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Electrocardiographic changes associated with serum electrolyte alterations

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ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH SERUM ELECTROLYTE ALTERATIONS

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The amount of literature written on the subject of electrocardiographic changes seen in electrolyte disturbances is very large indeed. In general there are certain basic changes associated with each of the types of disturbances and most authors are in agreement with these. This paper is a review of such literature and each of the electrolyte disturbances, limited primarily to potassiu, calcium, and magnesium, will be discussed. In addition, basic physiological aspects concerning electrolytes and their relationship with the myocardium will be presented in an attempt to explain the mechanisms behind the changes seen on the electrocardiogram.

Two major factors in the past several years have been responsible for the continuation of research and the recent progress in the field of electrophysiology. One of these although not so new itself, is the use of radioactive isotopes. The more recent factor is the technique of using micro-electrodes which are inserted into the single muscle fiber for more detailed study of intracellular physiology.

The action potential when recorded from a single cardiac fiber using the micro-electrode technique is monophasic and its shape is represented by a very rapid upstroke, occuping a fraction of one millisecond

followed by a slow return of the membrane potential to the resting level. The resting potential corresponds to the diastolic phase of the cardiac cycle and is characterized by a fairly constant voltage which exists between the inside and outside of the cell with the inside negative to the outside. This resting potential as measured by some authors is approximately 60mV.[1] Another worker recorded a resting potential somewhat higher, 84.5mV.[2] When the systolic phase of the cardiac cycle begins there is a sudden reversal of polarity of the membrane potential which corresponds with the rapid upstroke of the action potential mentioned previously. In a small percentage of observations the membrane potential becomes greater than its resting value and then returns to normal. This has been referred to as hyperpolarization. When a surface electrocardiogram is recorded simultaneously with the monophasic action potential, it shows that the QRS complex coincides with the sudden depolarization of the fiber and the T-wave coincides with the end of the repolarization process.[3] deMello and Hoffman,[4] using the technique of intracellular micro-electrodes, studied the effects of potassium on the electrical activity of single fibers from various areas of the heart. It was found that the fibers of the AV node, AV ring, SA node and pacemaker fibers in the crista terminalis were less

sensitive to the depolarizing action of potassium than atrial or ventricular muscle.

The part that electrolytes play in myocardial action must first be understood before one can explain the reason for some of the disturbances of myocaridal action brought about by their inbalances. The distribution of ions reveals that potassium ions are present in the cardiac myoplasm by a factor of about 30, while sodium ions are present at a 10 times lower concentration than in the interspace. Electrical evidence suggests that the surface membrane of resting cardiac fibers is permeable predominantly to potassium ions.[5] The high concentration of potassium and the low concentration of sodium within the cell and a reversal of this ration in the extracellular space results in a resting potential within the cell of about 90mV. When the treshold level of potassium concentration is passed initiating depolarization, the sodium enters into and potassium diffuses out of the cell causing the potential to quickly fall to zero and overshoot to a positive potential. This is followed by a short rapid phase of return, a plateau, and a slower repolarization to the resting potential as potassium is regained and sodium lost from the cell. Studies on the physico-chemical changes that enter into the contractile cycle of heart muscle fibers have shown that potassium

enters into the oxidative-phosphorylation cycle with production of the major energy source, adenosine thriphosphate.[6] Brady and Woodbury[7] have suggested the depolarization is probably due to a sudden large increase in membrane sodium conductance. This conductance falls off rapidly, but is still greater than the resting membrane conductance for about 100 milliseconds and since the potential is near zero, sodium conductance must be greater than potassium conductance and their sum during this period must be less than it is during rest. In other words potassium conductance has fallen. An important supporting fact for the concept of the membrane potential of muscle and nerve being a diffusion potential was the demonstration of a rectilinear relationship between the logarithm of the external potassium concentration and the measured membrane potentials.[8] Wilde[9] has shown by the use of K^{42} that the release of potassium from the cardiac fiber is pulsatile in nature. He was less firm in stating that the release begins during the plateau phase of the action potential and continues with repidity during the quick phase of the repolarization wave as recorded with intracellular

electrodes. Schreiber[10] has shown using the radioactive isotopes K^{42} and Na^{24}, that intracellular potassium in the working ventricle exists in two phases or components which exchange at different rates. The slowly exchanging phase is sensitive to the amount of work performed, external concentration of potassium and failure of the contractile mechanism. This author also indicates that the digitalis glycoside, ouabain, causes an inhibition of entrane of potassium into the slowly exchanging phase while the fast component exchanges freely. The fact that digitalis in general causes a rapid release of myocardial potassium with slower repayment of the potassium debt and also that glucose and insulin inhance the digitalis effect suggests that the degree of digitalis effect is related to both the extracellular potassium concentration and the state of the intracellular potassium (bound or ionic)[11] which in turn may explain the differences in rates of exchange of potassium in the myocardium since some intracellular potassium in bound and some is in the ionic form.

The effects of calcium have also been studied by means of intracellular microelectrodes. Changes in concentration of this ion alter the time course of the action potential recorded from the auricle and ventricle but have little effect on the action potential recorded

from conducting tissue. Changes in the magnesium concentration have little effect on the transmembrane potentials of cardiac muscle unless the calcium is low, which with a simultaneous decrease in magnesium causes a marked prolongation of the action potential duration recorded from both auricle and ventricle.[12]

The final part of this paper will be devoted to the changes seen on the electrocardiogram as brought about by alteration in electrolytes. Several articles which also discussed this topic were reviewed for obtaining information as well as for ideas on organizing and writing this peper.[13-17]

Hyperpotassemia: The changes seen on the electrocardiogram as a result of hyperpotassemia are essentially the same whether the high potassium level is caused by an organic condition such as renal insufficiency, iatrogenically induced or whether it is experimentally induced either in humans or animals. The first change noted almost consistently is an increased amplitude of the T-wave appearing tall and peaked. This usually appears when the serum potassium level is in the range of 5-7 mEq/L. One article[18] studied reported, that in certain individuals, a "tent-shaped" T-wave of normal amplitude, rather than the tall, peaked T-wave, was the sole change in the

electrocardiogram in potassium intoxication. However, it was pointed out that this finding is not always associated with electrolyte changes but when it is, the potassium is high and the serum sodium is low. It may also, in certain instances result from the diminutive projection of the abnormal T-wave vector upon certain planes of the body. Following the appearance of the tall, peaked T-wave the R-wave decreases along with an increase in the amplitude of the S-wave component. Next in sequence are the disappearance of the P-wave which usually occurs at potassium levels of 9 to 11 mEq/L.[19] progressive depression of the ST segment appearing at potassium levels of 8 to 10 mEq/L. and widening of the QRS complexes giving the appearance of a smooth biphasic curve of the QRS-T. With increasing levels of potassium the electrocardiographic pattern is not so clear cut. Probably the simplest thing that can happen is the appearance of interventricular block causing the heart rate to fall progressively until there is cardiac arrest in diastole which has been reported to take place with potassium levels in the range of 14 to 16 mEq/L.[20-23] Other possibilities which tend to confuse the picture at very high levels of potassium are sinus

arrhythmias, auricular fibrillation, ectopic ventricular complexes, bundle branch blocks and idioventricular (nodal) rhythm. All of which can appear with increasing potassium concentration.[24]

The electrocardiographic changes resulting from potassium intoxication described above are those which are recorded from a "normal" heart. What about the patient with pre-existing heart disease. In the case of myocardial infarction whether acute or chronic, complicated by hyperpotassemia the usual finding is an augmentation of the characteristic ST-T changes. In general there is a decreased-tolerance to higher potassium levels.[25-27] Wasserburger and Corliss[28] advocate the use of oral potassium salts to differentiate the functionally inverted T-wave from the inverted T-waves due to myocardial infarction. All functionally inverted T-waves were reverted to normal 90 min. after ingestion of salts. Organically inverted T waves were generally unaltered following ingestion of potassium salts. Hyperpotassemia, complicating left ventricular ischemia, causes the mean T vector to increase in magnitude with little or no change in direction. The characteristic pattern for left ventricular ischemia is a normal QRS loop, an abnormally directed mean spatial T vector which

points away from the left ventricle resulting in an abnormally wide QRS-T angle of 90-100 degrees, and the absence of a measurable ST vector. Hyperpotassemia accompaning left ventricular strain results in an increase in the magnitude of the mean spatial T vector with little or no change in the magnitude or direction of the ST vector. The pattern for left ventricular strain is a QRS-T angle of nearly 180 degrees and a definite ST vector which is relatively parallel with the T vector.[29] To complicate the picture even more, there are several conditions which have been reported in the literature as simulating those changes seen on the electrocardiogram caused by hyperpotassemia. One of these is the "dying heart" which recores disorganized complexes as conduction becomes depressed over large areas of the myocardium. Slow nodal rhythm though rare and usually due to anoxia, myocarditis or severe arterio-sclerotic heart disease, is another. Organic bundle branch block many simulate the biphasic waves of severe, potassium intoxication.[30] There are a few cases reported in the literature of hyperpotassemia giving an electrocardiographic picture similar to that seen in myocardial infarction. The close resemblance was reported as being in the RS-T junction,

T-wave and Q-wave. It is felt that the correct diagnosis can usually be made by other electrocardiographic features of hyperpotassemia such as low or absence of P-wave, first degree heart block, widening of the QRS interval and tall, peaked T waves.[31-32]

Hypopotassemia: The electrocardiographic pattern of hypopotassemia is much less clear cut than that presented for hyperpotassemia. There are certain criteria set forth, but still these do not always appear in situations of low serum potassium, particularly those in which the potassium deficit is moderate in degree,[33] and when they do appear they frequently take on such different degrees of change that interpretation is not easy. Probably the most prominent electrocardiographic characteristic of hypopotassemia is the change in the T-wave which may appear in one of several different forms. The T-wave may be rounded with decreased amplitude, it may even be inverted, it may be of normal amplitude but increased in duration which is questioned by some workers as will be pointed out later, or it may appear normal except for an additional wave either superimposed on it or following it in various degrees.[34] This additional wave is refered to as a U-wave. Other criteria include increase in the amplitude and width of the P-wave,

increase in the PR-interval, increase in the duration of the QRS complex and depression of the ST-segment.[35-41] Other electrocardiographic changes produced by experimentally induced hypopotassemia are various degrees of atrio-ventricular and interventricular block, auricular standstill or fibrillation, ventricular tachycardia and ventricular fibrillation and standstill.[42-43] Two articles[44-45] reviewed used a different method in analyzing the electrocardiographic changes of hypopotassemia. The criteria used were: (1) amplitude of the U-wave greater than one millimeter, (2) a ratio greater than one of U-wave to T-wave amplitude in the lead with the tallest U-wave and (3) ST-segment depression greater than 0.5 millimeters. The presence of a U-wave in the electrocardiographic tracing is considered as one of the most important criteria for hypopotassemia. Considerable work has been done to explain the mechanism behind this wave.[46-48] Probably the best explanation of the U-wave is that it corresponds to potential differences produced during the descending limb of a negative afterpotential caused by potassium ions which have left the cell during repolorization, leaving the cell membrane slightly depolarized, and are only slowly reabsorbed during diastole. The descending branch of the action potential of the heart, which corresponds

to the T-wave of the electrocardiogram is very probably caused by exit of potassium from the cell. If the external potassium is high, less potassium can be reabsorbed during diastole. The negative after potential can therefore be expected to become smaller. Decrease of the extracellular potassium can be expected to have the opposite effect. Therefore the U-wave is very prominent with low serum potassium.

A somewhat different approach to the problem of electrocardiographic findings of lowered plasma potassium was done in a study[49] in which hypopotassemia was produced in dogs by hemodialysis or by intravenous administration of glucose and insulin. Both methods resulted in a similar decrease in plasma potassium concentration and similar electrocardiographic changes even though potassium was withdrawn from the cell during dialysis while it entered the cells during glucose-insulin infusion.

Another study[50] related the electrocardiographic changes of potassium depletion to the concentration of potassium in the red blood cells. In this study certain electrocardiographic characteristics of hypopotassemia, particularly depression of the ST-T segment and lowering of inversion of the T-wave followed by a prominent U-wave, were found only in those

with diminished concentration of potassium in the red cell regardless of the concentration inthe serum. This study indicates that the electrocardiographic pattern of hypopotassemia is frequently associated with a low concentration of potassium in red cells. The relationship of potassium in red blood cells to that of the myocardium is not know.

The effect of increased cardiac activity in a subject with hypopotassemia apparently causes no unusual electrocardiographic patterns.[51]

Currens and Crawford[52] studied the electrocardiographic tracings from patients with a variety of diseases in which alterations of electrolyte balance including potassium metabolism were apparent. In this study there was a lack of correlation between the electrocardiographic abnormalities and serum potassium levels.

The electrocardiographic pattern of hypopotassemia may be mistaken for other conditions which show QRS-T changes. For instance the RS-T depression and T-wave inversion may resemble that associated with an acute subendocardial infarction.[53]

Certain myocardial changes have been described as occurring in potassium deficiency in experimental animals. Widespread myocardial fibrosis with a patent coronary artery system free of disease has been

described. Another change reported is one in which focal areas of necrosis are present. The two changes have been reported together effecting the same heart.[54] To complete the discussion of alterations of serum potassium and the electrocardiographic manifestations it may be well to correlate some of the electrophysiological aspects presented earlier in this paper with the actual changes seen on the electrocardiogram. As a review, the slowly descending plateau (phase 2) of the transmembrane action potential is due to the exit of potassium and the rapidly descending portion (phase 3) is due to the acceleration of this exit through increase of potassium permeability. The negative after potential (phase 4) has been ascribed to potassium which has left the cell during phases 2 and 3 and only slowly reabsorbed from the surface of the cell membrane. The ST- segment corresponds to phase 2, the T-wave to phase 3 and the U-wave to phase 4. In hypopotassemia the potassium gradient across the cell membrane increases. Phase 2 becomes steeper and prolonged while phase 3 shows a decrease in slope resulting in a more obtuse angle between phases 2 and 3. This explains the depressions of the ST segment with the diphasic T-wave. As more potassium leaves the cell and is reabsorbed more will remain outside causing

a greater negative after-potential which could explain the elevation of the U-wave. In hyperpotassemia the gradient is diminished, phase 2 is less steep and phase 3 more steep resulting in a less obtuse angle and the after potential is diminished, all of which can explain the peaked, elevated T-waves and Absense of the U-waves.[55-57]

Hypercalcemia: In contrast to the number of changes seen on the electrocardiogram due to disturbances of potassium levels, there are only a few simple changes associated with calcium alterations. The principal effect of hypercalcemia on the electrocardiogram is the shortening of the ST- segment. However, for practical purposes, a more accurate measurement can be obtained by measuring the Q-otc segment, which gives an accurate electrocardiographic guide to levels of serum calcium up to 20 mg%. Measurement of the Q-Tc is inversly proportional to the serum calcium level only up to levels of 16 mg%. The reason for this difference is the result of another change upon the electrocardiogram when calcium levels increase above 16 mg%, namely that of a prolongation of the T-wave resulting in a QT-wave which is disproportionately long. By using the Q-otc segment this factor can be avoided up to levels of 20 mg%. Other less commonly associated changes include in increase in

duration of the PR-interval and a bradycardia which only occurs with an acute elevation of the serum calcium produced as by calcium infusions. In the digitalized patient high calcium levels augment the effects of the digitalis and arrhythmias may also be present.[58-59]

Hypocalcemia: As in hypercalcemia, the electrocardiographic changes due to hypocalcemia are few and simple. In fact the changes are just the opposite with the exception of the effect on the PR-interval of which there is no effect. Prolongation of the Q-Tc interval is observed in almost all cases, usually noted first when the serum calcium decreases to levels of 6 to 7 mg%. Several changes in contour of the T-wave have been observed consisting of a slight elevation with peaking and displacement of the apex to the end of the QT- interval, to T-waves which are flattened, to tall, peaked T-waves. Acute depression of the serum calcium level as by infusion of chelating agents causes a tachycardia.[60-61] It has been suggested that in hypocalcemia due to hypoparathyroidism there may be two distinct effects produced on the myocardium. One, related to the ionic calcium and the permeability of the cell membrane, is responsible for the increased duration

of the repolorization phase of the ventricular complex and the other related to organic calcium and the contractile substance of the myocardium which could perhaps effect the configuration of the T-wave.[62-63] To conclude the discussion of electrocardiographic changes due to serum calcium alteration it would be well to consider some conditions which produce similar changes on the electrocardiogram. Two other conditions have been reported which cause marked shortening of the QT-interval, digitalis effect and acute pericarditis. The shortened Q-Tc interval associated with digitalis effect is usually if not always accompanied by a sagging or depression of the ST-segment and a diphasic T-wave. Less common are the appearances of premature ventricular contractions and prolongation of atrioventricular conduction. In acute pericarditis, shortening of the QT-interval is commonly associated with other changes. These include elevation of the ST-segment in the precordial leads and the limb leads except in aVR where the ST-segment is depressed. Later in the course of pericarditis the ST-segment becomes isoelectric and the T-wave may be inverted. Prolongation of the QT-interval, essentially the sole effect of hypocalcemia on the electrocardiogram is also a predominent feature of hypopotassemia. Prolongation of the QT-interval with

hypocalcemia is largely due to lengthening of the ST-segment whereas in hypopotassemia it is caused principally by sidening of the T-wave. There is also usually a lowering or inversion of the T-wave, depression of the ST-segment and appearance of U-waves in hypopotassemia.[64-65]

The last electrolyte to be considered in this paper is magnesium, the least understood of the electrolytes. Magnesium, one of the most abundant cations in the body is, like potassium, located almost entirely within the cell. Bone contains one half of the body magnesium, Also, as with potassium, the plasma level of magnesium is by no means a guide to the amount of the ion in the cell, nor can a satisfactory response to the administration of magnesium necessarily be taken as evidence of depletion.[66]

Hypermagnesemia: The problem of magnesium intoxication is probably most commonly associated with both acute and chronic renal failure. In general this increased magnesium parallels that of potassium and furthermore, the electrocardiographic changes associated with hypermagnesemia are similar to those of hyperpotassemia which makes for a difficult if not impossible situation when interpreting such electrocardiograms.[67]

The presence of hypermagnesemia as the sole

electrolyte disturbance in a clinical case is a rare situation. Only one case was reported in the literature reviewed.[68] Most of the work done on electrocardiographic changes associated with increased levels of magnesium has been done on an experimental basis using both animals and humans. The usual sequence of electrocardiographic changes include an early tachycardia which appears as the serum magnesium level increases from 2 to 5 mEq/L. This initial tachycardia then gradually gives way to a bradycardia associated with depressed intracardiac conduction which presents as a progressive increase in the PR-interval and widening of the QRS complex beginning at a concentration of 5 to 10 mEq/L and continuing till death. In occasional cases sino-atrial and atrio-ventricular block of various grades occur at levels greater than 15 mEq/L.[69-71]

Hypomagnesemia: Very little has been reported concerning the electrocardiographic changes associated with low serum levels of magnesium. In fact no actual clinical case was reported in the literature reviewed. Experimentally it has been shown that low magnesium levels cause a progressive prolongation of the monophasic action potential and the QT-interval of the electrocardiogram only when there is a simultaneous

decrease of calcium which raises the question of rather or not low magnesium levels have any effect on the electrocardiogram since these very changes are associated with hypocalcemia alone.[72]

The action of magnesium on the heart is not known definitely. Studies reveal only that magnesium has a direct depressive action on the conductive system. There is apparently no effect on the myocardium itself.[73-74]

SUMMARY

1. Two major factors in the past several years have been responsible for the recent progress in research in the field of electrophysiology, radioactive isotopes and microelectrodes.

2. The monophasic action potential of the myocardial fiber is correlated with the electrical complex as recorded by the electrocardiogram and with the electrolyte changes occuring during this period of activity.

3. The electrocardiographic changes associated with hyperpotassemia include: a tall, peaked T-wave, decrease in amplitude of the R-wave, increase in the S-wave component and disappearance of the P-wave. With very high levels of potassium the ST-segment becomes progressivily depressed and the QRS complex becomes widened until eventually a smooth biphasic curve of the QRS-T results.

4. Hypopotassemia results in an electrocardiographic pattern characterized by a low, rounded T-wave usually accompanied by a U-wave. Other less common changes include an increased amplitude and width of the P-wave, increase in the PR-interval, increase in the duration of the QRS complex and depression of the ST-segment.

5. The principal effect of hypercalcemia on the electrocardiogram is shortening of the ST-segment.

An increase in the duration of the PR-interval is less commonly observed.

6. Hypocalcemia causes a prolongation of the QT-interval and several nonspecific T-wave changes.

7. Electrocardiographic changes associated with alterations in serum magnesium levels are very non-specific. In fact there is very little clinical evidence that any changes what-so-ever are observed. Hypermagnesemia depresses intracardiac conduction resulting in an increase in the PR- interval and widening of the QRS complex. No definite changes have been associated with hypomagnesemia alone.

8. The electrophysiological basis for the electro-cardiographic changes seen with alterations in serum electrolytes is discussed.

BIBLIOGRAPHY

1. Burgen, A.S.V. and Terroux,K.G.: The Membrane Resting and Action Potentials of the Cat Auricle, J. Physiol. (Lond.), 110: 139-52, 1953.

2. Ware, F.Jr., Bennett, A.L. and McIntyre, A.R.: Membrane Potentials in Normal, Isolated, Perfused Frog Hearts, Am. J. Physiol. 190: 194, 1957.

3. Woodbury, L.A., Woodbury, J.W. and Hecht, H.H.: Membrane Resting and Action Potentials of Single Cardiac Muscle Fibers, Circulation. 1:264, 1950.

4. de Mello, W.C. and Hoffman,B.F.: Potassium Ions and Electrical Activity of the Heart, The Physiologist. 2:32, 1959.

5. Weidmann, S.: Resting and Action Potentials of Cardiac Muscle, Ann. N.Y. Acad. Sci. 65: 663-76, 1957.

6. Sampson, J.J.: Relationship of Potassium to Cardiac Disease, Dis. Chest. 42:334, Sept.62.

7. Brady, A.J. and Woodbury, J.W.: Effect of Sodium and Potassium on Repolorization in Frog Ventricular Fibers, Ann. N.Y. Acad. Sci. 65:687, 1957.

8. Ling, G. and Gerard, R.W.: External Potassium and the Membrane Potential of Single Muscle Fibers, Nature (Lond.). 165: 113, 1950.

9. Wilde, W.S.: The Pulsatile Nature of the Release of Potassium from Heart Muscle During the Systole, Ann. N.Y. Acad. Sci. 65:693, 1957.

10. Schreiber, S.S.: Potassium and Sodium Exchange in the Working Frog Heart: Effects of Overwork, External Concentrations of Potassium and Ouabain, Amer. J. Physiol. 185: 337-47, 1956.

11. Blackmon, J.R., Gillespie, L., Berne, R.M. and Hellerstein, H.K.: The Effects of Digitalis Glycosides on the Electrolyte Balance of the Myocardium: Alteration of these effects by Glucose and Insulin and Potassium Chloride, J. Lab. and Clin. Med. 48:784, 1956.

12. Hoffman, B.F. and Suckling, E.E.: Effect of Several Cations on Transmenbrane Potentials of Cardiac Muscle, Am. J. Physiol. 186:317, 1956.

13. Bellet, S.: The Electrocardiogram in Electrolyte Imbalance, A.M.A. Arch. Int. Med. 96:618-37, Nov. 1955.

14. Merrill, A.J.: The Significance of the Electrocardiogram in Electrolyte Disturbances, Am. Heart J. 43:634, 1952.

15. Green, J.P. Giarman, N.J. and Salter, W.T.: Combined Effects of Calcium and Potassium on Contractility and Excitability of the Mammalian Myocardium, Am.J. Physiol. 171: 174, 1952.

16. Garb, S.: The Effects of Potassium, Ammonium, Calcium, Strontium and Magnesium on the Electrogram and Myogram of Mammalian Heart Muscle, J. Pharmacol. & Exper. Therap. 101:317, 1951.

17. Greco, F.D. and Grumer, H.: Electrolyte and Electrocardiographic Changes in the Course of Hemodialysis, Amer. J. Cardiol. 9:43-50, Jan. 62.

18. Levine, H.D.' Vazifdar, J.P., Lown, E. and Merrill, J.P.: "Tent-shaped" T-Waves of Normal Amplitude in Potassium Intoxication, Amer. Heart J. 43:437-50, 1952.

19. Crismon, J.M., Crismon, C.S. Calabresi, M. and Darrow D.C.: Electrolyte Redistribution in Cat Heart and Skeletal Muscle in Potassium Poisoning, Am. J. Physiol. 139: 667, 1943.

20. Winkler, A.W., Hoff, H.E. and Smith, P.K.: Electrocardiographic Changes and Concentrations of Potassium in Serum following Intravenous Injection of Potassium Chloride, Amer. J. Physiol. 124: 478, 1938.

21. Stewart, H.J., Shepard, E.M., and Harger, E.L.: Electrocardiographic Manifestations of Potassium Intoxication, Am.J. Med. 5:821, 1948.

22. Tarail, R.: RElation of Abnormalities in Concentration of Serum Potassium to Electrocardiographic Disturbances, Am. J. Med. 5:828, 1948.

23. Steward, H.J., Shepard, E.M. and Horger, E.L.: Electrocardiographic Manifestations of Potassium Intoxication, Am. J. Med. 5:821, 1948.

24. Levine, H.D., Merrill, J.P. and Somerville, W.: Advanced Disturbances of the Cardiac Mechanism in Potassium Intoxication in Man, Circulation. 3:889, 1951.

25. Bellet, S., Gazes, P.C., and Steiger, W.A.: The Effect of Potassium on the Electrocardiogram in the Normal Dog and in Dogs with Myocardial Infarction, Am.J. Med. Sci. 220:237, 1950.

26. Bellet, S., Steiger, W.A. and Gazes, P.C.: The Effect of Different Grades of Myocardial Infarction upon the Tolerance to Potassium: An Experimental Study in Dogs, Am.J. Med. Sci. 220:247, 1950.

27. Brown, H., Tanner, G.L. and Hecht, H.H.: The Effects of Potassium Salts in Subjects with Heart Disease, J.Lab. and Clin. Med. 37: 506, 1951.

28. Wasserburger, R.H. and Corliss, R.J.: Value of Oral Potassium Salts in Differentiation of Functional and Organic T-Wave Changes, Amer. J. Cardiol. 10:673-87, Nov. 62.

29. Dodge, H.T., Grant, R.P. and Seavey, P.W.: The Effect of Induced Hyperkalemia on the Normal and Abnormal Electrocardiogram, Amer. Heart J. 45:725-40, 1953.

30. Finch, C.A., Sawyer, C.G. and Flynn, J.M.: Clinical Syndrome of Potassium Intoxication, Am. J. Med. 1:337, 1946.

31. Nora, J.R. and Pilz, G.P.: Pseudoinfarction Pattern Associated with Electrolyte Disturbance, A.M.A. Arch. Int. Med. 104:300, 1959.

32. Weintraub, L.R. and Reynolds, E.W.: Electrocardiographic Changes Simulating Myocardial Infarction in Potassium Intoxication with Special Reference to QRS Changes, Univ. Mich. Med. Bull. 26:348-53, Oct. 60.

33. Schwartz, W.B., Levine, H.D. and Relman, A.S.: The Electrocardiogram in Potassium Depletion, Am. J. Med. 16:395, 1954.

34. Bellet, S., Steiger, W.A., Nadler, C.S. and Gazes, P.C.: Electrocardiographic Patterns in Hypopotassemia: Observations on 79 Patients, Am. J. Med. Sci. 219:542, 1950.

35. Stewart, H.J., Smith, J.J., and Milhorat, A.T.: Electrocardiographic and Serum Potassium Changes in Familial Periodic Paralysis, Am. J. Med. Sci. 199:789, 1940.

36. Young, J.V. and Daugherty, G.W.: Use of the Artificial Kidney in the Production and Study of Experimental Hypokalemia, Proc. Staff Mayo Clin. 31:357, 1956.

37. McAllen, P.M.: The Electrocardiogram Associated with Low Levels of Serum Potassium, Brit. Heart J. 13:159, 1951.

38. Surawicz, B. and Lepeschkin, E.: The Electrocardiographic Pattern of Hypopotassemia with and without Hypocalcemia, Circulation. 8:801-28, 1953.

39. Nadler, C.S., Bellet, S. and Lenning, M.: Influence of the Serum Potassium and Other Electrolytes on The Electrocardiogram in Diabetic Acidosis, Am. J. Med. 5:838, 1948.

40. van Buchem, F.S.P.: The Electrocardiogram and Potassium Metabolism: Electrodardiographic Abnormalities in Primary Aldosteronism and Familial Periodic Paralysis, Am.J. Med. 23: 376, 1957.

41. Habib, Y.A. Nichopoulos, G.C. and Overman, R.R.: Effect of Acute Removal of Potassium from the Body on Tissue Electrolytes, Am.J. Physiol. 193:634, 1958.

42. Chamberlain, F.L., Scudder, J. and Zwemer, R.L.: Electrocardiographic Changes Associated with Experimental Alterations in Blood Potassium in Cats, Amer, Heart J. 18:458, 1939.

43. Weller, J.M., Lown, B., Hoigne, R.V., Wyatt N.F., Criseitiello, M., Merrill, J.P. and Levine, S.A.: Effects of Acute REmoval of Potassium from Dogs: Changes in the Electrocardiogram, Circulation. 11:44, 1955.

44. Surawicz, B., Brown, H.A., Crum, W.B., Kemp. R.L., Wagner, S. and Bellet, S., : Quantitative Analysis of the Electrocardiographic Pattern of Hypopotassemia, Circulation. 16:750, 1957.

45. Weaver, W.F. and Burchell, H.B.: Serum Potassium and the Electrocardiogram in Hypokalemia, Circulation. 21:505, 1960.

46. Lepeschkin, E.: The U-Wave of the Electrocardiogram. AMM.A. Arch. Int. Med. 96:600-14, Nov. 1955.

47. ———: Genesis of the U-Wave, Circulation. 15:77, 1957.

48. Holzmann, M.: Various Typers of Fusion Between T and U-Waves, Circulation. 15:70, 1957.

49. Surawicz, B., Kunin, A.S. and Sims, E.A.H.: Effects of Hemodialysis and of Glucose-Insulin Administration on Plasma Potassium and on the Electrocardiogram, Circ. Res. 12:145, Feb. 63.

50. Soloff, L.A., Kanosky, S.A. and Boutwell, J.H. Jr.: The Relationship of the Electrocardiographic Pattern of Potassium Depletion to the Concentration of Potassium in the Red Blook Cells, Amer. J. Med. Sci. 240:280-90, Sept. 60.

51. Soloff, L.A. and Fewell, W.J.: Abnormal Electrocardiographic Responses to Exercise in Subjects with Hypokalemia, Amer. J. Med. Sci. 242:724-8, Dec. 61.

52. Currens, J.H. and Crawford, J.D.: The Electrocardiogram and Disturbance of Potassium Metabolism, New Eng. J. Med. 243:843, 1950.

53. Myers, G.B.: Other QRS-T Patterns That May be Mistaken for Myocardial Infarction. IV. Alterations in Blood Potassium: Myocardial Ischemia; Subepicardial Myocarditis; Distortion Associated with Arrhythmias, Circulation. 2:75, 1950.

54. McAllen, P.M.: Myocardial Changes Occurring in Potassium Deficiency, Brit. Heart J. 17:5, 1955.

55. Lepeschkin, E.: An Electrophysiologic Explanation of the Electrocardiographic Hypo-and Hyperpotassemia Patterns, Circulation. 12:738, 1955.

56. Surawicz, B., Lepeschkin, E., Herrlich, H.C. and Hoffman, B.F.: Effect of Potassium and Calcium Deficiency on the Monophasic Action Potential, Electrocardiogram and Contractility of Isolated Rabbit Hearts, Am. J. Physiol. 196:1302-7, 1959.

57. Gettes, L.S., Surawicz, B. and Shine, J.C.: Effect of High K, Low K and Quinidine on QRS Duration and Ventricular Action Potential, Am. J. Physiol. 203:1135-40, 1962.

58. Bronsky, D., Dubin, A., Waldstein, S.S. and Kushner, D.S.: Calcium and the Electrocardiogram. II, III. The Relationship of the Intervals of the Electrocardiogram to the Level of Serum Calciu, Am.J. Cardiol. 7:840, 1961.

59. Boen, S.T., Leijnse, B. and Gerbrandy, J.: Influence of Serum Calcium Concentration on QT-Intefval and Circulation, Clin. Chim. Acta. 7:432-6, May 62.

60. Ljung, O.: The Electrocardiogram in Hypocalcemia with Special Reference to the T-Wave, Acta. Med. Scand. 136-56, 1949.

61. Kalliomäki, J.L., Markkanen, T.K. and Mustonen, V.A.: Standard Electrocardiogram in Artificial Hypocalcemia, Ann. Med. Intern, Fenn. 50: 163, 1961.

62. Bronsky, D., Dubin, A., Waldstein, S.S. and Kushner, D.S.: Calcium and the Electrocardiogram. I. The Electrocardiographic Manifestations of Hypoparathyroidism, Am. J. Cardiol. 7:823, 1961.

63. Ware, F., Jr., Bennett, A.L. and McIntyre, A.R.: Effects of Calcium Deficiency on Cell Membrane Potentials of Isolated Frog Hearts, Am. J. Physiol. 198:597, 1960.

64. Ernstene, A.C. and Proudfit, W.L.: Differentiation of the Changes in the Q-T Interval in Hypocalcemia and Hypopotassemia, Amer. Heart. J. 38:260, 1949.

65. Yu, P.N.G.: The Electrocardiographic Changes Associated with Hypercalcemia and Hypocalcemia, Am. J. Med. Sci. 224:413, 1952.

66. Magnesium, Brit, Med. J. 1:1111, 1958.

67. Wacker, W.E.C. and Vallee, B.L.: A Study of Magnesium Metabolism in Acute Renal Failure Employing a Multichannel Flame Spectrometer, New Eng. J. Med. 257:1254, 1957.

68. Smith, W.O. and Hammersten, J.F.: Serum Magnesium in Renal Diseases, A.M.A. Arch. Int. Med. 102:5, 1958.

69. Miller, J.R. and Van Dellen, T.R.: Electrocardiographic Changes Following The Intravenous Administration of Magnesium Sulfate. An Experimental Study on Dogs, J. Lab. & Clin. Med. 23: 914, 1938.

70. Stanbury, J.B. and Farah, A.: Effects of the Magnesium Ion on the Heart and on Its Response to Digoxin, J. Pharmacol. & Exper. Therap. 100:445, 1950.

71. Smith, P.K., Winkler, A.W. and Hoff, H.E.: Electrocardiographic Changes and Concentration of Magnesium in Serum Following Intravenous Injection of Magnesium Salts, Amer. J. Physiol. 126:720, 1939.

72. Surawicz, B., Lepeschkin. E. and Herrlich, H.C.: Low and High Magnesium Concentration at Various Calcium Levels: Effect on the Monophasic Action Potential, Electrocardiogram, and Contractility of Isolated Rabbit Hearts, Circulation Research. 9:811, 1961.

73. Szekely, P.: The Action of Magnesium on the Heart, Brit. Heart J., 8:115, 1946.

74. Van Dellen, T.R. and Miller, J.R.: Electrocardiographic Changes Following the Intravenous Administration of Magnesium Sulfate. An Experimental Study on Dogs, J. Lab. & Clin. Med. 24;840, 1938.