Functional and metabolic adaptation in uraemic cardiomyopathy

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1. ABSTRACT

Cardiovascular complications are the leading cause of death in patients with chronic kidney disease (CKD). The uraemic heart undergoes substantial remodelling, including left ventricular hypertrophy (LVH), an important determinant of heart failure. LVH results in a shift in myocardial substrate oxidation from fatty acids towards carbohydrates however, whether this metabolic adaptation occurs in the uraemic heart is unknown. The aim of this study was to investigate the progression of kidney dysfunction in parallel with cardiac remodelling in experimental uraemia. Experimental uraemia was induced surgically *via* a subtotal nephrectomy. At 3, 6 and 12 weeks post-surgery, renal function, LVH, *in vitro* cardiac function and metabolic remodelling using ^{13}C-NMR were assessed. Uraemic animals exhibited anaemia and kidney dysfunction at 3 weeks, with further deterioration as uraemia progressed. By 12 weeks, uraemic hearts showed marked LVH, preserved cardiac function and markedly reduced fatty acid oxidation. This change in substrate preference may contribute to the deterioration of cardiac function in the uraemic heart and ultimately failure.

2. INTRODUCTION

Cardiovascular complications remain the leading cause of mortality in patients with chronic kidney disease (CKD), accounting for approximately 50% of all deaths (1). Cardiac risk is increased 10-20 times in uraemic patients when compared to the aged matched general population (2-3). Interestingly, the relative importance of arteriosclerotic disease is diminished and those of left ventricular hypertrophy (LVH), heart failure and sudden cardiac death increased in patients with CKD (4). Uraemia is characterised by anaemia and hypertension which contribute to phenotypic cardiac alterations including a reduction in capillary density, fibrosis and LVH (5).

LVH is the most frequently observed cardiac alteration, present in up to 75% of CKD patients (6). Although initially beneficial in terms of reducing wall tension and preserving systolic function, the hypertrophied heart is accompanied by a plethora of cellular alterations, which can ultimately produce a pathophysiological phenotype leading to heart failure (7). Experimental models of volume-overload (8) and pressure-

overload (9-10) cardiac hypertrophy have shown a switch in substrate usage from fatty acids, towards glucose utilisation, known as metabolic remodelling (11-13). The change in substrate preference is consistent with a re-expression of the foetal phenotype and may represent a beneficial adaptation in LVH to reduce oxygen consumption and sustain function (11). However, in the longer-term, this remodelling may result in complications including lipid accumulation and energy depletion (14). Specifically, the build up of fatty acyl components, due to the reduced oxidation of lipids, can lead to sequestration of CoA and consequently a reduction in the CoA to acetyl-CoA ratio (15). This would subsequently lead to an inhibition of the key enzyme involved in glucose oxidation, pyruvate dehydrogenase (PDH), thus limiting oxidative capacity and depleting the heart of energy, initiating the transition to heart failure (15).

Little research has been undertaken to determine the profile of myocardial substrate utilisation in uraemia. However, given that LVH is frequently observed in both experimental models of CKD and in the clinical scenario, it is feasible that the metabolic remodelling characteristic of LVH also occurs in the uraemic heart and may contribute to cardiac failure. Furthermore, experimental models of CKD have observed a decrease in the myocardial phosphocreatine/ATP ratio, suggesting that the heart is depleted of energy reserves, potentially reflecting altered myocardial energy metabolism (16).

To understand the complex relationship between the heart and kidney, and to reduce the high impact of cardiac complications on the mortality associated with CKD, a robust and reliable experimental animal model is required. Several models have been developed employing different strategies of renal mass reduction or renal ischaemia to produce phenotypic alterations with a clinical similarity to those observed in CKD patients (17). The aim of this study was to characterise the progression of kidney dysfunction longitudinally (using the 5/6th nephrectomy model) and sequence of events relating to the development of LVH, cardiac dysfunction and altered energy metabolism.

3. MATERIALS AND METHODS

3.1. Experimental model of uraemia
All animal experiments conformed to the UK Animals (Scientific Procedures) Act 1986. Uraemia was induced in male Sprague-Dawley rats (approximately 250 g) (Charles River, Sussex, UK), via a one-stage 5/6th nephrectomy as described previously (16, 18-19). Briefly, animals were anaesthetised using a mixture of halothane in oxygen (2.5% in 1L), a laparotomy was performed, the left kidney exposed, and approximately two-thirds removed. Subsequently, the right kidney was removed. Care was taken to ensure no damage was done to the adrenal glands. For control animals, a sham operation was performed whereby both kidneys were decapsulated and replaced intact.

Animals were maintained for 3, 6 or 12 weeks post induction of uraemia, housed individually and pair-fed with control animals. Water was available ad libitum. Blood pressure was monitored at 3 and 6 weeks in conscious animals using tail plethysmography (19). Cardiac hypertrophy was assessed at the time of sacrifice by determining wet heart weight/body weight (HW/BW) and HW/tibia length.

3.2. Isolated heart perfusion
Following anaesthesia with sodium thiopentone (100 mg/Kg body weight), hearts were rapidly excised and cannulated via the aorta. Hearts were perfused in an isovolumic Langendorff mode, as described previously (20), using Krebs-Henseleit buffer containing 3% BSA and the following components (mmol/L) NaCl (118.5), $NaHCO_3$ (25), KCl (4.8), KH_2PO_4 (1.2), $MgSO_4$ (1.2), $CaCl_2$ (2.5), glucose (5), sodium pyruvate (0.1), sodium lactate (1), sodium palmitate (0.3), glutamine (0.5) and 0.1 mU/ml insulin. The buffer was gassed with 95% O_2, 5% CO_2 and maintained at 37°C.

Cardiac function was recorded continuously via a fluid filled balloon (inserted into the left ventricle) and a physiological pressure transducer (SensoNor, Norway) connected to a bridge amplifier and Powerlab 4/30 (20). Data were recorded using Chart 5.5 software (AD Instruments, Hastings UK). The end diastolic pressure (EDP) was set to 5-7 mmHg by adjusting the balloon volume and hearts were paced at 300 bpm. Effluent samples were taken every 15 minutes and oxygen content measured using a blood gas analyser (ABL77 Radiometer, Copenhagen, Denmark). Oxygen consumption (MVO_2) was calculated as the product of arterio-venous oxygen content difference and coronary flow rate (ml/min) normalised to wet heart weight (21). Heart rate (HR), left ventricular developed pressure (LVDP) and +/- dP/dt were recorded. As a measure of cardiac work, rate pressure product (RPP) was calculated from LVDP $\times$ HR and the ratio RPP/MVO_2 used as an indicator of myocardial efficiency.

After a 20-minute equilibration period, the perfusion medium was switched to an identical buffer replacing unlabelled substrates with 1-^{13}C labelled glucose and U-^{13}C palmitate for 45 minutes. Hearts were then freeze-clamped using Wollenberger tongs and extracted using 6% perchloric acid for ^{13}C NMR analysis (22).

3.3. ^{13}C- NMR spectroscopy
High-resolution ^{1}H decoupled ^{13}C NMR spectra were collected at 500 MHz using an 11.7 Tesla ultra-shielded superconducting vertical wide bore Bruker magnet and 5mm broadband probe interfaced with a Bruker spectrophotometer. Free induction decays (FIDs) were acquired over 32000 scans with a 90° pulse (9.95 us pulse duration and 1 s inter-pulse delay) and fourier transformed for analysis using Bruker Topspin (1.3) software. The relative contributions of glucose and palmitate to oxidative metabolism were determined using the TCAcalc program provided by Dr Mark Jeffrey (University of Texas, Southwestern Medical centre, TX) (10)
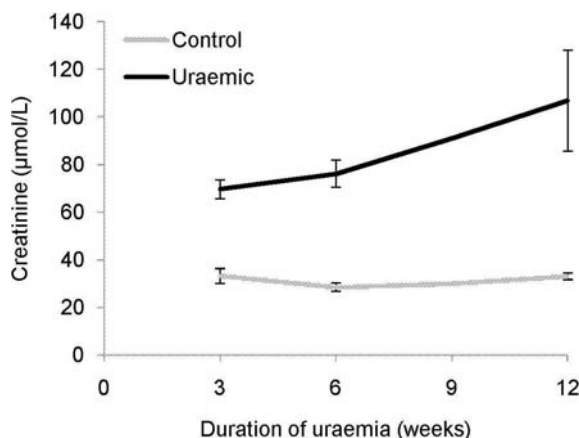
Figure 1. Serum creatinine concentrations over the duration of uraemia (* *p* less than 0.05 vs. control). 3-week: control n=7 uraemic n=7; 6-week: control n=8 uraemic n=9; 12-week: control n=15 uraemic n=10.

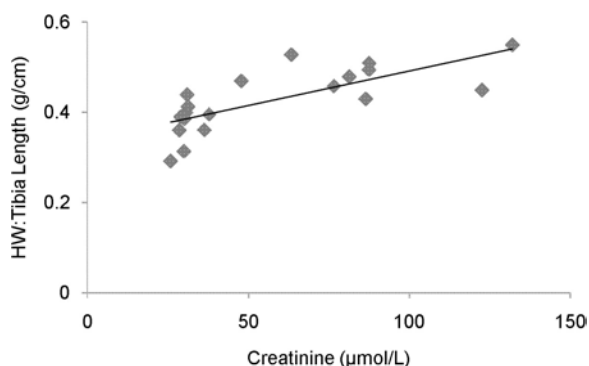**Figure 2.** Correlation between serum creatinine concentration and HW/tibia length in 12-week animals (r=0.74 *p* less than 0.05)

3.4. Haematocrit and serum metabolite analysis

Immediately after excision of the heart, blood samples were collected from the chest cavity into heparinised syringes for determination of haematocrit using the blood gas analyser or centrifuged at 3000 g for 10 minutes at 4°C. Serum was removed and stored at -20°C for metabolite analysis. Serum urea and creatinine were analysed at the clinical biochemistry department, Hull Royal Infirmary, Hull and East Yorkshire Hospitals NHS trust.

3.5. Protein expression

Expression of peroxisome proliferator-activated receptor alpha (PPAR-alpha) and CD36 proteins in 12 week uraemic and control hearts were determined by western blotting as described previously (23). Briefly, samples containing 50μg protein were separated using 10% SDS PAGE and transferred onto nitrocellulose membranes. Membranes were incubated with the primary antibodies (PPAR-alpha 1:1000 dilution rabbit polyclonal, Santa Cruz Biotechnology Inc, USA, CD36 1:6000 dilution rabbit polyclonal, Abcam, Cambridge, UK and actin 1:1000 dilution rabbit monoclonal, New England Biolabs)

followed by secondary antibodies, PPAR-alpha (1:4000 dilution donkey anti-rabbit Santa Cruz Biotechnology Inc, USA), CD36 (1:8000 dilution goat anti-rabbit Santa Cruz Biotechnology Inc, USA) and actin (1:2000 dilution anti-rabbit Santa Cruz Biotechnology Inc, USA). Protein bands were visualised using enhanced chemiluminescence (ECL) (Amersham, Uppsala, Sweden) and quantified using scanning densitometry and ImageJ software.

3.6. Statistical analysis

Results are expressed as mean +/- SEM. Statistical significance was determined using an unpaired *t* test (for single mean comparisons) or two-way ANOVA where appropriate (using the Scheffe post-hoc test). Pearsons analysis was used to determine the significance of bi-variate correlations. Statistical analysis was performed using SPSS software (16.0) and level of significance was set at *p* less than 0.05.

4. RESULTS

4.1. Characterisation of the experimental model

Characteristics of the experimental model are given in Table 1. Serum creatinine was significantly elevated in uraemic animals compared to controls at 3 weeks, and progressively increased throughout uraemia, indicating worsening kidney function with time. By 12 weeks, the serum creatinine concentration was approximately 282% higher (Figure 1) and the serum urea concentration 448% higher (data not shown) in uraemic animals than in respective control animals.

Uraemic animals exhibited a reduced haematocrit when compared to controls, highlighting development of anaemia. The degree of anaemia did not alter during the progression of kidney dysfunction. Hypertension was also observed from 3 weeks uraemia (18-19).

At 3 and 6 weeks, the percentage water content of the lungs was comparable between control and uraemic animals. 12-week uraemic animals had an increased water content of the lungs relative to controls.

At 3 weeks uraemia, there was no evidence of LVH (Table 2). By 6 weeks, uraemic animals showed a significant increase in HW/BW (*p* less than 0.05) and at 12 weeks, wet heart weight, HW/BW and HW/tibia length were significantly increased in uraemic animals compared to controls (Table 2). In addition, a positive correlation was observed between serum creatinine concentration and HW/tibia length (r=0.74 *p* less than 0.05) (Figure 2) and between haematocrit and HW/tibia length (r=0.60 *p* less than 0.05) (Figure 3) at 12 weeks.

4.2. *In vitro* cardiac function

At 3, 6 and 12 weeks, myocardial LVDP, RPP and contractility (+dP/dt) were comparable between the two groups (Figure 4 a-c). Furthermore, at 3 and 6 weeks uraemia, MVO_2 and cardiac efficiency were similar to controls (Figure 5). Interestingly, 12-week uraemic hearts exhibited a relative reduction in MVO_2 (0.83 +/-0.03 vs. 0.94 +/-0.03 umol/ g wet heart weight/ min *p* less than

Table 1. Characteristics of the experimental model

	3 Week		6 Week		12 Week	
	Control (n=6)	Uraemic (n=7)	Control (n=7)	Uraemic (n=8)	Control (n=23)	Uraemic (n=28)
Remnant Kidney (g)	1.67 +/- 0.15	1.55 +/- 0.06	1.49 +/- 0.07	1.58 +/- 0.10	1.48 +/- 0.04	1.58 +/- 0.07
Haematocrit (%)	38 +/- 2	32 +/- 1*	38 +/- 1	33 +/- 1*	42 +/- 1	33 +/- 1*
Lung Water (%)	77.6 +/- 0.6	77.9 +/- 0.2	76.9 +/- 0.1	76.8 +/- 0.2	76.8 +/- 0.16	78.0 +/- 0.32*

*p less than 0.05 vs. control

Table 2. Indices of cardiac hypertrophy

	3 Week		6 Week		12 Week	
	Control (n=6)	Uraemic (n=7)	Control (n=7)	Uraemic (n=8)	Control (n=23)	Uraemic (n=28)
BW[1] (g)	407 +/- 7	362 +/- 16*	432 +/- 11	401 +/- 11	530 +/- 9	514 +/- 13
HW[2] (g)	1.64 +/- 0.07	1.66 +/- 0.08	1.57 +/- 0.04	1.73 +/- 0.11	1.73 +/- 0.04	2.11 +/- 0.06*
HW[2]/BW[1] (g/Kg)	4.04 +/- 0.18	4.61 +/- 0.20	3.65 +/- 0.12	4.31 +/- 0.24*	3.27 +/- 0.07	4.15 +/- 0.12*
HW[2]/TL (g/cm)	0.40 +/- 0.02	0.41 +/- 0.02	0.36 +/- 0.01	0.41 +/- 0.02	0.39 +/- 0.01	0.47 +/- 0.01*

Abbreviations: body weight[1], heart weight[2] (*p less than 0.05 vs. control)

0.05) resulting in an apparent improvement in cardiac efficiency compared to control hearts (Figure 5).

4.3. Myocardial metabolism

The relative contributions of substrates to myocardial oxidative metabolism over the duration of uraemia are given in Figure 6 (a-c). At 3 weeks, no change in substrate utilisation was observed. By 6 weeks, there was a decrease in the contribution of palmitate in uraemic hearts (27.5 +/-1.9 vs. 20.0 +/-1.5% p less than 0.05). Palmitate utilisation remained depressed by 12-weeks in uraemic compared to control hearts (26.7 +/-1.9 vs. 19.2 +/-1.0% p less than 0.05) however this was compensated for by a significant rise in glucose (12.7 +/-0.6 vs. 15.5 +/-0.8% p less than 0.05) and unlabelled substrate utilisation (60.6 +/- 1.6 vs. 65.2 +/-0.9% p less than 0.05).

4.4. Protein expression

At 12 weeks, cardiac PPAR-alpha expression was similar in control and uraemic animals (1.00 +/-0.11 vs. 1.00 +/-0.17), whereas CD36 expression decreased significantly in uraemic hearts compared to controls (1.00 +/-0.08 vs. 0.78 +/-0.04 p less than 0.05) (Figure 7).

5. DISCUSSION

5.1. Experimental model of CKD

Surgical induction of uraemia using the 5/6th nephrectomy model induced kidney dysfunction as evidenced by the increased serum creatinine and development of anaemia. This is in keeping with previous observations from our group (18-19), and others (24-25).

Uraemic animals had a reduced haematocrit by 3 weeks, which remained depressed when the duration of uraemia was extended to 12 weeks. The anaemia observed may be due to decreased erythropoietin (EPO) production from the damaged kidney, which parallels observations from uraemic patients (26). Indeed, anaemia is present in 60-80% of patients with end stage renal disease (ESRD) and low EPO levels correlate with a reduction in haematocrit (27-28). EPO resistance also occurs in CKD patients as a consequence of high circulating levels of inflammatory cytokines including TNF-alpha and IL-6, potentially contributing to worsening anaemia (29-30). Low haematocrit levels are associated with an increased risk of hospitalisation in CKD patients and improving haematocrit decreases risk (31-32).

Cardiac hypertrophy was observed from 6 weeks post-surgery, increasing after 12 weeks of uraemia. The development of LVH during CKD is complex and incompletely understood. However, the association and persistence of haemodynamic factors, including increased afterload (hypertension and aortic stiffening) and increased preload (anaemia and hypervolaemia) in addition to metabolic and endocrine abnormalities will undoubtedly play a role (33).

Hypertension, in this model, is observed at 3 weeks post induction of uraemia (systolic blood pressure 138 +/-4 vs. 164 +/-5 mmHg p less than 0.05) (18), however the mechanisms underlying this remain incompletely understood. Activation of the renin-angiotensin-aldosterone system (RAAS) is considered a key contributor. Indeed, a major impact on the mortality associated with CKD patients has been achieved through treatment with angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) (34). The release of angiotensin II acts directly on vascular smooth muscles cells as a potent vasoconstrictor and also regulates renal sodium and water absorption *via* release of aldosterone. Furthermore, angiotensin II affects cardiac contractility and heart rate through activation of the sympathetic nervous system. Locally generated angiotensin II is also involved in paracrine signalling and has a mitogenic effect, acting as a growth factor in the development of LVH (35). Interestingly, several large multicentre trials have proposed renoprotective effects of ACEi independent of their anti-hypertensive actions (36-37).

Clinical and experimental studies have shown that administration of antihypertensive agents during CKD leads to a decrease in blood pressure correlating with
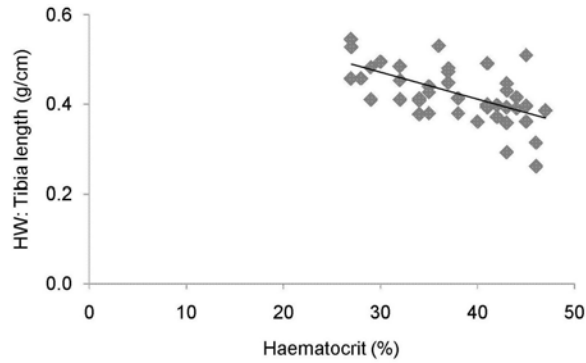
Figure 3. Correlation between haematocrit and HW/tibia length in 12-week animals (r=0.60 *p* less than 0.05).
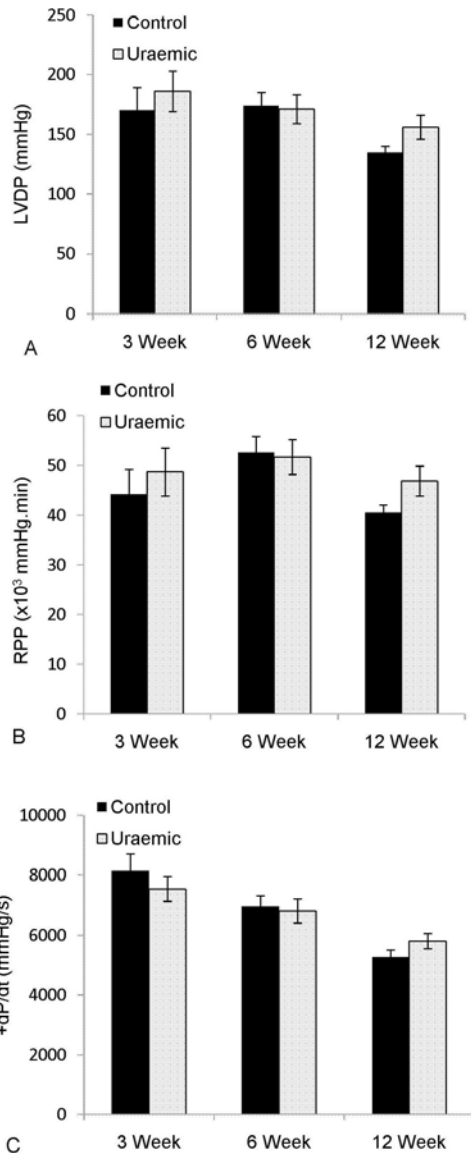

Figure 4. Isolated heart function: LVDP (a), RPP (b) and +dP/dt (c) from 3, 6 and 12 week animals. 3-week: control n=6 uraemic n=7; 6-week: control n=5 uraemic n=5; 12-week: control n=8 uraemic n=7

regression of LVH (38-39). Conversely, experimental studies have shown that LVH persists despite normalisation of blood pressure (40). Furthermore, LVH was observed in a mouse model of CKD without a corresponding increase in blood pressure, suggesting that development of hypertrophy during uraemia can be partly dissociated from hypertension (41).

Anaemia can also contribute to the development of LVH, independent of blood pressure changes. A combination of decreased blood viscosity and increased flow due to low tissue oxygenation cause an increase in demand and cardiac output (42). Both experimental (43) and clinical studies (44-45) have shown that EPO treatment is associated with an improvement in haematocrit and reduction in LVH. However, controversy exists over the degree of anaemia correction, with some studies finding that partial, rather than full correction of haematocrit is associated with LVH regression (46-47)

5.2. *In vitro* cardiac function

At 3 and 6 weeks uraemia, little change in myocardial function or efficiency was observed in uraemia in keeping with previous results (18). In contrast, experimental studies using the working heart preparation have shown cardiac dysfunction at early stages of uraemia (16) and clinical studies suggest that cardiac dysfunction occurs early in the progression of renal failure (48-49). However, it is difficult to extrapolate results from experimental studies to the clinical setting due to the existence of co-morbidities, such as diabetes, which are frequently present in CKD patients.

At 12 weeks, no differences were observed in myocardial function, however there was a reduction in MVO_2 resulting in an increased cardiac efficiency in uraemic compared to control hearts consistent with a compensatory phase of LVH. This is in contrast to previous studies showing impaired contractility by 4 weeks uraemia (16). McMahon *et al.* (2002) demonstrated impaired relaxation (evidenced by prolonged calcium transients) in isolated cardiomyocytes from uraemic hearts compared to controls in the presence of 4 mM $[Ca^{2+}]$ (50). Thus, a combination of uraemia with additional stresses such as elevated $[Ca^{2+}]$ or increased pacing may unmask dysfunction in uraemic hearts.

5.3. Myocardial metabolism

In this study, by 6 weeks, palmitate utilisation decreased in uraemic hearts and when the duration was extended to 12 weeks, palmitate oxidation was reduced with a corresponding rise in glucose and unlabelled substrate utilisation compared to control hearts. The decrease in palmitate utilisation may account for the reduction in MVO_2 in uraemic hearts as glucose utilisation is more oxygen-efficient than fatty acid oxidation.

Few studies have investigated the metabolic profile in the uraemic heart. Reddy *et al.* (2007) showed no alterations in substrate utilisation at 3 or 6 weeks uraemia
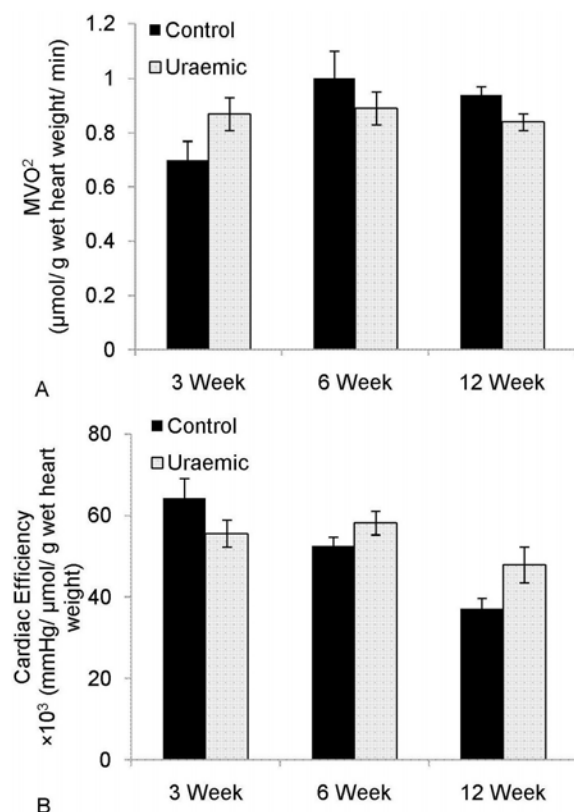
Figure 5. MVO$_2$ (a) and cardiac efficiency (b) of control and uraemic hearts at 3, 6 and 12 weeks. 3-week: control n=6 uraemic n=7; 6-week: control n=5 uraemic n=5; 12-week: control n=8 uraemic n=7

when hearts were perfused using 1.25mM calcium (18). However, increasing buffer calcium concentration could highlight changes in metabolism due to the increased contractile demand. In support of these alterations, Raine *et al.* (1993) found a decreased phosphocreatine/ATP ratio highlighting diminished energy stores in experimental uraemia, possibly reflecting a change in cardiac energy metabolism (16).

At 6 and 12 weeks, uraemic animals demonstrated marked LVH compared to controls, and the altered profile of substrate use observed consistent with findings from models of both pressure (9-10, 13) and volume overload hypertrophy (8). Here, consistent with the observed decrease in fatty acid oxidation (FAO) is the down-regulation in CD36 protein expression in uraemic hearts. This parallels observations in patients with hypertrophic cardiomyopathy exhibiting CD36 deficiency (51). Moreover, in an experimental model of angiotensin II-induced hypertension, cardiac CD36 mRNA expression was significantly decreased compared to controls (52). In contrast, models of pressure-overload hypertrophy have shown CD36 expression remains unaltered despite reduced FAO (10, 53). Given that metabolic remodelling is a feature of LVH, which persists despite normalisation of hypertension in uraemic cardiomyopathy (40-41), the

alteration in substrate use may occur independently of changes in blood pressure.

Experimental studies of LVH have shown the metabolic remodelling to reflect a re-expression of the foetal gene programme. The foetus relies primarily on glucose for ATP production (54). After birth, the upregulation of FAO parallels mitochondrial development and an increased expression of the regulatory transcription factor PPAR-alpha (11). PPAR-alpha interacts with the heterodimeric receptor RXR (retinoid X receptor), which together bind to the consensus DNA sequence known as the peroxisome proliferator response element (PPRE). Gene transcription is initiated upon activation of the complex by the co-factor PGC-1 (peroxisome proliferator receptor co-activator-1) (55).

During hypertrophy, expression of myocardial PPAR-alpha is reduced, causing a reduction in the expression of FAO enzymes including carnitine palmitoyl transferase 1 (CPT1) and medium chain acyl CoA dehydrogenase (MCAD) (56). In this study however, PPAR-alpha expression was unchanged in uraemic hearts at 12 weeks despite the decrease in palmitate utilisation. It is the combination of all three elements PPAR-alpha, PGC-1 and RXR that are required to modify transcription, therefore reduced PGC-1 may account for the reduced impact of PPAR-alpha in this model. In support of this, Garnier *et al* (2003) showed a down-regulation of PGC-1 in an experimental model of chronic heart failure (57). Furthermore, PGC-1 mRNA is decreased when Akt is overexpressed (58). Given that uraemia is associated with high levels of Angiotensin II, which activate the Akt pathway, this may reduce PGC-1 and therefore account for the decreased FAO in this model (59). In support of this, angiotensin II directly reduced palmitate oxidation in cultured adult cardiomyocytes (60). Interestingly, Barger *et al.* showed the activity of PPAR-alpha can also be regulated by post-transcriptional modification involving the extracellular signal-regulated kinase (ERK) and mitogen activated protein kinase (MAPK) pathways, which may also account for the reduced impact of PPAR-alpha without the change in protein expression (56).

The shift towards glucose utilisation may be initially beneficial in terms of oxygen efficiency. Indeed, stimulating glucose utilisation with drugs such as ranolazine, is associated with improved cardiac function in the ischaemic rat heart (61-62). However, the change in metabolic profile may in the longer-term potentially result in complications including accumulation of lipids and energy depletion. The build up of fatty acyl components can lead to sequestration of CoA and consequently decrease the CoA to acetyl-CoA ratio, inhibiting PDH and resulting in a limited capacity to utilise both fatty acids and glucose leading to energy starvation (15). A number of experimental studies have shown that increasing PPAR-alpha activity and thus FAO, leads to improved cardiac function and slows the progression towards heart failure (63-64). However, Young *et al.* (2001) demonstrated that inappropriate reactivation of PPAR-alpha during cardiac hypertrophy exacerbates dysfunction (65). This suggests
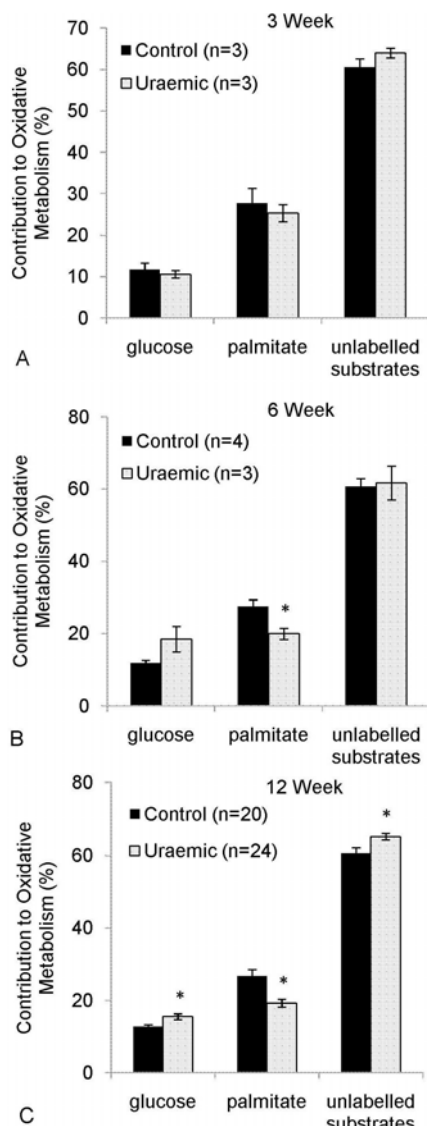
Figure 6. Contribution of substrates to oxidative metabolism at 3 weeks (a), 6 weeks (b) and 12 weeks (c) (*p less than 0.05 vs. control).
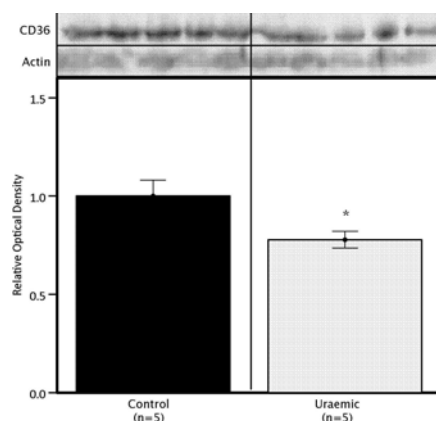

Figure 7. Protein expression of CD36 normalised to actin (*p less than 0.05 vs. control)

that down-regulation of PPAR-alpha and reduced FAO may be essential for sustaining cardiac function during hypertrophy.

6. CONCLUSIONS

In this model, kidney dysfunction was evident from 3 weeks uraemia, without cardiac hypertrophy. When the duration of uraemia was prolonged to 6 and 12 weeks, animals showed marked LVH, evidence of metabolic remodelling but no change in function highlighting a compensatory phase of hypertrophy. To our knowledge, this is the first study to show a decrease in palmitate utilisation in the hypertrophied uraemic heart. This remodelling may be a factor in the transition from compensatory LVH into dysfunction and heart failure in uraemia.

7. ACKNOWLEDGEMENTS

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