Physiol. Res. 46: 427–433, 1997

Effect of Chronic Renal Insufficiency on the Function and Metabolic Parameters of the Isolated Rat Heart

M. TUTTEROVÁ, H. VAVŘÍNKOVÁ, M. BOHDANECKÁ, L. KAZDOVÁ

Institute for Clinical and Experimental Medicine, Prague, Czech Republic

Received January 24, 1997
Accepted October 15, 1997

Summary

Chronic renal insufficiency (CRI) is often associated with cardiovascular disease; however, its underlying mechanisms are not completely understood. Therefore, in the present study, myocardial functions and metabolic changes were investigated using an animal model of CRI in subtotally nephrectomized rats. In addition, some other parameters, considered risk factors of cardiovascular diseases, were determined. Subtotal nephrectomy led to an elevation in blood pressure (144±2.8 vs 114±2.5 mm Hg), left ventricular hypertrophy (290±12 vs 200±40 mg/100 g b.w.), hypertriglyceridaemia (2.96±0.31 vs 0.77±0.07 mmol/l), and impaired glucose tolerance (AUC 836±12.4 vs 804±10.4 mmol . l^{-1} . 120 min). Isolated perfused hearts of uraemic rats exhibited diminished basal functions (coronary and aortic flow, stroke volume) by 20–30 % compared with the controls. Interestingly, the tolerance of isolated heart to global 20-min no-flow ischaemia was improved in uraemic rats. The most marked differences in heart function recovery during reperfusion concerned aortic flow (90±2.3 vs 66±10 %) and stroke volume (97±2.7 vs 68±5.6 % of pre-ischaemic values). Pre-ischaemic myocardial glycogen content was distinctly increased (by 50 %) in uraemic rats compared with the controls.

Key words

Chronic renal insufficiency – Subtotal nephrectomy – Isolated rat heart – Heart ischaemia – ATP – Glycogen

Introduction

Chronic renal insufficiency (CRI) results in premature development of atherosclerosis (Lindner *et al.* 1974) and cardiovascular disease, manifested by heart failure as the main cause of mortality in dialysis patients (Degoulet *et al.* 1982). Uraemic patients show increased incidence of the main cardiovascular risk factors including hypertension, lipid metabolism abnormalities, left ventricular hypertrophy and glucose intolerance (Wochos *et al.* 1976, Herrera-Acosta 1982, Ma *et al.* 1992, Shoji *et al.* 1992, Harnett *et al.* 1994, Eidemak *et al.* 1995). The multifactorial pathogenesis of cardiac dysfunction and the development of uraemic cardiomyopathy have not been fully clarified as yet. Cardiac dysfunction in CRI is manifested by typical haemodynamic findings. The volume and pressure overload is associated with dilated hypertrophy and subsequent disorders of diastolic function, reduction of cardiac performance, arrhythmias and cardiac failure (Messerli *et al.* 1984, Parfrey *et al.* 1987, Harnett *et al.* 1988, Parfrey *et al.* 1988).

There is still inadequate and controversial information whether mechanical cardiac dysfunction can be demonstrated by *in vitro* experiments in the absence of concomitant factors in the circulating blood *in vivo*. In most of these cases, the effects of acute uraemia or uraemia lasting only a few days were reported (Kreusser *et al.* 1983, Rambausek *et al.* 1986). Changes in dynamic and biochemical parameters of the isolated myocardium in CRI, mediated by metabolic changes occurring in the organism during a prolonged period of time, have not yet been sufficiently studied. Information is also lacking on the resistance of the uraemic myocardium to ischaemia.

It was for the above reasons that our study was designed to monitor the function of the isolated myocardium of rats in which chronic uraemia had been

induced by subtotal nephrectomy. Experiments were conducted 10 weeks after 5/6 nephrectomy when the kidneys exhibited advanced glomerulosclerosis (Rossmann *et al.* 1990). Other parameters monitored using the isolated heart included the tolerance to ischaemia and some biochemical markers. At the same time, changes in the serum creatinine, impaired lipid metabolism and glycoregulation were also determined in the uraemic rats.

Methods

The study was carried out on female rats of the inbred AVN line, derived from the Wistar strain (body weight 180–220 g). The animals were fed standard chow and water *ad libitum*. CRI was induced by 5/6 nephrectomy performed under ether anaesthesia. The experiments were discontinued at 10 weeks after subtotal nephrectomy. This interval was chosen on the basis of previous experiments (Rossmann *et al.* 1990) according to the histologically determined status of renal parenchyma. At week 10, residual parenchyma displayed, besides interstitial fibrosis and tubular dilatation, also focal and segmental glomerulosclerosis.

At the beginning and end of the experiments, blood pressure was measured by the tail-cuff plethysmography in animals of the control and subtotally nephrectomized groups. Three days prior to the end of the experiments, both studied groups had a 120-min oral glucose tolerance test (OGTT) performed, whereby the animals were given 3 g of glucose per kg of body weight after 14 h fasting. Before decapitation, the animals were placed in metabolic cages and urine was collected for total protein and potassium determinations (standard tests by Lachema, Brno, Czech Republic). Decapitation under ether anaesthesia was followed by removal of the heart which was subsequently rinsed. The wet and dry weights of the heart and both ventricles were determined. Serum creatinine, urea, glucose and triglyceride concentrations were determined using standard Lachema tests. In another series of experiments, the removed heart was rapidly placed into ice-cool saline and once the heart had stopped beating, the aorta was connected to a perfusion system. The heart was retrogradely perfused with oxygenated (95 % O_2 + 5 % CO_2) Krebs-Henseleit bicarbonate solution, at pH 7.4 and 37 °C according to Langendorff (1895). The perfusate contained (in mmol/l): 118.0 NaCl, 4.7 KCl, 2.5 $CaCl_2$, 1.2 $MgSO_4$, 1.2 KH_2PO_4, 25.0 $NaHCO_3$, 0.5 NaEDTA, 11.0 glucose. After 15 min stabilization of the preparation, the heart was switched to 20 min retrograde perfusion (working heart) according to Neely *et al.* (1967) at an aortic afterload of 60 mm Hg and at a left atrial preload of 8.8 mm Hg. This was followed by 20 min global (no-flow) ischaemia (37 °C), 15 min retrograde and 15 min antegrade reperfusion periods. At the end of reperfusion, the heart was frozen, powdered in liquid nitrogen and ATP and lactate were determined enzymatically in a neutralized perchloric acid extract (Lamprecht and Trautschold 1963). Glycogen was determined enzymatically in the chloroform-methanol sediment after acid hydrolysis similarly as glucose (Huggett and Nixon 1957). Heart function was assessed before ischaemia and at the end of reperfusion by measuring coronary and aortic flow, aortic pressure and heart rate. In separate experiments, the hearts were only perfused for 30 min according to Langendorff (1895). After inserting a polyethylene cannula with a balloon (volume 60 μl, H. Sachs, Germany) *via* the left atrium into the left ventricle, the left ventricular pressure developed (the difference between maximal systolic pressure and minimal diastolic pressure) and the peak velocity of pressure changes (dP/dt) were determined. These hearts were paced at 300 beats/min.

Results are given as means ± S.E.M. Statistical significances between the groups were evaluated using unpaired Student's t-test.

Results

Ten weeks after the beginning of the experiments, the body weight of rats in the control group did not significantly differ from that of subtotally nephrectomized animals. Renal insufficiency in the latter group of animals led to increased serum creatinine and urea levels (Table 1). Subtotally nephrectomized animals also showed elevated serum triglyceride levels. By contrast, glucose levels in fasting animals were significantly lower in chronic uraemia.

Table 1. Characteristics of subtotally nephrectomized rats at 10 weeks after 5/6 renal ablation

	Controls	Subtotal nephrectomy
Creatinine (μmol/l)	45 ± 1.5	142 ± 10.0***
Urea (mmol/l)	6.0 ± 1.0	41 ± 5.0***
Glucose (mmol/l)	5.13 ± 0.13	4.15 ± 0.25*
Triglycerides (mmol/l)	0.77 ± 0.07	2.96 ± 0.39***
Body weight (g)	217 ± 7.4	204 ± 7.1
Heart weight (mg)	583 ± 15.3	759 ± 33.8***
LV weight (mg)	441 ± 17.6	600 ± 30.3***
LV dry weight (%)	21.4 ± 0.5	22.1 ± 0.4
RV weight (mg)	142 ± 3.9	158 ± 6.2
RV dry weight (%)	21.2 ± 0.5	22.1 ± 0.4

*Significantly different from the control group: * $p < 0.05$, *** $p < 0.001$, $n = 7–14$ rats per group, LV – left ventricle, RV – right ventricle*

Uraemia enhanced proteinuria (1.96±0.46 vs 252±21 mg/24 h, $p<0.001$) and calciuria (10.4±2.5 vs 38±7.7 μmol/24 h, $p<0.001$). Over the 10-week experimental period, the blood pressure of uraemic rats rose significantly from 113±1.5 to 144±2.8 mm Hg ($p<0.001$), while it remained essentially unchanged in the control group of animals (110±1.8 and 114±2.5 mm Hg). Hypertension was accompanied by a 36 % enlargement of the left ventricle; right ventricular weight remained virtually unaltered (Table 1). The percentage of dry weight of the left heart ventricle was similar in uraemic and control group.

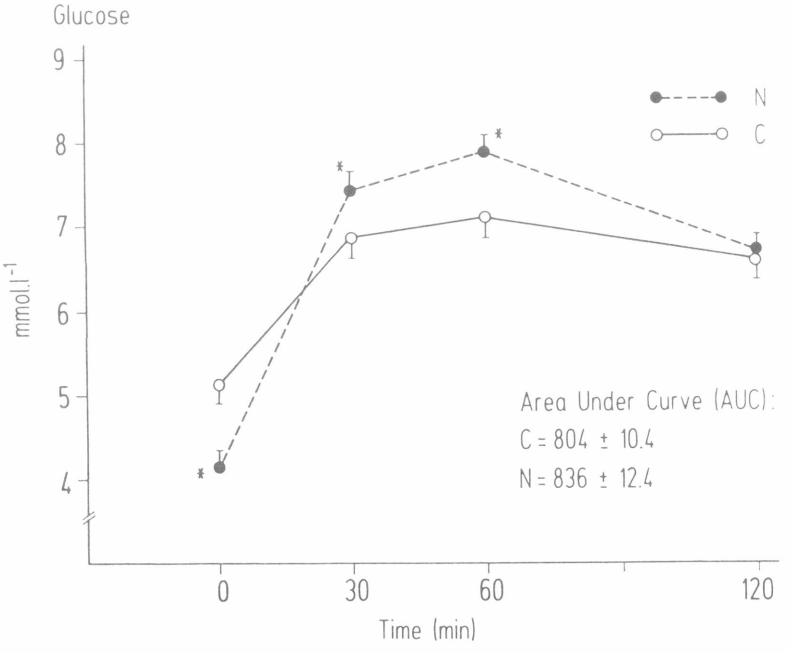

Fig. 1. *Oral glucose tolerance tests in control (C) and subtotally nephrectomized (N) groups of rats. Significantly different from the control group: * $p<0.001$, n = 6 rats per group.*

Table 2. Effect of subtotal nephrectomy on functional parameters of isolated rat heart

	Controls	Subtotal nephrectomy
Coronary flow (ml/min)	11±1.0	10±0.4
Aortic flow (ml/min)	33±3.4	39±1.0
Stroke volume (μl/beat)	186±4	209±6
Coronary flow (ml/min/g d.w.)	99±9.3	71±3.0*
Aortic flow (ml/min/g d.w.)	359±14	276±7.6*
Stroke volume (ml/beat/g d.w.)	1.84±0.04	1.47±0.04**
LVP developed (mm Hg)	94.5±8.1	88.7±5.6
dP/dt max (mm Hg/s)	1975±209	1695±171
dP/dt min (mm Hg/s)	−2003±137	−2120±49

*LVP – left ventricular pressure. Significantly different from the control group: * $p<0.05$, ** $p<0.01$, *** $p<0.001$, n = 6 hearts per group*

Subtotal nephrectomy had a deleterious effect on glucose tolerance (Fig. 1). After the oral glucose test, the area under the glycaemic curve (AUC) was significantly greater in uraemic rats (836±12.4 $mmol.l^{-1}$.120 min) compared with that in the control group (804±10.4 $mmol.l^{-1}$.120 min).

The basal pre-ischaemic haemodynamic parameters in both tested groups are shown in Table 2. Stabilized basal function of the isolated myocardium before ischaemia was not different in uraemic and control rats. However, when calculated per unit of dry heart weight, coronary flow in uraemic hearts was decreased by almost 30 %, aortic flow by 23 % and stroke volume by 20 % in comparison with the control group. Recovery of myocardial mechanical function during reperfusion following 20 min global ischaemia in the group of rats with CRI was superior to that in the control group in all the monitored parameters. Aortic flow recovered to 90.2±2.3 % vs 65.7±10 % in controls, systolic aortic pressure to 101±1.3 % vs 92.2±2.3 %; by contrast, diastolic pressure declined (Fig. 2). Stroke volume recovery in the hearts of subtotally nephrectomized rats was to 97±2.7 % of pre-ischaemic values vs 68±5.6 % in the control group. Recovery of coronary flow did not differ in either group (105±2.8 % vs 98±7.0 %).

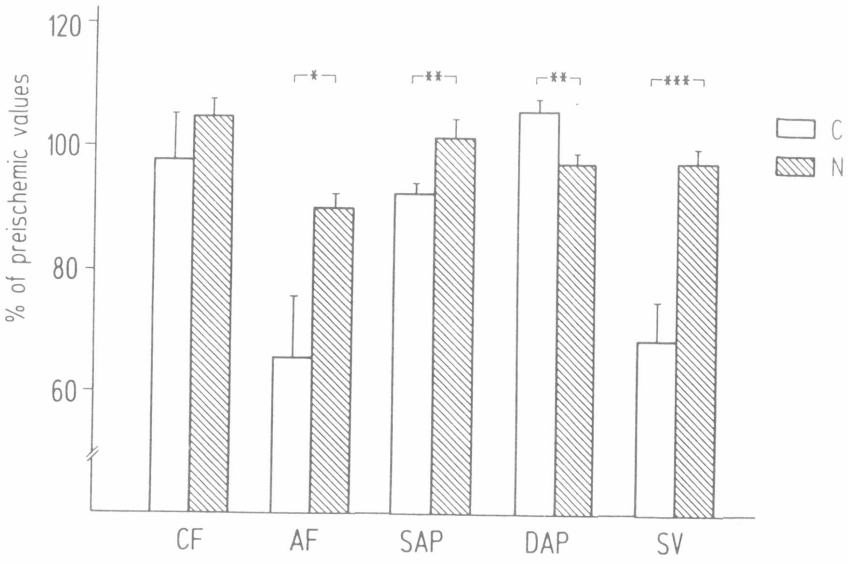

Fig. 2. *Effect of subtotal nephrectomy on recovery of functional parameters of isolated rat heart after ischaemia (20 min) and reperfusion (30 min). CF – coronary flow, AF – aortic flow, SAP – systolic pressure, DAP – diastolic pressure, SV – stroke volume. Significantly different from the control group: * $p<0.05$, ** $p<0.01$, *** $p<0.001$, $n = 6$ rats per group.*

Table 3. Effect of ischaemia and reperfusion on heart ATP and glycogen contents (μmol per g of dry heart weight)

	Controls	Subtotal nephrectomy
Preischaemia (35 min)		
ATP	17.3±1.3	19.3±1.4
Glycogen	84.4±4.8	128±13.4*
Ischaemia (20 min)		
ATP	7.25±1.0	8.84±0.5
Glycogen	29.9±2.9	65.4±16.0*
Reperfusion (30 min)		
ATP	14.2±1.3	17.9±0.4*
Glycogen	59.1±5.7	95.7±4.6***

*Significantly different from the control group: * $p<0.05$, ** $p<0.01$, *** $p<0.001$, $n = 6-7$ hearts per group*

Post-ischaemic recovery of heart function was not related to the myocardial ATP content before or during ischaemia, which did not differ. However, after reperfusion, ATP levels already corresponded to improved uraemic heart function (Table 3). On the other hand, before ischaemia the uraemic hearts had a reserve of energy substrate, i.e by about 50 % higher glycogen content than controls. The increased myocardial glycogen content persisted even during ischaemia and reperfusion. The levels of lactate in control and uraemic myocardium did not differ either before ischaemia (13.5±2.6 vs 12.1±1.4) or at the end of ischaemia (165±12.3 vs 172±19.8 (μmol/g d.w.).

Discussion

Using an experimental model of chronic renal insufficiency (CRI), the functional and associated metabolic parameters of the isolated perfused rat myocardium were investigated in the present study under the conditions simultaneously eliminating the effect of *in vivo* operating metabolites and hormones. We found marked functional and biochemical alterations in the isolated myocardium elicited by long-lasting uraemia in this model of CRI and we demonstrated, for the first time, an increased tolerance of the uraemic myocardium to ischaemia under our experimental conditions. Some peripheral changes associated with uraemia, which may have adverse effects on heart function and could be regarded as risk cardiovascular factors, were also monitored in this experimental model of CRI.

In the present rat model of CRI, just as in human renal failure (Wochos *et al.* 1976, Herrera-Acosta 1982, Shoji *et al.* 1992, Ma *et al.* 1992, Harnett *et al.* 1994, Eidemak *et al.* 1995), the main features of the uraemic disorder were observed. Our subtotally nephrectomized rats exhibited hypertension, left ventricular hypertrophy, hypertriglyceridaemia, and disturbed glycoregulation. Their blood pressure was only moderately elevated, in spite of marked left ventricular hypertrophy. These findings are in agreement with the observation reported by Harnett *et*

al. (1988). Other studies have shown that even pharmacological treatment of hypertension in experimental hypertrophy did not normalize myocardial weight (Rambausek *et al.* 1985). Apart from hypertension, a role in the development of myocardial hypertrophy is presumably played by other changes associated with CRI. These may include, in particular, activation of the renin-angiotensin system, sympathetic activation, secondary hyperparathyroidism, humoral factors and abnormal calcium homeostasis (Brecht *et al.* 1975, London *et al.* 1987, Zhang *et al.* 1994, Harnett *et al.* 1994).

Marked hypertrophy is a factor which may affect the haemodynamic function of the heart. In our experiments, stabilized basal function of the isolated uraemic myocardium did not differ from that in the controls. Compensatory hypertrophy of the myocardium was still capable of maintaining unaltered haemodynamic parameters. However, when calculated per unit of dry weight, the functional parameters monitored in uraemic hearts were deteriorated, including coronary and aortic flow as well as stroke volume. These changes were observed concomitantly with increased myocardial glycogen content but unchanged myocardial ATP content, as determined at the end of the stabilization period (before ischaemia). Under different experimental conditions, after a shorter period of CRI, a decrease in ATP concentration was noted in myocardial biopsy samples (El-Belbessi *et al.* 1986) as well as in isolated myocytes (Smogorzewski 1995).

Under our experimental conditions, the recovery of haemodynamic function following global ischaemia was distinctly better in the uraemic myocardium than in the controls. These findings are difficult to interpret. Before ischaemia, after ischaemia, and following reperfusion, myocardial glycogen content was markedly higher in uraemic rats than in the controls. However, the decrease in glycogen levels in the isolated myocardium and lactate production during ischaemia were similar in both groups.

The changes in myocardial functions, observed in our experiments, resemble those seen in the isolated hearts of diabetic rats (Khandoudi *et al.* 1990, Mochizuki *et al.* 1991). In experimental diabetes, an increased glycogen content in the isolated myocardium was likewise demonstrated (Rösen *et al.* 1986, Mochizuki *et al.* 1991). The simultaneous differences in the rate of intracellular pH recovery during diabetic heart reperfusion were explained by a decreased activity in the Na^+/H^+ exchange compared to controls (Khandoudi *et al.* 1990). This hypothesis is supported by the finding that pharmacological blockade of the Na^+/H^+ exchanger by amiloride resulted in slowed normalization of intracellular pH during reperfusion and, also, in improved functional recovery in the hearts of normal rats (Khandoudi *et al.* 1990). The decrease in the rate of Na^+/H^+ exchange and the subsequent slower influx of calcium *via* Na^+/Ca^{2+} exchange into myocytes might be one of the causes of altered recovery of post-ischaemic myocardial function (Tani and Neely 1989).

The lower calcium overload during reperfusion, i.e. at the time of return of oxidative conditions, could also explain the reduced myocardial injury following ischaemia in the myocardium of CRI rats. This is suggested by the decreased activity of membrane pumps involved in calcium transport in sarcolemmic vesicles prepared after subtotal nephrectomy in rats (Zhang *et al.* 1994). A slowing of pH recovery in skeletal muscle, preceding the changes in transport activities, was also detected after relative ischaemia in haemodialysis patients (Duzorard *et al.* 1993). It can be speculated that the paradoxically enhanced myocardial resistance to ischaemia in uraemic cardiomyopathy and, similarly, in experimental diabetes, is the consequence of changes in Na^+/H^+ antiport and Na^+/Ca^{2+} exchange. Both these processes play a pivotal role in cardiac function recovery at the start of reperfusion (Tani and Neely 1989). Although the reasons for the changes in the activities of transport processes in uraemia and experimental diabetes may be different, it is likely that an alteration of calcium homeostasis is involved in both cases.

It can be summarized that, in experimental chronic uraemia, functional and metabolic changes can be demonstrated even in the isolated myocardium, i.e under conditions when negative humoral changes cannot play a role. It was surprising finding that the tolerance of isolated myocardium to ischaemia was enhanced in uraemic rats. The observed abnormalities could be a consequence of disorders in membrane transport systems and could possibly be responsible for the frequently reported heart failure in the terminal stages of renal insufficiency, especially in dialysis and, hence, in volume- and ion-overloaded patients (Parfrey *et al.* 1988).

Acknowledgements

This study was supported by grant No. 2023-3 (Internal Grant Agency of the Ministry of Health of the Czech Republic).

References

BRECHT H.M., ERNST W., KOCH K.M.: Plasma noradrenaline levels in regular hemodialysis patients. *Proc. Eur. Dial. Transplant Assoc.* **12:** 281–289, 1975.

DEGOULET P., LEGRAIN M., REARCH I., AIME F., DEVRIES C., ROJAS P., JACOBS C.: Mortality risk factors in patients treated by chronic hemodialysis. *Nephron* **31:** 103–110, 1982.

DUZORARD D.P., PIMMEL P., BARETTO S., CAILLETTE A., LABEEUW M., BAVEREL G., ZECH P.: ^{31}P NMR spectroscopy investigation of muscle metabolism in hemodialysis patients. *Kidney Int.* **43:** 885–892, 1993.

EIDEMAK I., FELDT-RASMUSSEN B., KANSTRUP L., NIELSEN S.L., SCHMITZ O., STRANDGAARD S.: Insulin resistance and hyperinsulinaemia in mild to moderate progressive chronic renal failure and its association with aerobic work capacity. *Diabetologia* **38:** 565–572, 1995.

EL-BELBESSI S., BRAUTBAR N., ANDERSON K., CAMPESE V.M., MASSRY S.G.: Effect of chronic renal failure on heart. Role of secondary hyperparathyroidism. *Am. J. Nephrol.* **6:** 369–375, 1986.

HARNETT J.D., PARFREY P.S., GRIFFITHS S.M., GAULT M.H., BARRÉ P., GUTTMANN R.D.: Left ventricular hypertrophy in end-stage renal disease. *Nephron* **48:** 107–115, 1988.

HARNETT J.D., KENT G.M., BARRÉ P.E., TAYLOR R., PARFREY P.S.: Risk factors for the development of left ventricular hypertrophy in a prospectively followed cohort of dialysis patients. *J. Am. Soc. Nephrol.* **4:** 1486–1489, 1994.

HERRERA-ACOSTA J.: Hypertension in chronic renal disease. *Kidney Int.* **22:** 702–712, 1982.

HUGGETT A.S.G., NIXON D.A.: Use glucose oxidase, peroxidase, and o-dianisidine in determination of blood and urinary glucose. *Lancet* **1:** 368–370, 1957.

KHANDOUDI N., BERNARD M., COZZONE P., FEUVRAY D.: Intracellular pH and role Na^+/H^+ exchange during ischaemia and reperfusion of normal and diabetic rat hearts. *Cardiovasc. Res.* **24:** 873–878, 1990.

KREUSSER W., MANN J., RAMBAUSEK M., KLOOKER P., MEHLS O., RITZ E.: Cardiac function in experimental uraemia. *Kidney Int.* **24** (Suppl. 15): S83–S88, 1983.

LAMPRECHT W. TRAUTSCHOLD J.: Adenosine-5-triphosphate determination with hexokinase and glucose-6-dehydrogenase. In: *Methods of Enzymatic Analysis.* H.U. BERGMEYER (ed.) Academic Press, New York, 1963, pp. 543–551.

LANGENDORFF O.: Untersuchungen am überlebenden Saugentiereherzen. *Pflügers Arch.* **61:** 291–332, 1895.

LINDNER A., CHARRA B., SHERRARD D., SCRIBNER B.H.: Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N. Engl. J. Med.* **290:** 697–701, 1974.

LONDON G.M., DE VERNEJOUL M.C., FABIANI F., MARCHAIS S.J., GUERIN F., LONDON A.M., LLACH F.: Secondary hyperparathyroidism and cardiac hypertrophy in hemodialysis patients. *Kidney Int.* **32:** 900–990, 1987.

MA K.W., GREENE E.L., RAIJ L.: Cardiovascular risk factors in chronic renal failure and hemodialysis. *Am. J. Kidney Dis.* **19:** 505–513, 1992.

MESSERLI F.H., VENTURA H.O., ELIZARDI D.J., DUNN F.G., FROHLICH E.D.: Hypertension and sudden death. Increased ventricular ectopic activity in left ventricular hypertrophy. *Am. J. Med.* **77:** 18–22, 1984.

MOCHIZUKI S., OZEKI T., TANAKA F., NAGANO M.: Regulation of substrate utilization and ventricular function in diabetic heart. In: *The Diabetic Heart.* N. NAGANO, N.S. DHALLA (eds), Raven Press, New York, 1991, pp. 351–363.

NEELY J.R., LIEBERMEISTER H., BATTERSBY E.J., MORGAN H.E.: Effect of pressure development on oxygen consumption by isolated rat heart. *Am. J. Physiol.* **212:** 804–814, 1967.

PARFREY P.S., HARNETT J.D., GRIFFITHS S., GAULT M.H., BARRÉ P.E., GUTTMANN R.D.: Low-output left ventricular failure in end-stage renal disease. *Am. J. Nephrol.* **7:** 184–191, 1987.

PARFREY P.S., HARNETT J.D., GRIFFITHS S.M., GAULT M.H., BARRÉ P.E.: Congestive heart failure in dialysis patients. *Arch. Int. Med.* **148:** 1519–1525, 1988.

RAMBAUSEK M., RITZ E., MALL G., MEHLS O., KATUS H.: Myocardial hypertrophy in rats with renal insufficiency. *Kidney Int.* **28:** 775–785, 1985.

RAMBAUSEK M., MANN J.F.E., MALL G., KREUSSER W., RITZ E.: Cardiac findings in experimental uremia. *Contr. Nephrol.* **52:** 125–133, 1986.

ROSSMANN P., ŘÍHA I., MATOUŠOVIC K., BOHDANECKÁ M., BUKOVSKÝ A.: Experimental nephropathy. *Pathol. Res. Pract.* **186:** 491–506, 1990.

RÖSEN P., WINDECK P., ZIMMER H.G., FRENZEL H., BÜRRIG K.F., REINAUER H.: Myocardial performance and metabolism in nonketonic, diabetic rat hearts: myocardial function and metabolism in vivo and in the isolated perfused heart under the influence of insulin and octanoate. *Basic Res. Cardiol.* **81:** 620–635, 1986.

SHOJI T., NISHIZAWA Y., NISHITANI H., YAMAKAWA M., MORII H.: Impaired metabolism of high density lipoprotein in uremic patients. *Kidney Int.* **41:** 1653–1661, 1992.

SMOGORZEWSKI M.: PTH, chronic renal failure and myocardium. *Miner. Electrolyte Metab.* **21:** 55–62, 1995.

TANI M., NEELY J.R.: Role of intracellular Na^+ in Ca^{2+} overload and depressed recovery of ventricular function of reperfused ischaemic rat hearts. *Circ. Res.* **65**: 1045–1056, 1989.

WOCHOS D.N., ANDERSON C.F., MITCHELL J.C.: Serum lipids in chronic renal failure. *Mayo Clin. Proc.* **51**: 660–664, 1976.

ZHANG I.B., SMOGORZEWSKI M., NI Z., MASSRY S.G.: Altered cytosolic calcium homeostasis in rat myocytes in CRF. *Kidney Int.* **45**: 1113–1119, 1994.

Reprint requests

M. Tutterová, Institute for Clinical and Experimental Medicine, Vídeňská 800, 140 00 Prague 4, Czech Republic.