Sodium, Potassium and Magnesium Balance During Recovery from Congestive Heart Failure due to Cor Pulmonale and Other Heart Diseases

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Five cases of congestive failure due to varied causes were studied metabolically during recovery. The cases of cor pulmonale showed changes in cations and osmotically active base, similar to changes in heart failure due to other causes. A difference in the movement of water was noted between three of the present cases and the usual case of congestive heart failure.

Although excessive secretion of the salt-retaining corticoid, aldosterone, appears to be responsible for the ultimate retention of sodium in congestive heart failure,1, 2, 3 the exact mechanism whereby the adrenal cortex is stimulated to secrete this steroid is not known. It is entirely conceivable that following cardiac and circulatory failure, an altered physicochemical balance of certain vital cells may initiate the train of events leading to excessive aldosterone secretion and hence to sodium retention.

Disturbances in cellular metabolism of fluid and electrolytes in congestive cardiac failure have been demonstrated previously by indirect balance methods4, 5, 6, 7, 8, 9 and by direct tissue analysis.10, 11, 12, 13 These studies have shown consistent cellular depletion of potassium and frequent cellular depletion of sodium. In most instances the cells also appeared to be overhydrated with water.4, 7, 8, 11 These changes were described in high-output failure (beri-beri),5 as well as in the usual low-output failures.

In order to determine the disturbances of cellular metabolism in various types of heart failure, a case of cor pulmonale and a case of cor pulmonale with hypertensive heart disease were studied metabolically during recovery and the results were compared with those obtained in three other cases of etiologically more common cardiac disorders. A gain in cellular potassium and sodium and inactivation of cellular base were demonstrated in these studies.

Methods

Precise metabolic balance studies for sodium, potassium, chloride, magnesium, nitrogen and water were conducted for a total period of nine days in three cases (J. B., cor pulmonale; J. H., cor pulmonale and hypertensive heart disease; and S. L., rheumatic and hypertensive heart disease) during regression of their edema. Two other patients (A. M. and J. N.) were studied in a similar manner for all of the above components except chloride. Intake of food was limited to a special 50-mg sodium diet, previously described.4 The exact composition of this diet was determined by direct analysis of the individual components in the final preparation. Each lot of Lonalac powder used in the preparation of the diet was analyzed. An identical tray of food was analyzed during the last four days of study in case 5 (J. N.). Urine was collected and analyzed daily. Stools were pooled for two or three days and the studies were divided into periods of two or three days each. The amount of water drunk by the patients was measured to account for the magnesium present in tap water (0.6 mEq. per liter). Venous blood samples were obtained at the beginning of each metabolic period and at the end of the study.

* The composition of Lonalac used in this study varied somewhat from that used in the previous study because of slight changes in the preparation of this product.
Analyses for sodium and potassium were done by flame photometry. Chloride was determined titrimetrically. Nitrogen was analyzed by the macro-Kjeldahl method and magnesium was determined by spectrographic and colorimetric methods.

Calculations were made for intracellular and extracellular partition of water and electrolytes, according to methods described by Darrow and Elkinton. The final extracellular volume was taken at 16 per cent of the final weight and the changes in extracellular volume were calculated backward to the beginning of each period, utilizing the plasma chloride level and chloride balance. The nonchloride space was considered to represent intracellular space, including bone tissue, but excluding collagenous connective tissue. The osmolar activation of cellular base was calculated from the total balance of osmotically active bases corrected for the external balance of the bases. The total osmotically active base at the end of the study was calculated as being equal to the product of the total body water, assumed to be 66 per cent of the final body weight, and the total osmotically active base concentration, determined to be equal to the sum of concentrations of plasma sodium, potassium and magnesium plus 2.5 mM. per liter for calcium. Since the nitrogen balances were near equilibrium, corrections for water, potassium and magnesium balances due to changes in protein metabolism were not made.

Cardiac, pulmonary, and renal hemodynamic studies in the patient with cor pulmonale were determined by cardiac catheterization technic.* Renal clearances of inulin and sodium paraaminohippurate were performed in the usual manner with a catheter in the right renal vein for determination of true renal plasma flow.

**Case Reports**

Case 1, J. B. (29106). This 51-year-old white man was admitted because of severe peripheral edema and moderate dyspnea, recurrent for two years. These manifestations were progressive and refractory to treatment for the past four weeks. There was a history of chronic cough, productive of a large amount of sputum, for 20 years prior to admission. Examination showed a patient with marked peripheral edema and moderate dyspnea. The mucous membranes were cyanotic and the neck veins were distended. The chest cage was expanded and hyperresonant to percussion. Coarse rales were audible throughout both lung fields. Examination of the heart showed right ventricular hypertrophy. The liver was moderately enlarged, but there was no ascites. X-ray films of the lungs showed marked pulmonary fibrosis and probable chronic bronchiectasis. The electrocardiogram was diagnostic of right ventricular hypertrophy. The venous pressure was 192 mm. of saline and the arm-to-tongue circulation time, using Decholin, was 26 seconds. The blood hemoglobin was 16.7 Gm. per 100 cc. and the white blood cell count was 9,000 per cubic millimeter. The urinalysis was negative and the blood urea nitrogen was 22 mg. per 100 cc. The plasma carbon dioxide content was 80 volumes per cent. The circulating plasma volume, using T-1824 dye, was 3,602 ml. and the blood volume was 6,880 ml. Cardiac and renal-vein catheterization was performed before and after evacuation of edema fluid (table 1). The findings established the diagnosis of congestive heart failure, due to chronic cor pulmonale. Metabolic studies were conducted for a period of nine days with three periods of three days each (tables 2 and 3). During the study the patient lost 7.2 Kg. of weight; there was no further loss after the study.

Case 2, J. H. (69228). This 67-year-old white man developed progressive shortness of breath, paroxysmal nocturnal dyspnea and peripheral edema approximately four months prior to admission. He was told that he had hypertension one year previously. Patient complained of a mildly productive cough of one year's duration. Examination revealed an undernourished patient with orthopnea, dyspnea and moderate peripheral edema. The temperature was 98 F., pulse 70 per minute, respirations 22 per minute, and blood pressure 162/90. The fundi showed changes compatible with mild hypertension. The neck veins were considerably distended. The chest was markedly emphysematous and coarse ronchi were heard throughout. There were both right and

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* Cardiac catheterization studies were made with the aid of Dr. Harper K. Hellemes and his staff.
left ventricular hypertrophy, rapid auricular fibrillation, and a harsh systolic apical murmur. The liver was enlarged 5 cm. below the right costal margin, but was not tender. Clubbing of the finger tips was present, but cyanosis was not noted. Urealysis showed 1 plus albuminuria and occasional white blood cells in the sediment. The plasma carbon dioxide content was 55 volumes per cent, blood urea nitrogen 25 mg. per 100 cc., serum albumin 3.4 Gm., and globulin 2.5 Gm. per 100 cc. Blood hemoglobin was 16.1 Gm. per 100 cc., and the hematocrit 58.55 per cent. Circulating plasma volume was 3,353 ml., and blood volume 7,310 ml. Pneumococci (group E) were recovered from the sputum. Roentgenogram and fluoroscopic examination of the chest showed both right and left ventricular enlargement, pulmonary congestion, and chronic pulmonary emphysema. The electrocardiogram showed auricular fibrillation and left ventricular hypertrophy. The venous pressure was 195 mm. saline and the circulation time 90 seconds. It was felt that the patient had cardiac decompensation from chronic cor pulmonale and hypertensive heart disease. The patient was digitalized and started on metabolic studies, using a synthetic 50 mg. sodium diet. There was a 3.5 Kg. weight loss and moderate improvement of dyspnea and edema. After completion of the studies, there was an additional weight loss of 8.0 Kg.

Case 3, S. L. (12116). This 36-year-old white woman was admitted with severe congestive heart failure for the third time in one year. Shortness of breath, followed by peripheral edema, was first noted three years earlier, at which time she was discovered to have hypertension and rheumatic heart disease. The examination revealed an orthopenic dyspneic patient with moderately severe peripheral edema. The heart was enlarged both to the right and left and revealed the characteristic murmurs of mitral insufficiency and stenosis. There was also a murmur of tricuspid insufficiency with a pulsatile liver. Rales were audible at both lung bases. The blood pressure was 234/140. The venous pressure was 256 mm. saline and the arm-to-tongue circulation time 53 seconds. The patient was placed on the synthetic low sodium (50 mg.) diet for nine days and Mercuhydrin was given on the second, fifth and eighth days. The patient lost 3.8 Kg. during the study and 4.9 Kg. more after the study.

Case 4, A. M. (68415). A 59-year-old white man was admitted because of peripheral edema and dyspnea on exertion, gradually progressive for the previous two months. Examination showed temperature 98.6 F., pulse 92 per minute, respirations 24 per minute, and blood pressure 148/118. The fundi showed grade II hypertensive changes. The discs showed secondary optic atrophy. Neck veins were distended. Marked enlargement of the heart was noted and a harsh grade II systolic murmur was heard over the mitral area. Bilateral basal rales were present and the liver was enlarged 5 cm. below the costal margin. The extremities showed marked
edema. The venous pressure was 207 mm. saline and the circulation time 64 seconds. Circulating plasma volume was 4,471 ml. and blood volume 8,003 ml. The blood urea nitrogen was 32 mg. per 100 cc., serum albumin 3.1 and globulin 2.4 Gm. per 100 cc., plasma carbon dioxide content 53 vol. per cent, and fasting blood sugar 72 mg. per 100 cc. The blood hemoglobin was 13.3 Gm. per 100 cc. The electrocardiogram showed left ventricular hypertrophy. A diagnosis of hypertensive heart disease with congestive heart failure was made and the patient was studied for nine days, during which time there was a weight loss of 16.9 Kg. No further loss occurred after the study. The venous pressure at the end of the study was 61 mm. saline and the circulation time 25 seconds.

Case 5, J. N. (24063). This 62-year-old white man was admitted because of paroxysmal nocturnal dyspnea and peripheral edema. These symptoms were first noted one year previously, but did not recur until one week before admission. The patient had also noted intermittent claudication for the past year. Examination showed an orthopneic edematous patient with a blood pressure of 190/95, temperature 98 F., pulse 85 per minute and respirations 20 per minute. Fine rales were present in both lungs. The heart was enlarged to the anterior axillary line and a to-and-fro murmur was heard in the aortic area. Pulsations of the dorsalis pedis artery were weak. The roentgenogram of the heart showed an enlarged left ventricle and an aneurysmal dilatation of the ascending aorta with calcific deposition in this segment. The blood serology was positive for syphilis, blood urea nitrogen 19 mg. per 100 cc., and serum albumin 3.8 and globulin 1.8 Gm. per 100 cc. Diagnoses of hypertensive and syphilitic heart disease with congestive heart failure and atherosclerosis obliterans were made and the patient was studied metabolically for eight days for sodium, potassium and magnesium balances. There was a total weight loss of 2.6 Kg. during the study.

RESULTS OF THE METABOLIC STUDIES

The results of the metabolic studies carried out during recovery from congestive failure in the proven case of cor pulmonale and in the other four cases are presented in table 2. The derived values for intracellular and extracellular changes in the first three cases are presented in table 3.

Changes in Sodium Metabolism

As would be expected, sodium was eliminated in considerable quantities. The total external balance in the case of cor pulmonale (case 1) amounted to -816.6 mEq. during the nine-day period of study, with most of the sodium being eliminated during the first six days. A total of -643.1, -600.4, -1,781.9 and -466.9 mEq.
of sodium was lost externally by cases 2, 3, 4 and 5, respectively. Calculations possible only in the first three cases showed that the amount of sodium lost externally was less than the calculated loss of sodium from the extracellular compartment. A significant quantity of sodium thus entered a nonchloride space (presumably the cell) during the period of recovery, 849.8 mEq. in case 1, 172.1 mEq. in case 2, and 213.9 mEq. in case 3.

Changes in Potassium and Magnesium Metabolism

A slight, but distinctly positive, balance of potassium, +74.6, +123.0, +73.5, +41.9, and +153.6 mEq., was observed in cases 1 to 5, respectively. Since there was some loss of potassium from the shrinking extracellular space, the total positive intracellular balance in those cases in which calculation was possible was slightly greater than the observed external balance. Case 1, with cor pulmonale, showed a positive intracellular potassium balance of +120.4 mEq.; case 2, +139.3 mEq. and case 3, +101.6 mEq.

A positive balance of magnesium was observed in cases 1, 2 and 5, but a negative balance was seen in cases 3 and 4.

Changes in Water Metabolism

Total loss of water, as judged by loss of weight during the eight- to nine-day period, varied from 2.6 to 7.2 Kg. Calculations in the first three cases indicated a loss of extracellular water amounting to −10.9, −5.2 and −5.3 L., and a slight gain of intracellular water of +3.7, +1.7 and +1.5 L. in cases 1, 2 and 3, respectively.

Osmotic Activation of Intracellular Base

The net change of total osmotically active base, corrected for external balances of sodium, potassium and magnesium, will determine the net changes in osmotically active intracellular base, since electrolytes in the extracellular fluid are, for practical purposes, osmotically completely active. A net change with a negative value will imply inactivation of the cellular base and a positive value will indicate activation of the cellular base elements.

In all five cases a distinctly negative value of osmotic activity was obtained, −738.1, −201.9 −146.1, −836.6 and −67.5 mM, respectively.

Discussion

The diagnosis of chronic cor pulmonale in congestive heart failure in case 1 was made clinically from the history and physical signs, and was established by cardiac catheterization, with the findings of a normal pulmonary “capillary” pressure, an elevated pulmonary artery, right ventricular end-diastolic, right auricular and renal vein pressures, a relatively normal cardiac index, and an oxygen-desaturated arterial blood. Following diuresis and weight loss of 7.2 Kg., evidence of right ventricular failure disappeared, but the pulmonary artery pressure remained elevated. The cardiac index rose to a supernormal level, compatible with the diagnosis of chronic pulmonary disease with cor pulmonale. The total oxygen consumption of 235.2 ml. per minute, the absence of a purulent sputum, and the absence of fever or leukocytosis ruled out the possibility of a superimposed acute infection complicating the picture of cor pulmonale. It is interesting to note that renal hemodynamic studies showed a glomerular filtration rate within the normal range at the height of congestive heart failure and an almost identical filtration rate after recovery from failure. Observations, such as this, indicate that tubular activity is more important in the pathogenesis of sodium and water retention than changes in glomerular filtration rate.

Metabolic studies carried out on this patient revealed, in addition to extracellular evacuation of sodium and water, a cellular uptake of all three electrolytes, sodium, potassium and magnesium (1,007 mEq. or 988.5 mM total), far in excess proportionately to the gain in cellular water (3.7 L.). The fluid entering the cells was thus hypertonic and composed of cations in a concentration of 262 mM. per liter, with the sodium ion comprising the major share (230 mM. per liter). Comparison of cases 2 and 3 with case 1 revealed a qualitative similarity in regard to the fluid entering the cell during recovery, but the concentration of
Electrolytes during recovery from heart failure

Cations was not as high (195 mM per liter in case 2 and 174 mM per liter in case 3) and the concentration of sodium was decidedly lower (101 mM per liter in case 2 and 142 mM per liter in case 3). The greater propensity for gain in cellular sodium found in case 1 could have been due partly to the nature of the underlying disease responsible for congestive failure, since it has been shown recently that acidosis of respiratory origin is buffered to a significant degree by the emergence of base from the intracellular compartments. If such a mechanism had been operating in case 1 during development of congestive failure, it would be relatively simple to explain the greater uptake of sodium by the cells, coincident to improvement in the cardiopulmonary function.

Apparently emergence of magnesium from the cells during recovery from congestive failure was not responsible for migration of sodium and potassium into the cells, since in three of the patients a positive magnesium balance was observed. In two patients a negative balance was found. In case 3, the negative balance was caused primarily by loss of magnesium in the stools, as well as by periodic loss of magnesium in the urine, following Mercuhydrin injections. Whether or not Mercuhydrin contributed toward excess fecal loss could not be determined from the data on hand. The external loss of magnesium in this patient was accompanied by a fall in the serum magnesium to subnormal levels, a phenomenon frequently observed during rapid mercurial diuresis. A negative balance of magnesium observed in case 4 was apparently not due to Mercuhydrin, since the patient had received no diuretic agents. Urinary loss of magnesium, however, was quite considerable. In this particular case, the negative balance of magnesium could have reflected the elimination of magnesium retained by renal decompensation prior to the onset of study. The volume of urine or the total weight of the stools appeared to have no definite influence on the loss or gain of magnesium during recovery from cardiac failure. If these two cases (cases 3 and 4) with a negative magnesium balance are regarded as exceptions to the rule because of interfering factors, it can be concluded that a positive magnesium balance occurs during recovery from congestive heart failure.

Movements of water and cations in all three cases were such that the intracellular osmolarity tended to increase during recovery from congestive failure. Since osmotic equilibrium between the cells and the extracellular fluid can be assumed to be maintained at all times, any tendency toward a rise in intracellular osmolarity would necessitate either a rise in osmolarity of the intracellular fluid, migration of water into the cells, or an osmotic inactivation of the free base residing within or entering the cells. Since the osmolarity of the extracellular fluid tends to fall during recovery from congestive failure, the first two possibilities appear unlikely. Measurements made according to the method of Elkinton consistently showed inactivation of intracellular base in all five cases during recovery from failure. The relative magnitude of this change with respect to total weight loss was the greatest in case 1, suggesting again the possibility of some effect conditioned by decompensated respiratory acidosis.

The question of whether migration of sodium and potassium into the cells (possibly in exchange for hydrogen ions) had caused inactivation of cellular base, or whether the inactivation of cellular base had occurred first and had caused transfer of sodium and potassium into the cells, remains problematic. There is no reason to doubt that both events could have occurred simultaneously in a given patient recovering from congestive heart failure. Transfer of water in the first situation would be into the cells and in the second situation, out of the cells. With both events taking place simultaneously, the direction of transfer of water would depend upon the more prominent factor. Of the three cases in which calculations of water transfer were possible, patient J. B. (case 1), showing 3.7 L net gain of cellular water, had severe respiratory acidosis, as well as congestive failure. Correction of the acidosis may have resulted in migration of additional sodium and potassium back into the cells, causing iso-
osmotic transfer of water in the same direction. The magnitude of this transfer during recovery may have been so great as to overcome the tendency for water to leave the cell, due to primary inactivation of the intracellular base. The small net transfer of water into the cells in case 2, with hypertension and cor pulmonale, may also have been influenced by a low grade respiratory acidosis, which could not be demonstrated in the plasma carbon dioxide content. In case 3, mercurials were used frequently, so that shifts of water during recovery do not necessarily represent correction of an altered intracellular balance. A positive balance of intracellular water was also seen during recovery in one of the three beriberi cases studied previously. Minor changes in intracellular water were likewise seen in three of the seven cases previously studied, who had less than 3 Kg. of total fluid loss. In general, only patients with marked fluid loss (greater than 8 Kg.) during recovery from uncomplicated congestive heart failure show a significant loss of intracellular water. It is very probable that certain factors other than that associated with recovery from congestive heart failure per se may account for the uptake of water by the cells.

It would seem from these studies that the metabolic changes in congestive heart failure due to chronic cor pulmonale are essentially the same as in failure due to other causes. The cells appear to be deficient rather than overladen with water and depleted of more sodium, presumably due to complicating respiratory acidosis.

The exact mechanism for retention of sodium and water progressing to cardiac edema remains obscure, but the intrinsic osmotic activation of cellular base following cardiac and circulatory failure may in some way set in motion the train of events leading to this clinical condition. It is postulated that the increase in osmolarity of the cells and, temporarily, the relative decrease in osmolarity of the extracellular fluid provoke aldosterone activity to sodium retention, whereas the increase in osmolarity of the cells or the obligatory increase in osmolarity of the extracellular fluid provoke antidiuretic activity and water retention.

Summary

Five cases of congestive heart failure were studied metabolically during recovery. One unequivocal case and one probable case of cor pulmonale showed cellular uptake of sodium, potassium and magnesium and inactivation of cellular base in a manner similar to heart failure due to other causes. Cellular uptake of water during recovery, calculable in three cases, was contrary to previous findings, but was explainable by the greater than usual uptake of cations by the cells associated with chronic pulmonary insufficiency or by the frequent use of mercurial injections. The pathogenesis of congestive cardiac edema is discussed.

Acknowledgment

We are grateful to Drs. Clayton Shors and David Young and to Mrs. Maxine Adams, Mrs. Nancy Davenport and Mrs. Juanita Maxwell for their valuable assistance in conducting this study.

SUMMARIO IN INTERLINGUA

Cinque casus de congestive disfallimento cardiae esseva studiate metabolicamente durante le periodo del recuperation. Un casus inequivoce e un alte probable de corde pulmonal monstrava un reception cellular de natrium, kalium, e magnesiu e un inactivation del base cellular que esseva simile a correspondentemente phenomenos in casus disfallimento cardiae debite a alte causas. Le reception cellular de aqua durante le periodo de recuperation esseva calculate in tres casus e non se trovava de accordo con previe constatazioni. Iste discrepantia esseva explicable per le reception supra-usual de cationes in le cellulas que es associate con chronic insufficiencia pulmonar o per le frequente uso de injeciones mercuriale. Es discutite le pathogeneze de congestive edema cardiae.

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Circulation. 1955;12:1057-1064
doi: 10.1161/01.CIR.12.6.1057

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