Relation of plasma aldosterone concentration to diuretic treatment in patients with severe heart disease

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SUMMARY To assess the relation of hyperaldosteronism and potassium depletion to the intensity of diuretic therapy we have measured plasma aldosterone by radioimmunoassay and total exchangeable potassium by radioisotope dilution in 24 patients when they were stable at the end of their preparation for cardiac operation.

Some patients required intensive frusemide therapy to reach an optimal state for operation and many showed hyperaldosteronism. Plasma aldosterone was significantly related to daily dose of frusemide ($r=0.77$).

Depletion of total exchangeable potassium expressed in terms of predicted weight was significantly related to plasma aldosterone ($r=-0.64$). The reduction in total exchangeable potassium is interpreted as chiefly related to loss of lean tissue mass from the wasting that leads to cardiac cachexia, but evidence is presented on the basis of measurements of extracellular fluid volume as sulphate space (20 patients) of entry of sodium into the cells which may indicate a true cellular potassium loss.

Although plasma potassium is usually easily maintained with oral potassium supplements or aldosterone antagonists, we postulate that intensive diuretic therapy in severe heart disease may provoke hyperaldosteronism which accentuates potassium loss and may contribute to wasting and to intracellular potassium depletion in critical tissue, such as myocardium.

The fluid retention which is characteristic of chronic congestive heart failure arises from a disturbance of the homeostatic control of body sodium content (Merrill, 1946), mediated in part by the renin-angiotensin-aldosterone system which produces sodium retention in the distal renal tubule at the expense of loss of potassium and hydrogen ions. Until recently the part played by aldosterone has been difficult to define, partly because of technical factors as pointed out by Nicholls *et al.* (1974) and partly because of the paradoxical effect of diuretic therapy, which in the early stages of treatment of congestive failure reduces the activity of the renin-angiotensin-aldosterone system (Laragh, 1962; Genest *et al.*, 1968; Nicholls *et al.*, 1974), in contrast to the stimulation found with diuretics in normal subjects and in patients with hypertension (Laragh *et al.*, 1972). There is also a suggestion that the activity of the renin-angiotensin-aldosterone system is increased in heart failure as part of the general increase in sympathetic activity under these circumstances (Brod, 1972; Davis, 1974). Aldoster-

one antagonists are often recommended in treatment to prevent both sodium retention and potassium loss; they may be particularly useful for chronic treatment in the dried-out state, as Nicholls *et al.* (1974) have shown that hyperaldosteronism is a major feature in patients approaching dry weight on continued diuretic treatment.

Potassium depletion shown by a reduction in total exchangeable potassium is a major feature of patients with severe heart disease on diuretic treatment (White *et al.*, 1969) and has been thought to contribute to the risks of surgical correction (Lockey *et al.*, 1966). However, more recent studies of total body potassium (Davidson *et al.*, 1976; Lawson *et al.*, 1976) measuring the natural radioisotope (^{40}K) in a total body counter suggest that tissue potassium is only slightly depleted in relation to body size. The reduction in total exchangeable potassium may be, in the main, an indication of a loss of lean body mass as part of wasting which may be occult (Walesby *et al.*, 1978) or evident in the extreme as 'cardiac cachexia', but local critical reductions in intracellular K concentration cannot

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be excluded (Hamer, 1977). The plasma potassium seems to be part of a labile component of the body potassium which varies without relation to total body stores (Croxson *et al.*, 1972; Nagant de Deuxchaisnes and Mach, 1974; Nicholls *et al.*, 1976) and cannot be used to predict potassium depletion. Plasma potassium may be relatively easily maintained by dietary supplements or aldosterone antagonists with relatively little effect on tissue potassium (White, 1970; Croxson *et al.*, 1972; Davidson and Gillebrand, 1973; Kremer *et al.*, 1977). It is important to maintain a normal plasma potassium in patients being treated with digitalis as the tendency of digitalis to produce arrhythmias is potentiated by hypokalaemia (Naylor, 1975; Steiness and Olesen, 1976).

Aldosterone antagonists may be more effective than dietary supplements of potassium in the long-term correction of tissue potassium losses (Croxson *et al.*, 1972; Davidson and Gillebrand, 1973; Kremer *et al.*, 1977), perhaps on the basis of correcting cellular magnesium depletion (Lim and Jacob, 1972, 1978; Dyckner and Wester, 1978). With the possibility of the need for treatment with aldosterone antagonists in mind, the availability of a practicable and sensitive radioimmunoassay for plasma aldosterone led us to investigate the aldosterone and electrolyte status of our patients awaiting cardiac surgery.

Methods

We studied 24 patients (10 men and 14 women)

Table 1 Details of patients studied

Case no.	Age and sex	Height (cm)	Weight (kg)	Predicted weight (kg)	Weight of % predicted	Diagnosis
1	47 F	173	67.1	70.3	95	Mitral valve disease (mixed lesions)
2	62 M	169	65.4	71.0	92	Aortic stenosis
3	59 F	153	59.0	59.3	100	Aortic valve disease (mixed lesions)
4	49 M	170	77.1	73.0	106	Mitral regurgitation
5	67 M	160	75.3	64.4	117	Aortic stenosis, ischaemic heart disease
6	64 F	170	63.0	71.2	89	Mitral and aortic valve disease (mixed lesions)
7	51 M	168	52.2	71.2	73	Aortic valve disease (mixed lesions)
8	68 F	163	46.7	65.8	71	Mitral and tricuspid valve disease (mixed lesions)
9	34 F	163	42.0	59.9	70	Mitral valve disease (mixed lesions)
10	45 M	164	64.1	68.0	74	Mitral and aortic valve disease (mixed lesions)
11	30 M	178	57.5	77.1	75	Mitral stenosis
12	64 M	173	85.7	73.9	116	Aortic valve disease (mixed lesions)
13	62 M	165	72.2	68.0	106	Aortic stenosis
14	60 F	155	45.4	60.8	75	Mitral and aortic valve disease (mixed lesions)
15	50 M	164	59.2	68.5	86	Ischaemic heart disease, mitral regurgitation, ventricular septal defect
16	64 F	164	52.5	66.7	79	Mitral valve disease, tricuspid regurgitation, aortic valve disease
17	46 F	155	53.4	59.0	91	Mitral valve disease
18	62 F	160	51.0	64.0	80	Mitral valve disease
19	45 F	156	45.8	59.6	77	Mitral and aortic valve disease
20	60 F	167	60.2	69.4	87	Mitral valve disease, aortic regurgitation
21	61 F	155	79.5	60.8	131	Ischaemic heart disease, aortic valve disease
22	56 F	160	61.0	63.5	96	Ischaemic heart disease, coarctation
23	55 F	151	34.5	58.3	59	Mitral valve disease
24	69 M	163	55.5	66.2	84	Ischaemic heart disease

mostly with valve disease (Table 1) being prepared in hospital for surgical treatment. The patients agreed to take part in the study after a full explanation of the detailed procedure and assurance that their operation would not be delayed or otherwise affected by the study. All were in a stable state after optimal treatment (Table 2) to reduce oedema and pulmonary congestion, as judged by constant body weight, and were studied in the few weeks between admission to hospital and operation; 2 patients (cases 22 and 24) had slight detectable residual oedema. Ethical considerations forbade any change in diuretic treatment or in general ward management; all patients received normal ward diet with 'no added salt' at the table and unlimited fluid intake. In all but 4 patients (cases 4, 7, 9, and 12) diuretic therapy was thought necessary and was sometimes intensive (Table 2).

We attempted to maintain normal plasma potassium concentrations with potassium supplements (Slow K) or amiloride where necessary.

Total exchangeable potassium and sodium were estimated simultaneously with ^{43}K and ^{24}Na as suggested by Davies and Robertson (1973), but injecting 100 μCi ^{43}K and 20 μCi ^{24}Na to produce acceptable counting times.

^{43}K was obtained from the Medical Research Council Cyclotron Unit, Hammersmith Hospital, and the ^{24}Na from the Radiochemical Centre, Amersham. Activities were checked using a standard ionisation chamber. With the patient recumbent 30 ml blood were drawn into lithium heparin tubes without forearm exercise and venous occlusion as

Table 2 Diuretic therapy

Case no.	Frusemide (mg/day)	Amiloride (mg/day)	Slow-K (mg/day)	Navidrex-K (tablets/day)	Aldosterone (pmol/l)
1				2	180
2				2	222
3				2	266
4					278
5	40		1200		305
6	40	5			333
7					389
8				1	416
9					416
10	40	5			472
11	160	20			638
12					694
13	80	10			833
14	40		3600		1457
15	80	10			1665
16	160	15			1721
17	40	10			1804
18	40	5			1887
19	40				2359
20	80	10			2914
21	240	30			3053
22	1000	20			3608
23	320	20			4856
24	1000	15			6244

recommended by Brown *et al.* (1970); 20 ml were spun down and stored at -20°C for plasma aldosterone estimation; the remainder was used for the plasma electrolyte estimations. Twenty μCi ^{24}Na and 100 μCi ^{43}K (prepared by weight using strict aseptic procedures) were injected together in the same syringes. In 20 patients 30 μCi ^{35}S as sulphate were added for sulphate space estimation. After the intravenous injections all swabs, syringes, washes, etc., were counted against standards to account for the non-injected activity, the standards (^{24}Na , ^{43}K) being prepared by weight. Blood samples were taken without venous occlusion or forearm exercise at 1, 2, 3, and 4 hours for sulphate space determination, and again at 24 and 26 hours for potassium estimation with the mean of the 2 results being reported as the total exchangeable potassium. In 5 patients (see Table 4) the 2 values for total exchangeable potassium differed by more than 15 per cent of the mean, and these patients were excluded from the regression analysis. The excretion of ^{43}K and ^{24}Na in the first 24 hours was assumed to be 3 per cent (Oleson, 1967; White *et al.*, 1969). The calculation of total exchangeable sodium and total exchangeable potassium was carried out using a Hewlett Packard 9810A programmable calculator, with correction for radioactive decay during the counting period. Plasma sodium and potassium concentrations were taken as the mean of 2 values obtained by flame photometry. A predicted value for total exchangeable potassium (TEK) was obtained for each patient from a regression equation of $\log_e(\text{TEK})$ on $\log_e$ height derived from normal subjects by Flear *et al.* (1966).

Total body water was estimated as 'cation space', the volume occupied by the sum of total exchangeable sodium (TENa) (representing mainly extracellular fluid) and total exchangeable potassium (TEK) (representing mainly cell water), dividing total cation (TENa + TEK) by extracellular (i.e. plasma) total cation concentration ($\text{Na} + \text{K}$) expressed in terms of extracellular water and assuming osmotic equilibrium between cells and extracellular fluid (Oleson, 1967). We measured extracellular fluid volume as sulphate space, using the method of Savoie and Jungers (1965) as outlined by White *et al.* (1969), modified by using a new xylene-based liquid scintillator (NE 260, Nuclear Enterprises) to which plasma can be added directly without protein precipitation. Plasma was stored for 7 days in a deep freeze to ensure complete decay of ^{24}Na and ^{43}K before counting and ^{35}S was counted in a Beckman automatic liquid scintillation counter. The observed sulphate space was corrected for plasma water content, Donnan equilibrium, and the entry of radiosulphate into red cells by multiplying by a factor of 0.93, differing from the value of 0.87 used by White *et al.* (1969) as plasma proteins are not now removed before measurement.

Extracellular sodium was calculated by multiplying the corrected sulphate space by the overall extracellular fluid sodium concentration, estimated as plasma sodium multiplied by 1.02 (White *et al.*, 1969). The residual sodium, that is sodium in cells or to a small extent elsewhere not exchanging with the extracellular fluid (Leaf, 1974), was calculated as the difference between total exchangeable sodium and extracellular sodium.

Plasma aldosterone was determined by the radioimmunoassay procedure described by Jowett *et al.* (1973). $1,2^3\text{H}$ -aldosterone (50 Ci/mmol) was obtained from the Radiochemical Centre, Amersham, and from New England Nuclear. D-aldosterone was obtained from Koch-Light Laboratories and chromatography carried out using the Bush B5 system on Whatman's SG81 silica gel-impregnated paper. Antibody to aldosterone-3-carboxy-methoxime conjugated to bovine serum albumin was donated by Dr J. D. H. Slater (Middlesex Hospital) and used at a final dilution of 1:600. Standard curves were set from 0 to 160 pg/ml aldosterone.

Aldosterone assays were carried out in duplicate and the duplicate variation was between 1 and 2 per cent. Each sample was assayed on three separate occasions and the interassay variation was 10 per cent. A water blank was included with each batch of samples being assayed; blank values were always less than 6 pg/ml.

Aldosterone levels were measured in 8 normal

Table 3 Cardiac catheterisation findings

Case no.	Mean wedge pressure (mmHg)	Right atrial pressure (mmHg)	Pulmonary artery pressure mean (mmHg)	Pulmonary vascular resistance (units)	Cardiac output (l/min)	Aldosterone (pmol/l)
1	35	8	65	10.0	3.0	180
2	7	2	23	2.0	8.0*	222
4	22	5	28	1.9	3.2	278
6	24	6	31	2.4	2.9	333
8	20	6	35	4.3	3.5	416
10	8	5	13	1.2	4.2	472
11	29	3	38	2.3	4.0	638
12	10	5	18	1.6	5.0	694
14	18	7	55	10.0	3.7	1457
15	23	18	45	11.0	2.9	1665
16	25	8	45	5.0	4.0	1721
17	15	6	33	7.4	2.3	1804
18	24	6	32	3.2	2.5	1887
19	25	6	38	4.2	3.1	2359
20	28	7	75	11.8	4.0	2914

* High output attributed to extensive Paget's disease.

volunteers between 12 noon and 2 pm, the blood being taken with the subject recumbent after at least 4 hours in the erect posture.

In 15 patients cardiac catheterisation was carried out as part of their preoperative assessment (Table 3).

Results

The detailed findings, including plasma electrolyte values, are listed in Table 4 in order of plasma aldosterone concentration.

BODY WEIGHT

Eighteen of the patients (75%) were below the average weight for their age, sex, and height (Society of Actuaries, 1959).

POTASSIUM

The plasma potassium was in the normal range for all but 2 of our patients with a range of 3.55 to 5.50 mmol/l and a mean of 4.20 mmol/l for the group.

Exchangeable potassium was reduced compared with the predicted value in terms of expected weight in 12 patients and was below 70 per cent of the predicted value in 5. There was a significant correlation between total exchangeable potassium depletion, expressed as a percentage of predicted, and weight, expressed as a percentage of predicted on the basis of height ($r=0.56$, $P<0.02$).

SODIUM

Three patients had plasma sodium levels below 130 mmol/l. The range for the whole group was 121.5 to 145.5 mmol/l with a mean of 137.5 mmol/l.

The predicted total exchangeable sodium was

calculated for men from the regression $\log_e$ total exchangeable sodium on $\log_e$ height and also on $\log_e$ weight derived from normal subjects by Flear *et al.* (1966). No calculation was made for women as the correlation coefficients for the regression $\log_e$ total exchangeable sodium on $\log_e$ height and on $\log_e$ weight found by Flear *et al.* (1966) were very low.

Total exchangeable sodium was raised in 8 of the men with a mean of 14.1 per cent above predicted from height and was 9.4 per cent above predicted from weight for the whole group of 10 men.

CATION SPACE

This quantity, which is calculated from the sum of total exchangeable sodium and total exchangeable potassium, may be regarded as an estimate of total body water. Cation space expressed as a percentage of body weight averaged 67.4 per cent for the men and 58.6 per cent for the women. These findings are considerably greater than the values for total body water expressed as a percentage of body weight derived from normal subjects by McMurray *et al.* (1958) of 54.3 per cent for men and 48.6 per cent for women.

SULPHATE SPACE

Sulphate space, an estimate of extracellular fluid volume (Table 4), expressed as a percentage of body weight, gave a mean for the men of 19.4 per cent and for the women of 21.1 per cent. Standard values for normal subjects are 21.3 per cent and 17.4 per cent, respectively (Savoie and Jungers, 1965); so, on average, our patients showed little deviation from the normal.

Sulphate space expressed as a percentage of

predicted was not related to total exchangeable sodium expressed as a percentage of predicted and there was no correlation between sulphate space (i.e. extracellular fluid volume) and any of the cardiac catheterisation measurements.

ALDOSTERONE

The results in 8 normal controls were 278, 302, 291, 272, 413, 563, 161, and 250 pmol/l (100, 109, 105,

showed a relation to the plasma aldosterone expressed logarithmically.

There was a poor correlation between $\log_{10}$ aldosterone concentration and plasma potassium ($r=0.40$), but $\log_{10}$ aldosterone concentration correlated negatively with plasma sodium ($r=-0.5$, $P<0.01$).

Various methods for the correction of total exchangeable potassium (TEK) for body size made

Table 4 Aldosterone and electrolyte results

Case no.	Plasma sodium (mmol/l)	Plasma potassium (mmol/l)	Total exchangeable sodium (mmol/l)	Total exchangeable potassium (mmol/l)	Total exchangeable potassium predicted (mmol/l)	Total exchangeable potassium as % of predicted	Sulphate space (l)	Aldosterone (pmol/l)
1	140.0	3.70	3333	3122	2690	116	17.7	180
2	141.0	4.00	3517	3538	3040	116	16.6	222
3	138.5	3.55	2201	2052	2180	94	9.3	266
4	140.0	3.90	3453	5655*	3050	185	18.3	278
5	139.5	3.80	3285	3293	2660	124	14.2	305
6	143.0	4.45	2682	2813	1970	143	13.3	333
7	140.0	4.35	2683	3050	2840	107	11.3	389
8	128.5	4.35	1929	1859*	1840	101	11.7	416
9	138.5	4.90	2394	2372	2420	98	14.4	416
10	145.5	3.90	1368	3798*	2820	135	12.3	472
11	141.5	3.65	4495	2684	3430	78	10.8	638
12	140.0	4.35	3402	3507	3190	110	18.3	694
13	140.0	4.40	3017	2928	2860	102	13.7	833
14	139.5	4.75	1714	1443	2220	65	—	1457
15	138.5	4.75	2616	2567	2820	91	11.7	1665
16	133.5	3.95	2309	1755	1860	94	11.3	1721
17	138.0	3.90	2270	2181	2220	98	11.2	1804
18	136.5	4.05	2012	1453	1790	81	10.0	1887
19	142.0	4.30	1803	1564	2250	66	—	2359
20	139.0	3.70	2507	1148	1920	60	14.9	2914
21	136.5	4.30	4071	2142	1700	126	13.5	3053
22	136.5	3.90	3819	2634	2350	115	13.7	3608
23	124.0	5.50	1624	1358*	2120	64	—	4856
24	121.5	4.80	3073	1636*	2980	55	—	6244

* In these patients duplicate estimates of total exchangeable potassium differed by more than 15 per cent of the mean and they are excluded from the regression analyses.

98, 149, 203, 58, and 90 ng/l) (mean 316 pmol/l (114 ng/l) and standard deviation ± 114 pmol/l (± 41 ng/l)); these findings agree well with those published for erect subjects on normal diets: 366 ± 247 pmol/l (132 ± 89 ng/l) (Mayes *et al.*, 1970); 522 ± 69 pmol/l (188 ± 25 ng/l) (Bayard *et al.*, 1970); 413 ± 175 pmol/l (149 ± 63 ng/l) (Farmer *et al.*, 1973); 372 ± 283 pmol/l (134 ± 102 ng/l) (McKenzie and Clements, 1974); and 311 ± 302 pmol/l (112 ± 109 ng/l) (Castro *et al.*, 1974).

The levels in our patients (Tables 2, 3, 4, and 5) fall into 3 groups: 13 patients with normal or slightly raised levels up to 833 pmol/l (300 ng/l), a middle range (6 patients) with values between 833 and 2775 pmol/l (300 and 1000 ng/l), and a high range above 2775 pmol/l (1000 ng/l) (5 patients). In view of the wide variation in plasma aldosterone concentrations, regression analyses were carried out to determine whether any of our other measurements

little difference and a similar relation was found between $\log_{10}$ aldosterone concentration and unmodified total exchangeable potassium ($r=-0.63$, $P<0.01$), total exchangeable potassium/metre height ($r=-0.64$, $P<0.01$) (Fig. 1), and total exchangeable potassium/kg body weight ($r=-0.59$, $P<0.01$). There was no correlation between total exchangeable sodium and plasma aldosterone concentration.

There was a negative relation between $\log_{10}$ plasma aldosterone concentration and sulphate space ($r=-0.29$) (Fig. 2) which did not reach significant levels even for the subgroup of 9 men with sulphate space expressed as a percentage of body weight ($r=-0.46$, $P<0.1$).

Residual sodium was not related to $\log_{10}$ aldosterone concentration or total exchangeable potassium expressed per metre height, and similar results were obtained expressing residual sodium in terms of body weight.

There was no correlation of $\log_{10}$ aldosterone concentration with cardiac output and the correlations with mean pulmonary artery pressure ($r=0.33$), pulmonary wedge pressure ($r=0.33$), and right atrial pressure ($r=0.36$) were not significant.

DIURETIC THERAPY

A highly significant correlation was found in patients on frusemide between $\log_{10}$ frusemide and aldosterone concentration ($r=0.77$, $P<0.001$) (Fig. 3). The use of log frusemide dose necessarily excludes patients not on frusemide from this correlation. The correlation with $\log_{10}$ amiloride dose did not achieve significance ($r=0.51$, $P<0.1$).

Discussion

ROLE OF ALDOSTERONE IN CONGESTIVE HEART FAILURE

The part played by aldosterone in the different stages of congestive heart failure in relation to the response to diuretic therapy has been clarified with the measurement of plasma aldosterone by Nicholls *et al.* (1974), and the findings can be interpreted in relation to the two major stimuli to renin release; a reduction in the effective arterial volume and a fall in the sodium load reaching the distal tubule (Vander, 1967). At the onset of heart failure and in the untreated situation a moderate increase in plasma aldosterone is expected as part of the increase in sympathetic activity (Brod, 1972) and the primary stimulus to fluid retention (Davis, 1974) from a fall in effective arterial volume or a reduced sodium load in the distal tubule after enhanced reabsorption proximally.

During diuresis plasma aldosterone is suppressed to very low levels. The attribution of this response to a reduction in the initial stimulus as cardiovascular performance improves seems unlikely in view of the lack of haemodynamic improvement noted after diuretic therapy by Stampfer *et al.* (1968). The dramatic increase in sodium load to the distal tubule during diuresis seems to outweigh the effect of a fall in effective arterial volume at this stage in the treatment of heart failure. As the patient approaches dry weight plasma aldosterone rises again. It may be that continued diuretic treatment after loss of oedema further reduces effective circulating arterial volume, and the sodium load reaching the distal tubule will be less than in the diuretic phase. It has been suggested that reduced catabolism of aldosterone from impaired hepatic function plays a part in producing the high plasma aldosterone concentration in congestive heart failure (Yates *et al.*, 1958; Tait *et al.*, 1965; Genest *et al.*, 1968), but Nicholls *et al.* (1974) found that plasma renin

activity changed in parallel with the plasma aldosterone concentration, suggesting that the 'renin-angiotensin-aldosterone' system continues to operate.

RADIOISOTOPE METHODS

Oleson and Valentin (1973) confirmed the general validity of the radioisotope dilution method for total exchangeable potassium in the investigation of patients with treated heart failure. The apparent discrepancy with measurements of total body potassium from natural ^{40}K in a whole body counter is probably related to differences in interpretation (Hamer, 1977). The finding of near normal total body potassium in relation to current weight (Davidson *et al.*, 1976; Lawson *et al.*, 1976) is in keeping with the suggestion of Nagant de Deuxchaisnes *et al.* (1961) and Nagent de Deuxchaisnes and Mach (1974) that the loss of potassium seen with total exchangeable potassium measurements is a 'pseudodepletion' caused by loss of lean body mass. The main bulk of body potassium is contained in skeletal muscle. Because of the variable effects of fluid retention, obesity, and loss of lean tissue from cardiac cachexia the lean body mass bears no fixed relation to body weight in treated severe heart disease (Rich and Wright, 1978). Our assessments of depleted total exchangeable potassium are based on estimates of normal body size derived from height and are consistent with loss of lean body mass (White *et al.*, 1969).

The suggestion of Oleson and Valentin (1973) that sodium did not enter cells to replace lost potassium in treated heart failure may be the result of technical problems related to their use of ^{82}Br , an analogue of the chloride (Cl) ion as a marker of extracellular fluid volume (Hamer, 1977). The sulphate ion used here has advantages for the measurement of extracellular fluid volume in that it does not penetrate cells to a significant extent, but measurement is more complicated as back-extrapolation of the data to the time of injection is needed to allow for renal excretion of sulphate (Savoie and Jungers, 1965). The evidence that many patients have larger total exchangeable sodium than accounted for by sodium in the extracellular fluid (Fig. 4) indicates some entry of sodium into the cells consistent with a fall in intracellular potassium concentration, the 'true depletion' of Nagant de Deuxchaisnes *et al.* (1961) and Nagent de Deuxchaisnes and Mach (1974) as shown for skeletal muscle in primary hyperaldosteronism by Milne *et al.* (1967), and in Bartter's syndrome by Delaporte *et al.* (1978). The absence of such findings in our previous study (White *et al.*, 1969) on similar patients may relate to the difficulty of measurement of small changes when 'pseudo-

depletion' is the dominant factor. Though muscle wasting from the process of malnutrition (Walesby *et al.*, 1978) that leads to 'cardiac cachexia' seems to play a major role in reducing total exchangeable potassium from loss of lean body mass (i.e. a 'pseudodepletion'), some 'true depletion' producing a reduction of intracellular potassium concentration is difficult to exclude and could be of critical importance in the myocardium, changing the membrane potential to produce fatal ventricular arrhythmias as stressed by Lockey *et al.* (1966), though Oleson and Valentin (1973) failed to confirm any increased risk of death from arrhythmias with reduced total exchangeable potassium in their patients. Myocardial biopsies at operation show reduced cell potassium concentration (Schimert *et al.*, 1966), but Taggart and Slater (1970) have shown that similar changes may occur during operation, so they may not represent the preoperative state, and Ward and Cameron (1978) have shown in animals that the myocardium is relatively protected against potassium depletion.

The state of many of our patients on continued diuretic treatment after the loss of most of their oedema corresponds to the dried-out stage described by Nicholls *et al.* (1974) in which hyperaldosteronism is frequent.

Care was taken to ensure that the patients had reached a steady state, as far as the diuretic regimen was concerned, as indicated by a constant body weight and the patients were studied after several hours in the sitting position to minimise the effects of posture on plasma aldosterone. The very high concentrations found in some patients were in and beyond the range (up to 2 nmol/l = 720 ng/l) found by Nicholls *et al.* (1974) after relatively short periods of diuretic treatment in patients approaching dry weight, and are far beyond the range expected from postural variations. The 'no added salt' diet may have acted as a stimulus to renin secretion, producing a secondary rise in plasma aldosterone concentration. Though they were generally free from oedema our patients did not show extreme sodium depletion. There was also evidence from the tendency to a raised total exchangeable sodium in the men studied, from the increased cation space, and from the absence of any general fall in extracellular fluid volume (sulphate space), of persisting expansion of the extracellular fluid. Nevertheless, it is difficult to exclude a reduction in effective arterial volume provoking secretion of renin and a consequent hyperaldosteronism; such a change is suggested by the higher plasma aldosterone levels with reduced sulphate space and may be obscured in measurements of total extracellular fluid volume by a persisting increase in the volume of the venous

compartment and the pulmonary circulation. The absence of any correlation between plasma aldosterone and cardiac output may indicate that blood flow is not the critical factor, but is more likely to reflect the different conditions of study.

Previous studies (White, 1970) have shown that potassium supplements have only a partial effect in correcting the reduced total exchangeable potassium in keeping with the description of hypokalaemia as a simple potassium 'deficiency' by Nagant de Deuxchaisnes *et al.* (1961) and Nagant de Deuxchaisnes and Mach (1974), suggesting that treatment directed to reversing hyperaldosteronism might be a more useful approach to correcting potassium losses in the present situation. Relatively short-term treatment with amiloride has only a minor effect on tissue potassium (Croxxon *et al.*, 1972; Davidson and Gillebrand, 1973; Kremer *et al.*, 1977) and attempts to correct potassium depletion caused by loss of lean body mass may be inappropriate, short of haemodynamic correction. We are hopeful that more prolonged treatment or other approaches such as reducing cardiac load by chronic vasodilator therapy (Chatterjee *et al.*, 1976), or a metabolic approach by correcting magnesium depletion (Dyckner and Wester, 1978; Lim and Jacob, 1978), or the insulin and glucose regimen (Majid *et al.*, 1972) may restore potassium to the cells effectively; further study is clearly necessary to determine the best approach to management of these severely affected patients.

INTERPRETATION OF PRESENT FINDINGS

We were concerned to assess the aldosterone situation in our patients with treated heart disease in relation to their preparation for operation, and we did not think it ethically justifiable to modify the conditions of treatment or to defer the patients' operations for the study. We are forced to argue the sequence of events from the results in individual patients with widely differing degrees of impairment (Table 1). In view of the fundamental similarity of the disturbed physiology leading to congestive heart failure, and as no clear separation of high and low plasma aldosterone levels was evident in our results we used regression analysis to determine the relations between the status or treatment of our patients and the biochemical measurements.

Patients on spironolactone were excluded to avoid possible interference with the aldosterone assay by metabolites but we were able to maintain normal plasma potassium levels with oral potassium supplements or amiloride where necessary in our patients. It seems unlikely that potassium administration played a part in provoking aldosterone secretion in our patients. The effect described by

Fig. 1 Relation of plasma aldosterone concentration to total exchangeable potassium (TEK). TEK is expressed in terms of height to correct for variations in body size in the presence of cachexia. High plasma aldosterone concentrations (log scale) are associated with potassium depletion as shown by the negative correlation ($r = -0.64$, $P < 0.01$).

Laragh and Stoerk (1955) seems to be mediated by a direct action on the adrenal cortex, and the tendency to cellular potassium depletion in our patients might have the reverse effect, as suggested by Brunner *et al.* (1970).

Fig. 2 Relation between plasma aldosterone concentration (log scale) and extracellular fluid volume measured as sulphate space. The negative correlation ($r = -0.29$) which does not achieve statistical significance suggests that hyperaldosteronism is associated with reduced extracellular fluid volume.

A positive feedback effect of aldosterone antagonism leading to further aldosterone secretion as reported in Conn's syndrome (Kremer *et al.*, 1977) and in heart failure (Nicholls *et al.*, 1976) could frustrate attempts to correct potassium loss and may have played a contributory part in the hyper-

aldosteronism of some of our patients, though the correlation of plasma aldosterone with amiloride dose ($r = 0.51$) did not reach significance in the relatively few patients receiving this treatment (Table 2).

IMPLICATIONS OF POTASSIUM DEPLETION IN DIURETIC THERAPY

Previous studies (Lockey *et al.*, 1966; Hocking and Bain, 1974) have been interpreted as indicating an association between intensive diuretic therapy and potassium depletion. However, Edmondson *et al.*

Fig. 3 Relation of plasma aldosterone concentration to intensity of diuretic therapy expressed as daily dose of frusemide. Hyperaldosteronism is associated with intensive diuretic treatment as shown by the significant correlation ($r = 0.77$, $P < 0.001$).

(1974) concluded from a study of leucocyte electrolytes in cardiac and non-cardiac patients receiving diuretics that the heart disease rather than its treatment was responsible for the potassium depletion in cardiac patients, but their results are obscured by an apparent failure to consider the effects of digitalis glycosides which will also tend to deplete the leucocyte potassium concentration and may account for the difference between the 2 groups of patients (Astrup, 1974). We show here a clear relation between intensive diuretic therapy, hyperaldosteronism, and loss of body potassium (measured as total exchangeable potassium).

It may be that in severely affected patients, intensive diuretic treatment serves only to remove troublesome systemic and pulmonary oedema, reducing pulmonary vascular pressures and producing a fall rather than a rise in cardiac output in spite of clinical improvement from loss of congestion as described by Stampfer *et al.* (1968). We conclude that though the clinical condition of patients is improved by diuretic therapy, the persisting or accentuated reduction in effective arterial volume

Fig. 4 Relation of extracellular sodium to total exchangeable sodium. Extracellular sodium calculated from sulphate space and sodium concentration in plasma water is related to total exchangeable sodium ($r=0.43$) without statistical significance. To facilitate interpretation with the different axes the line of identity is shown. If all the body sodium is in the extracellular fluid the data should approximate to the line of identity. Deviation towards the horizontal axis indicates entry of sodium into cells so that exchangeable sodium exceeds extracellular sodium.

leads to severe hyperaldosteronism which produces potassium depletion and may be complicated by loss of lean body mass and cardiac cachexia. In addition there is risk of a fall in intracellular potassium concentration which can precipitate fatal ventricular arrhythmias (Dreifus *et al.*, 1974). It may be that less intensive diuretic therapy would avoid the provocation of hyperaldosteronism at the expense of some residual oedema, but the relative success of operating on dried-out patients makes us hesitant to abandon this policy.

Whatever the mechanisms, whether arrhythmic or through wasting of lean tissue (Walesby *et al.*, 1978), it is possible that hyperaldosteronism and potassium depletion may contribute to the mortality of surgical treatment such as valve replacement. If operation is feasible, our surgical colleague suggests that it should be considered before hyperaldosteronism occurs, as soon as intensive diuretic treatment becomes necessary to prevent troublesome symptoms of congestion (G. Rees, 1977, personal communication).

A preliminary account of this work was presented to the joint meeting of the British Cardiac Society and the Swedish Society of Cardiology in 1975, and appears in abstract in the *British Heart Journal*, 35, 534P; the findings are reviewed by Hamer (1977).

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