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Research Article

ELECTROLYTES IN HUMAN TISSUE. III. A COMPARISON OF NORMAL HEARTS WITH HEARTS SHOWING CONGESTIVE HEART FAILURE[1]

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Previous studies from Vanderbilt Medical School (Harrison, Pilcher and Ewing, 1930) (Calhoun, Cullen, Clark, and Harrison, 1930) have shown that the potassium content of heart muscle may be diminished in persons dying with congestive heart failure. The present study was planned to investigate the concentration of other important electrolytes under the same conditions and in normal hearts, i.e., hearts from persons killed in accidents. However, when the pathologic reports were analysed it was found necessary to divide the material into three groups—(1) Normal hearts; (2) an intermediate group of hearts from fatal accidents which show pathologic evidence of cardiac disease; and (3) hearts from persons dying with congestive heart failure. See Table I.

Seventeen hearts, 5 in Group 1, 4 in Group 2, and 8 in Group 3, were analysed for water content, calcium, magnesium, phosphorus, potassium and sodium.

The methods used in this study are those described elsewhere (Cullen and Wilkins, 1933). Special precautions were taken to determine accurately the water content of the tissues. The samples, which were shipped, were sealed in air-tight bottles, and any liquid which came out of the tissues during transit was included in the entire sample which was weighed and dried.

RESULTS

The determined values, in most cases based on duplicate analyses, for water, total phosphorus, potassium, sodium, calcium and magnesium are given in terms of wet muscle in Table II. In order to compare the osmotic relationship of the electrolytes in the tissue, the results were calculated to milliequivalents per kilo tissue water, as was done by Van Slyke, Wu and McLean (1923) for blood electrolytes. In this

[1] The experimental data in this report are taken from a thesis submitted by Walter E. Wilkins in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of Vanderbilt University.

TABLE I

Individual case data

Case number	Sex	Age	Heart weight	Chief diagnosis and cause of death
		years	*grams*	
Group 1				
1	M	34		Bullet wound of abdomen; hemorrhage; heart normal
2	M	24	400	Bullet wound of head; heart normal
3	M	25	265	Fracture of skull; ruptured liver and kidney; heart normal
4	M	33	400	Bullet wound through lungs and heart; heart normal
5	M	25		Bullet wound of abdomen; hemorrhage; heart normal
Group 2				
6	M	38	535	Fracture of skull
7	M	31		Bullet wound of abdomen; hemorrhage
8	M	49	450	Lacerations of head; dislocation of hip; (chloroform anesthesia) toxic hepatitis; myocardial hypertrophy; generalized arteriosclerosis
9	M		400	Multiple comminuted fractures of the pelvis; hemorrhage; alcoholic intoxication; generalized arteriosclerosis
Group 3				
10	M	25		Myocardial hypertrophy and dilatation; adhesive pericarditis
11	M	33	770	Myocardial hypertrophy and dilatation; syphilitic aortitis and insufficiency
12	F	23	450	Myocardial hypertrophy and dilatation; syphilitic myocarditis
13	M	72	400	Myocardial hypertrophy; generalized arteriosclerosis
14	M	40	860	Myocardial hypertrophy and dilatation; generalized arteriosclerosis
15	F	45	740	Myocardial hypertrophy and dilatation; generalized arteriosclerosis
16	M	69	550	Myocardial hypertrophy and dilatation; generalized arteriosclerosis
17	M	55	800	Myocardial hypertrophy and dilatation; generalized arteriosclerosis

calculation one millimol of phosphorus is considered one milliequivalent (see Peters and Van Slyke (1931), p. 1102). The average, maximum and minimum values for the several elements are summarized in Table III. In addition, in this table, is given a similar summary based on dry weight because much of the previous work has been reported in dry weight.

Water

Domagk (1924) and Scott (1931-*a*) have shown that the water content of the left ventricles of persons who died of tuberculosis was greater than that of the left ventricles of persons dying from a variety of other diseases. Apparently neither of these workers determined the water content of the right ventricles. Scott (1930, 1931-*a*) found no difference in the average water content of the left ventricles of cardiac heart and that from a number of persons who died from other diseases.

TABLE II

Inorganic constituents of ventricles of normal and diseased hearts

Case number	Right ventricle						Left ventricle					
	Per 100 grams wet tissue											
	H_2O *grams*	P *mgm.*	K *mgm.*	Na *mgm.*	Ca *mgm.*	Mg *mgm.*	H_2O *grams*	P *mgm.*	K *mgm.*	Na *mgm.*	Ca *mgm.*	Mg *mgm.*
Normals												
1	80.1	203	229	96	8.2	21.8	78.1	242	324	73	6.6	23.2
2	80.4	164	259	133	9.3	18.2	79.5	184	280	114	9.5	18.8
3	76.9	180	285	111	7.5	20.3	78.0	199	325	98	6.3	20.4
4	81.2	142	220	112	7.0	16.4	80.1	179	302	97	6.2	15.6
5	77.6	195	280	83	5.9	22.3	78.8	213	326	76	6.0	22.6
Average	*79.2*	*177*	*255*	*107*	*7.6*	*19.8*	*78.9*	*203*	*311*	*92*	*6.9*	*20.1*
Intermediate												
6	80.9	137	205	148	8.2	15.0	79.8	177	262	118	6.3	18.6
7	83.7	159	201	181	6.2	14.6	80.9	213	332	106	6.4	20.2
8	83.0	146	178	130	9.2	15.7	80.3	154	217	81	6.4	16.5
9	79.0	146	203	138	9.4	15.8	78.9	197	326	101	6.9	19.4
Average	*81.7*	*147*	*197*	*149*	*8.3*	*15.3*	*80.0*	*185*	*284*	*102*	*6.5*	*18.7*
Cardiacs												
10	82.0	143	223	129	6.4	15.1	82.1	149	237	128	5.6	15.4
11	82.3	152	209	155	5.4	13.8	80.4	178	226	115	4.4	15.7
12	83.6	122	134	186	8.9	11.6	81.9	142	209	154	6.7	14.0
13	82.9	150	174	153	9.9	14.6	81.5	176	236	132	10.9	15.6
14	82.4	142	180	147	7.2		80.4	173	277	92	5.6	
15	81.4	145	181	148	5.5		79.1	170	248	102	5.0	
16	78.2	158	235	120	8.7	14.6	78.9	185	325	94	7.1	18.0
17	79.3	183	265	101	4.5	18.5	79.4	188	303	100	4.4	16.3
Average	*81.5*	*149*	*200*	*142*	*7.1*	*14.7*	*80.5*	*170*	*258*	*115*	*6.2*	*15.8*

In the present study there is no evidence from the 5 normal hearts of a consistent variation in water content between right and left ventricles, but for the diseased group there is a definite tendency for each right ventricle to have a higher water content, by about 1 per cent, than that of the left from the same heart. Moreover, the heart from persons dying with congestive heart failure showed an average of about 2.3 per cent more water in the right ventricles and about 1.6 per cent more in the left ventricles than did the normal hearts. These changes stand out more emphatically when stated in terms of percentage solids. This

TABLE III

Averages of inorganic constituents of ventricles calculated on basis of dry-weight and of tissue water

Group	Mgm. per 100 grams dry tissue		m. Eq. per kilo tissue H_2O	
	Right ventricle	Left ventricle	Right ventricle	Left ventricle
		Phosphorus		
Normal average	852	962	72	83
Intermediate average	811	926	58	74
Cardiac average	808	870	59	68
		Potassium		
Normal average	1225	1475	83	100
Intermediate average	1081	1422	61	91
Cardiac average	1075	1314	63	82
		Sodium		
Normal average	521	436	58	51
Intermediate average	828	508	79	55
Cardiac average	786	594	76	62
		Calcium		
Normal average	36.9	32.7	4.8	4.4
Intermediate average	45.0	29.9	5.1	4.1
Cardiac average	38.8	33.4	4.3	3.9
		Magnesium		
Normal average	95.4	95.0	20.6	21.0
Intermediate average	84.0	93.5	15.4	19.2
Cardiac average	79.0	82.0	14.9	16.2

means a decrease from normal of 11 per cent of the total solids in the right ventricles and of 7.5 per cent in the left ventricles. Apparently the right ventricle shows a greater susceptibility to increase in water content or decrease in solids than does the left ventricle.

This is in agreement with the findings of Calhoun, Cullen, Clarke and Harrison (1930) who found that right and left ventricles in patients who died with congestive heart failure showed an increase in water content over the hearts of patients who died from a variety of other diseases. It is also of interest to note that the two right ventricles which contained the most water were also high in sodium. Of these, one showed also the lowest potassium content on any basis of calculation. This right

ventricle (case number 12), was also the lowest in magnesium and phosphorus per unit of wet weight. These facts indicate a definite tendency toward edema in diseased heart muscle, especially that of the right ventricle.

Phosphorus

The figures for phosphorus represent total phosphorus in each case; no attempt was made to determine the phosphorus fractions.

Scott (1931-*a*) reported a large series of phosphorus determinations on the left ventricles of persons who died with a variety of diseases and a group who died of tuberculosis. The following is a summary of his values:

	Maximum	Minimum	Mean
	mgm. per 100 grams of fresh tissue		
General diseases	233	139	176
Tuberculosis	193	129	153

In the present normal group the left ventricles contained an average of about 15 per cent more phosphorus than did the right. In the group of persons who died with congestive heart failure the left ventricles contained an average of about 14 per cent more phosphorus than the right. Both the right and left ventricles of the persons who died with congestive heart failure contained an average of about 16 per cent less phosphorus than did the corresponding ventricles of the normal group. These findings are in agreement with those of Laszlo (1928) who noted a decreased amount of phosphorus in the skeletal and cardiac muscles of persons who died with cardiac disease.

Potassium

In this study the individual left ventricles of each group showed without exception a higher concentration of potassium than did the right. This contrasts with the fact that the left ventricles of each group without exception showed a lower content of sodium than did the right. One case with extreme congestion of the lungs showed very low values for potassium and high values for sodium in both ventricles, but especially in the right.

When these values are expressed in milliequivalents per kilo of muscle water, the total concentration of sodium plus potassium in the right ventricles is of the same order as that of the left ventricles.

The hearts of individuals who died with congestive heart failure were poorer in potassium and richer in sodium than those of the normal control group. The figures show that there was some degree of overlapping, but the averages show a definite and appreciable difference.

This is true when the concentrations are expressed in milligrams per 100 grams of fresh tissue, milligrams per 100 grams of dried tissue, and in milliequivalents per kilo of tissue water.

These findings, in respect to potassium, confirm, with a different analytical method, those of Harrison, Pilcher and Ewing (1930), and those of Calhoun, Cullen, Clarke and Harrison (1930). The latter authors believe that overwork causes loss of potassium from cardiac muscle and that this loss is one of the predisposing factors to cardiac fatigue and failure. They also studied a number of different tissues from individuals who died of a variety of diseases, and suggest that potassium loss in congestive heart failure is not confined to the heart and skeletal muscle, but apparently holds for several other types of tissue. Later Calhoun, Cullen and Harrison (1930) found that overwork of the muscles of one leg of dogs, produced by continual stimulation of the sciatic nerve causing the leg to lift a weight, usually leads to a diminished content of potassium in the muscles as compared with those of the opposite unstimulated leg.

Harrison, Pilcher, and Ewing (1930) suggested the possibility that loss of potassium from the heart muscle is compensated for by an increase in one or more of the other basic elements. The present study shows that there is a "compensation" by sodium.

Scott (1931-*b*) who has made the most extensive study of the inorganic substances in human left ventricle heart muscle, failed to find a significant diminution of potassium in the left ventricles of persons who died of congestive heart failure compared with the left ventricles of persons who died from a variety of other diseases. He found highly variable amounts of both sodium and potassium in both groups. His average values for potassium in the left ventricle are much lower than those of other authors, including ourselves.

The discrepancy between Scott's values (1931-*b*) for potassium and the present results has been disturbing. The possibility that this is due to a difference in ashing is suggested by the following observations: When the present investigation was begun, a number of tissues were ashed in somewhat the same manner as were those of Scott, and results for potassium similar to his were obtained. These results were low as compared with the previous studies in this laboratory, and the ashing technic was scrutinized. It was found that if ashing were done in the muffle furnace without H_2SO_4, the potassium values were low. When a small amount of H_2SO_4 was added before ashing the duplicate ashings gave potassium figures which were higher, which checked closely, and which were within the range of those previously obtained when the wet ashing technic was used. Blanks were, of course, run under both sets of conditions.

In a more recent study with an improved method Scott (1931-*c*) reported much higher values for potassium in the left ventricles of a large number of hearts than he reported in the three previous studies. These later values are more nearly within the range of ours.

Sodium

Few figures are available on the sodium content of the various soft tissues, although its concentration in the blood has been the object of numerous investigations.

In the human, sodium appears to be present in much greater concentrations in the extracellular fluids than in any of the cells. In this respect it differs from potassium and magnesium, which appear in greater concentrations in the cellular structures. Of the anions, chloride appears to vary with sodium, while phosphate varies with potassium.

Loeb, Atchley and Palmer (1922) have shown that edema fluids may contain approximately the same concentration of sodium as blood serum. It follows that even a slight increase in the water content of a tissue may be accompanied by an appreciable increase in sodium.

In the present study the sodium content of the right and left ventricles of seventeen human hearts was determined. In all seventeen cases, with two exceptions, the right ventricles contained decidedly more sodium than did the left ventricles. In every instance, the opposite was true of potassium.

In both ventricles the normal hearts showed a higher average content of potassium than did the corresponding ventricles of persons who died with congestive heart failure. Just the reverse was the case with sodium. There was some overlapping with reference to sodium as well as with potassium, but most of the individual cases, as well as the averages, showed a definite increase in the sodium content of both ventricles of the persons who died with congestive heart failure.

The four left ventricles which had the highest potassium content showed the lowest values for sodium.

Scott (1930) reported a number of instances in which the normal K/Na ratios were almost reversed in the left ventricle. We found some tendency toward such a reversal in both ventricles of several persons who died with congestive heart failure, but found no such change in any heart in the normal group.

Scott's averages for the sodium content of the left ventricles are higher than those yielded by the present study. In view of the fact that his values for sodium were calculated by difference, his higher figures for this element may have been due to his failure to recover all of the potassium. This point has been discussed in the section on potassium.

Calcium and magnesium

Although the significance of changes in calcium concentration in the blood has been studied intensively, little is known concerning changes of calcium in tissue. Little is known concerning the importance of magnesium in either blood or tissue. Magnesium is essentially a tissue cation, calcium is in greater concentration in serum and other extracellular

fluids than it is in most soft tissues. Katz showed that human skeletal muscle contained about 7.5 mgm. per cent of calcium and 21 mgm. of magnesium per 100 grams fresh muscle. On a basis of milliequivalents this gives a Ca : Mg ratio of about 1–4. Scott found in the left ventricles of 14 hearts from patients with general disease an average of 8 mgm. of calcium and 17.4 mgm. of magnesium per 100 grams fresh tissue and in 14 hearts from patients dying with tuberculosis 9.0 mgm. calcium and 16 mgm. magnesium.

In another study (Cullen, Wilkins and Harrison (1933)) we found in autopsies from general disease that the right ventricles average 7.3 mgm. per cent of calcium and 18.4 mgm. per cent magnesium, and the left ventricles averaged 6.4 mgm. per cent calcium and 21 mgm. per cent magnesium. In the present study 15 of the 17 hearts show slightly less calcium and more magnesium in the left ventricle than in the right.

The variation in calcium content in both normal and diseased hearts is so great that, with the small number of cases, it is impossible to state whether or not there is less calcium in the diseased heart than in the normal. There is a tendency for the abnormal hearts to show a decrease in calcium proportional to the decrease in total solids which suggests that the calcium is related to the tissue protein in the same manner that it is related to serum protein. Scott, however, found no significant difference between the calcium content of the left ventricles of patients dying of heart failure and of those dying from other diseases.

In most cases the hearts showing cardiac disease have a decidedly lower magnesium content than do the normal hearts.

In general the variations of magnesium content parallel those of potassium and phosphorus.

GENERAL DISCUSSION

Total base determinations, as such, were not made on this group of tissues, but were calculated from the values for the individual bases. We found, in a former study, that some calcium and magnesium failed to come through during the removal of phosphate by the method of Stadie and Ross (1925). This fact has also been noted by Brown and Shohl (1931).

In all of the normal group the concentration of total bases (in milliequivalents per kilo of tissue water) was higher in the left ventricle than in the right, but both were within the same general range.

The right ventricles of the normal hearts show an average of 167 and the left ventricles an average of 176 milliequivalents per kilo of tissue water. The hearts from persons who died with congestive heart failure contained an average of 159 milliequivalents per kilo of tissue water in the right ventricles and 166 in the left. Thus the latter group showed in both ventricles a slight diminution in total base as compared with the normal controls.

Van Slyke, Wu and McLean (1923) have pointed out that the osmolar concentration of total electrolytes in the water of blood plasma and cells is practically equal despite the differences in the concentrations of the individual ions. They found, in a typical case, 162 milliequivalents of base per kilo of serum water and 174 per kilo of red blood cell water. Gamble, Ross and Tisdall (1923) have expressed the belief that this close relationship holds also for the cell water of muscles and probably for other tissues of the body. The present results support this view.

The total electrolyte concentration in the tissue is of importance in relation to the osmotic conditions existing there. Although the data given above do not give any direct evidence as to the cause of the shift in diseased tissue, it is significant that it is precisely what would be expected if the permeability of the tissue were increased. Then sodium would diffuse into the tissue cells from its higher concentration in extracellular fluids, and potassium, magnesium and phosphates would diffuse out from their higher concentration in the cells. Calcium, approximately equal in all fluids, would show little change. The relations between potassium, phosphorus and sodium are shown graphically in Figure 1. It is at once apparent that potassium and phosphorus parallel each other and that sodium fluctuates regularly in the opposite direction to potassium and phosphorus.

The question of the ratio of the individual elements to each other is of course important and the average ratios of P/K and K/Na are given in Table IV.

TABLE IV

Ratio of potassium to phosphorus and sodium based on concentration per kilo tissue water

	$\frac{\text{Millimols P}}{\text{Millimols K}}$		$\frac{\text{Milliequivalents K}}{\text{Milliequivalents Na}}$	
	Right ventricle	Left ventricle	Right ventricle	Left ventricle
Normal average	0.88	0.83	1.45	2.05
Intermediate average	0.96	0.82	0.78	1.65
Cardiac average	0.96	0.84	0.88	1.39

The data demonstrates unmistakably a real difference in the concentration of the important electrolytes in the two ventricles. It is important that both potassium and phosphorus, which are known to be involved in the buffer mechanism of muscle, are in the muscle which has the greatest work load. However, until the phosphorus distribution in these conditions is known, it is undesirable to speculate further.

We wish to acknowledge our indebtedness to Dr. Richard Austin of the University of Cincinnati; Drs. George M. Leiby and Kenneth M. Lynch of the Medical College of the State of South Carolina; Dr. C. W.

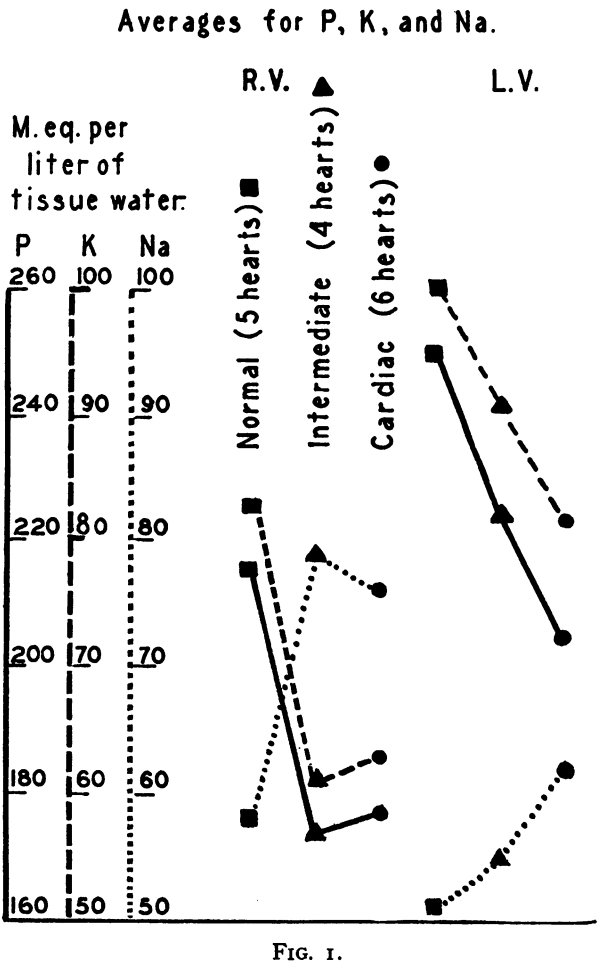

FIG. 1.

Muehlberger of the Coroner's Laboratory, Cook County Morgue, Chicago; and to the Department of Pathology of the Vanderbilt School of Medicine, for furnishing us the tissues used in this study.

SUMMARY

1. The right and left ventricles of seventeen human hearts were analyzed for water, phosphorus, sodium, potassium, magnesium and calcium. Of these hearts, five were normal, four were from persons who had cardiac disease but who died from other causes, and eight were from persons who died with congestive heart failure.

2. The water content of the diseased right ventricle tends to be slightly higher than that of the left ventricle. The water content of both ventricles of hearts from persons who died with congestive heart failure was found to be increased.

3. The normal left ventricle contains more total phosphorus and more potassium than the right. Both ventricles of diseased hearts showed a decrease in total phosphorus and potassium.

4. The normal right ventricle contains more sodium than the normal left ventricle. Sodium was increased in both ventricles of persons who died with congestive heart failure.

5. Usually the right ventricle contains a slightly higher concentration of calcium than does the left ventricle. No consistent variations were found in the calcium content of the ventricles of individuals who died with congestive heart failure.

6. Both the normal and diseased left ventricles were richer in magnesium than the corresponding right ventricles. Both ventricles of the diseased hearts showed a diminution in magnesium.

7. The sums of the individual bases when calculated in milliequivalents per kilo of tissue water show that the two ventricles do not differ essentially in their content of total base.

8. The K/Na ratio in the normal left ventricle is higher than in the normal right ventricle. Both ventricles of the diseased hearts showed a decrease in the K/Na ratio.

9. The P/K ratio was somewhat higher in the right ventricle than in the left. The diseased hearts had nearly the same P/K ratios in both ventricles as did the normal hearts, showing that the former had a proportionate decrease in phosphorus and potassium.

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