathological ECG changes of II degree in the control, non-thymectomized animals amounts to 76,91% and in the group of thymectomized — 40,0%, i. e. almost twice as less.

The statistical elaboration of the data regarding the changes in the individual teeth and sections of the electrocardiograms confirmed the reliability of the weaker affection of thymectomized animals as compared to non-thymectomized. In the latter group the lowering of the P, R and T waves is much greater and statistically reliable. Moreover in the thymectomized rats except for the R<sub>2</sub> wave after the third injection of streptococci, it is not altered in the remaining leads after the first and second injection.

The changes in the P and T waves are still more conspicuous and after the three streptococcal injections the results are statistically reliable. The P<sub>2</sub> tooth in the controls (non-thymectomized) rats is reduced after the I, II and III injection respectively by 28,5%, 23,5% and 35,2% from the initial level whilst P<sub>2</sub> in the thymectomized animals after the I and II injection is reduced respectively by 12,7% and 8,9% and is maintained at the same level — 18,9% — after the third injection. Much more striking are the results in the T wave. Thus for instance, T<sub>2</sub> of the non-thymectomized rats is reduced after I, II and III injection of streptococci by 27,9%, 35,9% and 53,7%, whereas in the thymectomized after identical injections, it is reduced by 20%, 34,6% and 37,3%. The same holds true for T<sub>3</sub> where the reduction of the wave after the third injection amounts to 50%, whereas T<sub>3</sub> in the thymectomized rats is reduced after the same injection merely by 27,0% i. e. almost twice as less.

The comparative study of electricardiographic changes and pathological data concerning myocardial impairment is of utmost interest and it will be discussed in a separate publication. In 85,7% of the control non-thymectomized animals, inflammatory changes in the myocardium were established in the course of pathohistological and histochemical investigations whilst in the group of thymectomized — 48,4%. Such a comparison indicates that 14,3% of the electrocardiographic changes in non-thymectomized rats are rather slight, promptly subsiding and lacking appropriate morphological substrate. Among the thymectomized animals the percentage of slight pathological ECG deflections is substantially higher — amounting to 40,0 per cent. The percentage of II degree changes in the same animals — 40,0% — virtually coincides with the percentage of the inflammatory changes in the myocardium, established during pathohistological investigation — 48,4 per cent.

The ECG data established in the study of animals with experimentally induced myocarditis demonstrate a marked heavier affection of non-thymectomized animals as compared to those thymectomized.

In all likelihood, neonatal thymectomy inhibits the development of allergic reaction of delayed (cellular) type which lies at the base of the myocardial lesions in experimental myocarditis and rheumatism in humans.

There is some difference between the initial ECG data in thymectomized and non-thymectomized rats, but the extent to which thymectomy influences the electrocardiogram will be the subject of further investigations.

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### ЭЛЕКТРОКАРДИОГРАФИЧЕСКИЕ ИЗМЕНЕНИЯ ПРИ ЭКСПЕРИМЕНТАЛЬНОМ МИОКАРДИТЕ И АРТРИТЕ У НЕОНАТАЛЬНО ТИМЭКТОМИРОВАННЫХ КРЫС

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#### РЕЗЮМЕ

Авторы ставят перед собой цель произвести сравнительное электрокардиографическое изучение у неонатально тимэктомированных и интактных белых крыс с экспериментально вызванным миокардитом по методу, разработанном в Кафедре патологической физиологии ВМИ города Варны.

При записи электрокардиограммы использован поликардиоскрипт «Шварцер», со скоростью движения бумаги 100 мм/сек, что позволило получить более отчетливые зубец Р, расстояние ST и зубец Т.

Изменения разделены на две степени — первую и вторую. ЕКГ данные указывают на более тяжелое поражение нетимэктомированных животных и после трех введений стрептококковой суспензии. После третьего введения все нетимэктомированные животные дали ЕКГ-изменения и то в 76,19% II-ой степени, в то время как тимэктомированные в 20% случаев не дали изменений и только 40% дали изменения II-ой степени.

Представляет интерес сопоставление ЭКГ-данных с данными патохистологического исследования на поражение миокарда. Из нетимэктомированных животных у 85,7% были на лицо воспалительные изменения в миокарде, в то время как такие изменения у тимэктомированных животных наблюдались только у 48,4%.

ЭКГ-данные подтверждают вероятность, что неонатальная тимэктомия подавляет развитие аллергической реакции позднего (клеточного) типа, которая лежит в основе миокардных поражений при экспериментальном миокардите и ревматизме у человека.