cause. It would be interesting to know how many of the perinatal deaths in the "anoxic" group in Cardiff corresponded to deaths of unknown cause in mature infants and to know the age, parity, height, and social class of the mothers. Higher induction and section rates in these groups most at risk might have resulted in better figures.

Fedrick and Yudkin⁹ reported a reduction in the number of stillbirths in the Oxford area associated with a rising induction rate. The reduction was more apparent in induced than in non-induced births. As they pointed out themselves, however, when the induction rate is low only pregnancies at very great risk are included in an induced group, but as the induction rate rises, more and more relatively normal cases are induced. It is difficult, therefore, to draw firm conclusions about the benefits of induced labour from their method of analysing their data. Possibly the optimum induction rate will vary from area to area depending on the characteristics of the populations. By detailed analysis of our population and classification of the causes of our perinatal deaths, we were able to show where greatest improvement could

be made, and it would be valuable to compare our results with those from other centres. Our present findings strongly suggest that increased use of induction of labour has contributed to a reduction in perinatal mortality.

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Congestive cardiomyopathy in uraemic patients on long term haemodialysis

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Summary

Five uraemic patients who developed progressive cardiac failure with clinical evidence of congestive cardiomyopathy at the start or during haemodialysis treatment were studied. The diagnosis of cardiomyopathy, for which there was no apparent cause, was confirmed by angiocardiographic and haemodynamic studies. These showed a significant increase in left ventricular end-diastolic volume over normal values obtained in 12 patients without uraemia. The mean velocity of myocardial fibre shortening was significantly decreased, as was the index of normalised rigidity. Three of the five patients presented the complete picture of the disease. The other two also had considerable ventricular dilatation and a decreased index of normalised rigidity but normal ejection fraction and only moderately decreased myocardial contractility indices. This suggests that there may be primary involvement of normalised heart muscle rigidity followed by secondary changes in myocardial contractility in uraemic patients with congestive cardiomyopathy.

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Introduction

Cardiac failure remains one of the most important contributory causes of death in patients undergoing maintenance haemodialysis.^{1,2} Various factors are implicated in the pathogenesis of heart failure during chronic renal insufficiency—for example, coronary artery disease and hypertension,¹ pericarditis, hypokalaemia or hyperkalaemia, disorders of calcium metabolism, and possibly anaemia, acidosis, and overhydration with hypervolaemia.³⁻⁴ The question remains whether a specifically "uraemic" cardiomyopathy, due to the retention of normally excreted or metabolised substances, may also be implicated.⁵⁻⁶

In 1944 Raab⁷ suggested that cardiotoxic substances may exist in the blood and heart muscle in uraemia, and recent experimental evidence has supported the suggestion that uraemia may have a direct effect on myocardial function. During acute renal failure in rats Nivatpumin *et al*⁸ observed increased contractility in the myocardium, whereas Riecker *et al*⁴ suggested that the contractile state of the acutely uraemic heart was diminished after adrenergic stimulation in the guinea-pig in vivo. In experimental chronic renal failure Hennemann *et al*⁹ reported an increased isometric contraction force of isolated rat atria but a decreased myocardial ⁴⁵Ca uptake after stimulation with the beta-adrenergic agonist, isoproterenol. Scheuer *et al*¹⁰ provided indirect evidence that uraemic serum had a net depressant effect on myocardial performance in chronically uraemic rats in vivo. They also demonstrated depressed cardiac function when normal rat hearts were perfused with mixtures of urea, creatinine, methyl guanidine, and guanidinosuccinic acid.¹¹

In 1967 Bailey *et al*¹² described five patients with terminal renal insufficiency who developed severe heart failure that was reversed after intensive haemodialysis. Hypertension and anaemia seemed unlikely major causes of cardiac failure in these patients, and the authors suggested that uraemic "toxins" might be implicated. Recently Scheer *et al*¹³ and Rodger *et al*¹⁴ presented evidence that cardiomyopathy of unknown cause occurs

in uraemic patients who are undergoing intermittent haemodialysis. We performed ventriculographic and haemodynamic studies on patients undergoing maintenance haemodialysis who developed chronic heart failure and cardiomegaly of obscure origin and who presented symptoms and signs compatible with the diagnosis of congestive cardiomyopathy.¹⁵⁻¹⁷

Patients and methods

Cardiomegaly and heart failure are common complications of end-stage renal failure. In most cases they are reversible by haemodialysis. Out of a series of 450 patients on maintenance haemodialysis, however, we saw a few with signs and symptoms of congestive heart failure that developed either during terminal renal failure that remained unchanged by haemodialysis or months after starting haemodialysis. We studied five patients with clinical signs and symptoms¹⁵⁻¹⁷ of congestive cardiomyopathy who had no evidence of coronary heart disease, endocarditis, pericardial effusion, chronic overload state due to insufficient dialysis, severe anaemia, chronic electrolyte disturbances, or a history of acute myocarditis or infiltrative disease. Typical clinical signs were dyspnoea, chest pain, jugular vein distension, and, especially, a protodiastolic gallop. Their cardiopathy did not respond to intensive dialysis treatment, including major fluid depletion.

The clinical data and dialysis schedule of the five patients are summarised in table I. Haemodialysis was performed using a multi-layer plate kidney (RP5) in four cases and a coil kidney (Travenol UF 100) in one (case 2). The haemodialysis schedules were similar to those of all the patients in our centre. Fistula flow rates were not measured since there is no precise way of determining external flow. But dialysis blood flow measured during a dialysis session ranged from 110 to 260 ml/min (ultrasonic flow meter). The fistula providing the lowest flow clotted during the patient's stay in hospital. The low values were probably related to the poor haemodynamic state of the patients. Interdialysis weight changes were no different from those observed in the other patients in the centre.

Cardiological data on the five patients are shown in table II. One patient (case 2) had mild arterial hypertension, but the others were normotensive or had persistent hypotension and no history of long-standing arterial hypertension. Cardiomegaly was already present in one patient (case 5) when she started haemodialysis, but it developed months after the start of haemodialysis in the other four. Only one patient (case 1) had evidence of advanced hyperparathyroidism and soft tissue calcification. Three patients had electrical evidence of uraemic polyneuropathy when they were studied but only one of them had clinical signs and symptoms of polyneuropathy. Their diet contained 1 g protein/kg body weight/day or more, and none had signs of malnutrition before or at the onset of cardiomegaly. None of the patients received cobalt or ingested alcohol chronically. Plasma bicarbonate concentrations did not fall after dialysis in any patient, which suggested that none of them suffered from intradialysis acetate

intoxication.¹⁸ Four of the patients survived. The fifth (case 1) died in another hospital from massive gastrointestinal bleeding due to right heart failure, but no necropsy was performed.

INVESTIGATIONS

All patients underwent routine clinical examination every one to two weeks and routine electrocardiographic (ECG) and chest x-ray examination every three months, or more often if indicated. The patients also had their blood volume, plasma volume, erythrocyte volume, and cardiac index (radioisotope dilution method) measured. Plasma potassium, sodium, and calcium concentrations were measured several hours before cardiac investigation, and the values were all normal.

Ventriculography and haemodynamic studies—Each patient underwent left cardiac catheterisation according to the method described by Seldinger. Left ventricular pressures were recorded by fluid-filled catheter, and left ventricular cineangiography was performed using the oblique right anterior projection (French Cook Catheter No 6.7 F). Coronary arteriography completed the study in two patients (cases 3 and 4). In a third (case 5) coronary angiography was interrupted because of transient cardiac arrest at the moment of coronary catheterisation. Left ventricular volumes were calculated according to Greene's method.¹⁹ The ratio of stroke volume to end-diastolic volume (LVEDV) calculated angiographically represents the ejection fraction (EF). Contractility indices were calculated during the ventricular ejection period by measuring the equatorial diameter from frame to frame, thereby determining the maximum and mean velocity of myocardial fibre shortening (VCF).^{20, 21} Indices of normalised rigidity ($k = dP/dV.P$) and of instantaneous end-diastolic compliance ($(dV/dP)ED = 1/k.LVEDP$) were calculated by the method of Gaasch²² using the simplified diastolic pressure-volume relation $P = 0.43 e^{kV}$ and the values of left ventricular end-diastolic volume and pressure (LVEDP).^{21, 22} In man this simplified single co-ordinate method provides compliance and rigidity values similar to those obtained with the multiple co-ordinate method.²³ The index of normalised rigidity (k) was independent from the changes of ventricular filling because it was the coefficient of the diastolic pressure-volume exponential ($P = 0.43 e^{kV}$). Conversely, the index of end-diastolic compliance ($(dV/dP)ED$) depended on instantaneous ventricular filling, and was represented by the inverse value of the slope of the tangent of the diastolic pressure-volume exponential curve. Myocardial thickness was determined in the equatorial plan at the superior part of the left ventricle.

The five patients studied were compared with 12 controls, who included eight patients suffering from thoracic pain but with normal coronary arteriograms and ventriculograms, one with paracardiac tumour, one with cured pericardial effusion, one with unconfirmed suspicion of aortic dissection, and one with functional systolic murmur.

TABLE I—Patients' data

Case No	Sex	Age* (years)	Body weight* (kg)	Type of nephropathy	Nephric state*	Time on dialysis* (months)	Dialysis† schedule (per week; dialysis membrane 1m*)	Mean interdialysis body weight change‡ (kg)	Motor nerve conduction velocity in peroneal nerve (m/s)
1	M	50	54	Polycystic disease	Right nephrectomy	45	3 × 6 h	2.2	37
2	M	38	59	Chronic glomerulonephritis	Two kidneys	42	3 × 7 h	2.3	30
3	M	45	47	Chronic glomerulonephritis	Two kidneys	14	3 × 6 h	1.4	34
4	M	21	54	Chronic glomerulonephritis	Right nephrectomy	62	3 × 5 h	2.0	41
5	F	30	45	Chronic pyelonephritis	Right nephrectomy	7	2 × 6 h	0.9	49

*At time of study. †During year preceding haemodynamic investigation. ‡During month preceding haemodynamic investigation.

TABLE II—Cardiological data

Case No	Blood pressure* (mm Hg)	Cardiothoracic ratio	ECG*	Cardiac index* (ml/min/m ²)†	Total blood volume* (ml)†	Blood erythrocytes* (ml)†	Packed cell volume (%)‡
1	110/60	0.62	Normal	ND	ND	ND	35
2	150/100	0.60	Right bundle-branch block	4684 (+51%)	5480 (+25%)	897 (-47%)	20
3	100/70	0.69	Left ventricular hypertrophy	837 (-71%)	3110 (-12%)	1103 (-19%)	41
4	140/90	0.62	Left ventricular hypertrophy	ND	ND	ND	20
5	115/75	0.61	Anterolateral ischaemia	4570 (+64%)	3950 (+26%)	790 (-31%)	25

*At time of study. †Percentage deviation from patient's theoretical value is also shown. ‡Mean value in three months before study. ND = Not determined.

TABLE III—Haemodynamic and ventriculographic data

Case No	Heart rate (beats/min)	LVEDV (ml/m ²)	Wall thickness (cm)	LVEDP (mm Hg)	EF	Mean VCF (length/sec)	Maximum VCF (length/sec)	$k = \frac{dP}{dV.P}$	$\frac{dV}{dP} - ED$
1	64	228	1.0	18	0.25	0.34	0.54	0.0163	3.391
2	98	138	1.2	10	0.57	0.64	1.10	0.0228	4.385
3	105	253	0.95	30	0.23	0.10	0.40	0.0167	1.986
4	60	163	1.4	10	0.56	0.73	1.44	0.0193	5.180
5	96	170	1.0	20	0.28	0.43	0.85	0.0126	3.950
± SE of mean	84 ± 9	190 ± 21	1.1 ± 0.08	17 ± 3.7	0.37 ± 0.07	0.44 ± 0.11	0.86 ± 0.18	0.017 ± 0.001	3.77 ± 0.53
Control mean ± SE of mean	88 ± 4	71 ± 4	1.0 ± 0.03	8 ± 0.8	0.61 ± 0.03	1.25 ± 0.09	1.85 ± 0.14	0.041 ± 0.002	3.38 ± 0.39
U test: U _{xy} or U _{yx} (smaller of the two values)	29	0	14	6	10	0	4	0	25
P	NS	<0.01	NS	<0.01	<0.05	<0.01	<0.01	<0.01	NS

LVEDV = Left ventricular end-diastolic volume. LVEDP = Left ventricular end-diastolic pressure. EF = Ejection fraction. VCF = Velocity of myocardial fibre shortening. k = Normalised ventricular rigidity index. $(dV/dP)ED$ = End-diastolic compliance index.

We used the non-parametric U-test of Mann and Whitney²⁴ for statistical analysis because of the small number of subjects studied.

Results

The coronary arteries were normal in the two patients studied by coronary arteriography (cases 3 and 4). No localised dyskinesia or akinesia was observed. The haemodynamic and ventriculographic data of the patients are detailed in table III. The mean heart rate of the uraemic patients was not significantly different from that of the controls. The uraemic patients were characterised by a striking ventricular dilatation, as shown by an increase in left ventricular end-diastolic volume to values greater than any of the control values ($P < 0.01$). Similarly, the normalised ventricular rigidity index was significantly diminished ($P < 0.01$) in all five uraemic patients. End-diastolic compliance was within normal limits, as was end-diastolic myocardial wall thickness for the group as a whole. In contrast to the homogenous increase in left ventricular end-diastolic volume and decrease in the ventricular rigidity values, the ejection fraction was diminished in only three patients but was nearly normal in the remaining two (cases 2 and 4). The decrease was significant ($P < 0.05$), however, for the group as a whole when compared with controls. Similarly, left ventricular end-diastolic pressure was significantly increased ($P < 0.01$) in the uraemic group as a whole but was within normal limits in cases 2 and 4. Moreover, the contractility indices and the maximum myocardial fibre shortening were decreased ($P < 0.01$) when compared with those of control subjects. The contractility indices in cases 2 and 4 were only moderately decreased when compared with the striking decreases in the other three patients.

Discussion

Cardiac failure has long been known as a complication of chronic renal insufficiency.^{3, 4} Heart volume is often augmented, generally because of pericardial or myocardial involvement. Only a few studies of cardiac function have been performed in such patients,²⁵ however, and myocardial contractility and compliance have been poorly explored in uraemic patients. Recently Scheer *et al*¹³ described seven patients undergoing haemodialysis who had developed chronic heart failure and cardiomegaly of obscure origin. Four had evidence of cardiomyopathy: (a) a diminished ejection fraction and indices of myocardial contractility determined during the isovolumic phase, and (b) a significant increase in end-diastolic pressure. But values of end-diastolic ventricular volume or myocardial compliance were not given. Rodger *et al*¹⁴ reached a similar conclusion about the occasional development of congestive cardiomyopathy in patients on dialysis investigated by echocardiography. Using ventriculography and haemodynamic investigations we confirmed our clinical suspicion that some of our patients on haemodialysis had congestive cardiomyopathy.

The incidence of congestive cardiomyopathy in uraemic patients adequately treated by intermittent haemodialysis is not

known. Our incidence of 1.1% (5 out of 450) probably underestimates the real incidence since another seven of our patients showed early evidence of congestive cardiomyopathy but have not yet been investigated by ventriculography and haemodynamic studies. The prevalence of congestive cardiomyopathy in the general population is unknown. Its frequency in a selected population with cardiac disorders has been estimated at 2%.¹⁷ The incidence of congestive cardiomyopathy in haemodialysed patients is probably much higher than in the non-uraemic population.

Arterial hypertension is unlikely to have caused the cardiomyopathy in our patients since four of them had normal or low blood pressures and no history of hypertension. Furthermore, raised blood pressure causes myocardial hypertrophy²⁶ and not an increase in ventricular volume,²⁷ and we found no change in myocardial thickness but an increase in ventricular volume in all five patients. Coronary heart disease cannot be definitely excluded in three of the five patients since coronary arteriography was performed only in two. Nevertheless, normalised cardiac rigidity is not significantly changed in patients with coronary artery disease in the absence of previous myocardial infarction.²¹

Three of the five patients presented with the complete picture of the disease—that is, considerable ventricular dilatation and myocardial hypokinesia. The remaining two, despite having ventricular dilatation and a decreased index of normalised rigidity, had only a moderate decrease in myocardial contractility and normal ejection fractions. Possibly the cardiomyopathy initially affects normalised heart muscle rigidity, which leads to a primary dilatation of the ventricles. The change of myocardial contractility might be due to the chronic augmentation of systolic wall stress secondary to increased ventricular dimensions.

Studies of cardiac performance during experimental renal failure are scarce⁸⁻¹¹ and so far inconclusive. Most studies have been performed using the model of either acute renal failure or mild chronic renal failure. The contractile force of rat hearts *in vivo* was increased during acute failure, and probably decreased during chronic renal failure.¹⁰ Circulating toxic compounds in the uraemic blood have been incriminated in depression of cardiac contractility.^{7, 11, 18} The meaning of such results obtained during mild renal failure for endstage renal failure is not clear.

Our results are at variance with the experimental animal data in that the first event in the development of congestive cardiomyopathy in our patients seemed to be diminished normalised rigidity followed by a decrease in contractility. They are further at variance with the observations of Bailey *et al*,¹² who described a cardiomyopathy in uraemic patients that was reversed by adequate dialysis. The cardiomyopathy in four of our patients occurred after they had been on haemodialysis for many months and did not improve in spite of intensive haemodialysis. The moderate anaemia in four of our patients might have favoured ventricular dilatation but there is no apparent correlation

between the degree of severity of anaemia and of ventricular dilatation.

If congestive cardiomyopathy in chronically uraemic patients on dialysis is a syndrome of homogeneous origin and similar evolution in all cases then an intensified search for the factors that may cause it is indicated. In this way the syndrome could be diagnosed at an early stage and treated.

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CONDENSED REPORT

Accidental hypothermia and impaired temperature homoeostasis in the elderly

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Summary

A longitudinal study of the age-related decline in thermoregulatory capacity was made in 47 elderly people to try to identify those at risk from spontaneous hypothermia. During the winters of 1971-2 and 1975-6 environmental and body temperature profiles were obtained in the home, and thermoregulatory function was investigated by cooling and warming tests. Environmental temperature and socioeconomic conditions had not changed but the body core-shell temperature gradients were smaller in 1976, indicating progressive thermoregulatory impairment. People at risk of developing hypothermia also seem to have low resting peripheral blood flows, a non-

constrictor pattern of vasomotor response to cold, and a higher incidence of orthostatic hypotension.

Introduction

Each winter in the British Isles old people die at home as the result of cold. Indeed, accidental hypothermia (deep body temperature below 35°C) is now recognised as one of the natural hazards of old age. The problem is not simply one of unintentional accidental hypothermia resulting from a fall or accident at home and subsequent immobilisation and exposure, nor one entirely associated with concurrent illness^{1 2}; spontaneous hypothermia also occurs among apparently fit elderly people.^{3 4}

The main objectives of our investigations were to clarify the physiological basis of the ageing process in thermoregulation and to try to identify by physiological means those members of an elderly population sample living at home who seem likely to be at risk of developing hypothermia. We performed cross-sectional and longitudinal studies of a group of elderly volunteers; we obtained temperature profiles in their homes and made subsequent physiological studies in the geriatric research unit at University College Hospital, London, during the winter months (January-March) of 1972 and 1976.

Methods

We studied 47 elderly people (19 men and 28 women) living in the London Borough of Camden. In 1976 their ages ranged from 69 to 90

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