versus 0.170±0.010 mmol g⁻¹ DW, P < 0.001), while water retention was only moderate (0.68±0.119 versus 0.64±0.130 ml g⁻¹ wet weight; P < 0.001). This tissue Na⁺ excess relative to water occurred in the skin and in the muscle, while there was no significant bone Na⁺ storage. Muscle Na⁺ retention (0.220±0.029 versus 0.145±0.021 mmol g⁻¹ DW) in DOCA rats was compensated by muscle K⁺ loss (0.306±0.023 versus 0.346±0.019 mmol g⁻¹ DW), and hence an unchanged muscle (Na⁺ + K⁺)-to-water ratio. Skin Na⁺ retention (0.267±0.049 versus 0.152±0.014 mmol g⁻¹ DW; P < 0.001) in DOCA rats was not balanced by skin K⁺ loss. Hence, dietary salt loading increased the skin (Na⁺ + K⁺)-to-water ratio (0.225±0.025 versus 0.193±0.010 mmol ml⁻¹; P < 0.01) in DOCA rats, indicating osmotically inactive Na⁺ storage. In untreated control rats, dietary NaCl loading led to moderately osmotically inactive skin Na⁺ storage, while the Na⁺, K⁺, and water content in the muscle remained unchanged.

We conclude that volume homeostasis in DOCA rats is not only maintained by the renal DOCA escape, but also by an "internal" DOCA escape. Internal DOCA escape is characterized by excess Na⁺ accumulation relative to water in the tissues. This abundance of Na⁺ relative to water is achieved by two distinct mechanisms: osmotically inactive Na⁺ storage in the skin connective tissues, and osmotically active Na⁺ retention in the muscle that is balanced by muscle K⁺ loss. Internal DOCA escape allows the maintenance of volume homeostasis despite of a massive Na⁺ retention in the body.

**SP070 PROTEOMICS ANALYSIS OF CELLULAR RESPONSE TO OSMOTIC STRESS IN TALH-CELLS**

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Epithelial cells of the thick ascending limb of Henle’s loop (TALH-cells) play a major role in the uriné concentrating mechanism. They are normally exposed to variable and often very high osmotic stress, which is particularly due to high sodium and chloride reabsorption and very low water permeability of the luminal membrane. It is already established, that the elevation of the activity of aldose reductase and hence an increase in intracellular sorbitol are indispensable for the osmotic adaptation and stability of the TALH-cells. In order to identify new molecular factors potentially associated with the osmotic stress resistant phenotype in kidney cells, TALH-cells exhibiting low or high levels of resistance to osmotic stress were characterized using proteomic tools. 2D gel analysis showed a total number of 41 proteins which were differentially expressed in TALH-cells under osmotic stress. Twenty five proteins were overexpressed, whereas 16 proteins showed a down-regulation. Besides the sorbitol pathway enzyme aldose reductase, whose expression was 15 times increased, many other metabolic enzymes like glutathione-S-transferase, malate dehydrogenase, lactate dehydrogenase, alpha enolase, GAPDH, and triose phosphate isomerase were upregulated. The upregulation of the structure proteins vimentin and actin was confirmed by immunofluorescence staining, whereas tubulin was downregulated. Among the cytoskeleton associated proteins topomysin was downregulated whereas Annexin I, II and V were upregulated. The heat shock proteins as alpha crystalin chain B, HSP7a, and HSP90 were found to be overexpressed. In contrast to the results in oxidative stress the endoplasmic stress proteins GRP94, GRP78, GRP96 and calreticulin, and protein disulphide isomerase were downregulated under hypertonic stress.

**SP072 COMPARISON OF RHABDOMYOLYSIS (RM) AND ACUTE RENAL FAILURE (ARF) SEVERITY BETWEEN HEROIN (HU) AND OTHER NARCOTIC DRUG (ONDU) USERS**

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The present study was undertaken to evaluate and compare the severity of RM and ARF in HU and ONDU. Fifteen pts (male 12, female 3, mean age 27.6±5.4 years) with RM associated with ARF were classified in two groups; A. 8 HU and B, 7 ONDU. The severity of RM was evaluated by estimation, on admission, of serum CPK, SGOT, LDH, phosphorus (P) and Calcium (Ca) and by the presence of paraplegia (PPL) and the severity of ARF by estimation of serum creatinine (CR) and the presence of oligoanuria (OA) on admission, the days of hospitalization (DH), the total courses of hemodialysis (THD) and the total of pts who took blood transfusions (BT). Statistical analysis by ANOVA showed significantly higher mean values in group A than group B pts for CPK (142327± 80135 vs 39832± 14007 U/L, P=0.04), SGOT (1767± 1094 vs 406± 163 U/L, P=0.038), LDH (24327± 19342 vs 1720± 1322 U/L, P=0.03), P (9.2± 1.09 vs 6.0± 2.38 mg/dL, P=0.005) and CR (6.90± 4.87 vs 3.87± 2.3 mg/dL, P=0.035) and lower for Ca (6.23 vs 2.0± 1.02 vs 3.44± 3.23 mg/dL, P=0.035) and OA was significantly greater in group A than group B pts (5 vs 0, P=0.005) and (6 vs 2, P<0.005) as well as the total of pts who took BT during hospitalisation (6 vs 2, P<0.005). Finally DH and THD were significantly higher in group A pts, (27±0.12 34 vs 10± 2.86 days, P=0.04) and (10± 0.63 vs 2.0± 4.6, P=0.042) correspondingly.

**SP071 INCREASED ADHESION OF URAEMIC RED BLOOD CELLS TO VASCULAR ENDOTHELIUM CAUSES REDUCTION OF ENDOTHELIAL NITRIC OXIDE SYNTHASE EXPRESSION**

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Increased prevalence of atherosclerotic cardiovascular events accounts for much of the mortality among patients suffering from end-stage renal disease (ESRD). Endothelial dysfunction as a pathogenic mechanism might contribute to increasing the cardiovascular risk of ESRD. Reduced endothelium-dependent vasodilatation has consistently been observed in chronic renal failure patients. Since nitric oxide (NO) is the principal endothelium-derived vasodilator, a reduction in the NO bioavailability may be envisaged in ESRD patients. Increased adhesion of sickle erythrocytes to the vascular endothelium via enhanced surface exposure of phosphatidylserine (PS) on the outer leaflet of the erythrocyte membrane, may cause an impairment of eNOS. Because red blood cells from patients on haemodialysis have an increased propensity to adhere to human endothelial cells through surface exposed PS, it is possible that increased adhesiveness to vascular endothelium of uraemic erythrocytes might affect the endothelial NO synthetic pathway. To clarify whether exposure to erythrocytes from ESRD patients might modulate NO release by the endothelium, we evaluated endothelial NO synthase (eNOS) protein levels (Western Blot), eNOS mRNA quantity (Real Time PCR) and NOS activity (conversion of L-[3H] arginine in L-[3H] citrulline) in endothelial cultures stimulated by erythrocytes from healthy subjects and ESRD patients.

A time-dependent decrease in eNOS protein levels was evident in cultures treated with erythrocytes from ESRD patients (after 18 and 24 hours, the mean densitometric intensity in samples stimulated by RBC from ESRD patients was respectively almost 1.7 and 3 lower than the band intensity in samples stimulated by control RBC). This observation was consistent with the decreased eNOS mRNA quantities induced by erythrocytes from such patients. Moreover, as compared to controls, NOS activity exhibited a significant reduction after incubation with erythrocytes from ESRD patients. The observed eNOS reduction induced by erythrocytes from ESRD patients was totally abolished by Annexin V, able to mask RBC surface-exposed phosphatidylserine.

Our data demonstrate that adhesion of uremic RBC to endothelial cells in culture may cause a decrease in the levels of eNOS mRNA and protein, and inhibition of NOS activity. This mechanism may contribute to increased atherosclerosis and cardiovascular morbidity in ESRD patients.
The results of this study suggest that both RM and ARF are more severe in heroin users than in users of other narcotic drugs possibly due to the more severe myotoxic effect of heroin.

**SP073 GARLIC PREVENTS RADIOCONTRAST NEPHROPATHY**

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Radiocontrast nephropathy (RCN) is the third cause of hospital-acquired acute renal failure. Protective effect of N-acetyl cystein has been shown in many studies, because of similarities between aged garlic extracts (S-allylcysteine and S-allylmercapto cysteine) and N-acetyl cystein, we decided to evaluate its protective effect on RCN.

412 patients who were candidate for elective coronary angiography, all with serum creatinin(Scr) levels <1.7 mg/dl, randomly were received either aged garlic(at least12 months after harvesting, 15 gram daily orally one week before until three days after coronary angiography) and intravenous saline, or only saline(0.9%, 100 ml/h. 12 hours before and continued until 12 hours after angiography). all diabetics were received nisomnic, and all non-diabetics were received ionic contrast agent. Scr and BUN were measured just before and two and five days after angiography.

Randomly 179 non-diabetic patients(182±15 years) were enrolled to control group, and 148 patients(101±15 years), 57.9±12.5 years) received garlic, in control group Scr raised from a baseline of 0.95±0.19mg/dl to 1.05±0.186 and 1.189±0.174 mg/dl at two and five days after angiography, in garlic group Scr raised from a baseline of 0.907±0.181 to 0.908±0.187 and 0.923±0.184mg/dl at two and five days after angiography. In non-diabetics degree of serum creatinin elevation from the baseline were significantly lower in those who received garlic than those who didn’t receive it, both at two and five days after angiography (p<0.001). But in 27 diabetic patients who didn’t received garlic and 41 diabetic patients who received it, although this elevation were lower in garlic group but the differences were not significant.

Aged garlic has a protective effect against RCN, its sulfate groups by scavenging free- radicals protects endothelial cells from oxidative injury. This study was performed in patients with more significant degree of renal dysfunction and diabetics needs future study.

**SP074 CONSERVATIVE TREATMENT VERSUS RENAL REPLACEMENT THERAPY IN PATIENTS WITH ACUTE RENAL FAILURE: RESULTS OF THE SHARF STUDY**

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This multicentre study aims to compare outcome of different treatment modalities in acute renal failure (ARF) after correction for disease severity. Severity of disease was defined by a scoring system for hospital mortality in ARF patients that derived from the Stuivenberg Hospital Acute Renal Failure (SHARF) project. The SHARF score was developed in one centre and validated in 8 centres.

Qualified Belgian ICU units included all adult patients with a serum creatinine > 2 mg/dl that were consecutively admitted to the ICU. Patients were stratified according to the SHARF score in 3 classes (<30, 30-60, >60). Those in need for RRT received HD (intermittent hemodialysis during 4-6 hours daily) or CRRT (continuous venovenous hemofiltration). Outcome has been compared in patients with only conservative treatment and with RRT, using the SHARF score for adjustment for severity of illness.

Ten Belgian participating centres included 1303 consecutive patients with ARF. Mean age was 64 (range 15-96), 63% were male. RRT was required in 630 patients (49.9%). Among them, 38% received HD and 42% CRRT at their first day of treatment. At baseline, the mean SHARF score was 62.3 (SD 28.9), APACHE II score was 23.9 (SD 10.4) and SOFA 9.2 (SD 3.9). RRT patients showed a higher mortality than those with conservative treatment (59% versus 43%)(p<0.001) as well as a longer ICU (18 versus 10 days)(p<0.001) and hospital stay (38 versus 28 days)(p<0.001). The observed differences remained significant after correction for severity of disease. First, results were confirmed in each of the SHARF classes. Second, logistic regression revealed an increased risk of mortality for patients treated with RRT of RR=1.75 (95% CI 1.4-2.3), after a more in-depth individual correction for disease severity. Third, the increased risk remained in most severe subpopulations limiting the analysis to patients with a SHARF score >60 or taking only ventilated patients or patients with sepsis.

After correction for severity of disease, prognosis remained significantly worse in patients receiving RRT. This observation was confirmed in most severe subpopulations. As the indication for RRT differs widely, these conclusions needs to be validated in further prospective studies. However, a critical approach to the need of RRT in ARF patients seems to be warranted. (see also abstract 550768)

**SP075 CONTINUAL RENAL REPLACEMENT THERAPY IN PATIENTS WITH RENAL FAILURE IN CRITICAL STATUS**

Jaroslav Rosenberger, Luboslav Bena, Robert Roland. Dialysis Department, University Hospital, Kosice, Slovakia

Acute renal failure as the complication of in-patient care is connected with worsened survival, increased morbidity and cost of hospitalization. When renal replacement therapy is required, acute hemodialysis is usually the method of choice. However, in the case of patient in critical status, mainly with impaired hemodynamics and impossibility of transport to the dialysis center, continual renal replacement therapy (CRRT) can be used instead. Aim of this study is to explore the relationship between mortality and various demographic and clinical data in this cohort of patients treated with CRRT.

The sample consisted of 53 patients with renal failure with indication for renal replacement therapy, who were not suitable for standard hemodialysis treatment due to their critical status. The study is a retrospective analysis of all cases from a period of three years (2002-2004). Logistic regression analysis was performed in order to explore the relationship between mortality and various demographic and clinical data in this cohort of patients treated with CRRT.

The majority of patients required CRRT after cardiac surgery (51%); septic shock was the second most frequent cause (20.8%). Overall mortality was 66.0%, the worst was in the group of patients with sepsis (90.9%). Out of 17 survivors 6 patients were already in chronic dialysis program, the remaining 11 did not require renal replacement therapy after resolution of their principal diagnosis. Regression model with the best explanation of variance of mortality (51.8%) in these patients consisted of age, gender, presence of multiorgan failure, presence of isolated renal failure, cardiac surgery prior to kidney failure and chronic dialysis program. The probability of dying was significantly increased 8.2-times in the presence of multiorgan failure (p=0.05); 1.6-times in case of elective cardiac surgery (p=0.024) and 41.6-times in patients with isolated renal failure (p=0.02).

Mortality of patients in critical status with renal failure is very high, reflecting their severe diagnosis. The presence of multiorgan failure is of negative predictive value, while isolated renal failure and elective operations are good predictors. A prospective randomised study is needed to determine whether CRRT offers any significant advantage against standard hemodialysis treatment.
Acute renal failure – experimental, toxic nephropathies

In this retrospective study, we reviewed the charts for 97 liver transplantations from 91 patients in order to determine the predictive factors for acute renal failure (ARF). The mean age of the patients was 52 ± 10 years: 69.2% were men. End-stage liver disease, leading to orthotopic liver transplantation (OLT), was related to alcohol (n = 33), hepatitis C virus (n = 23), or to other causes (n = 35). In addition, 33 cirrhotic patients had hepatocarcinoma lesions. At transplantation, the Child-Pugh stages A, B, or C were found in 21%, 25%, and 54% of patients, respectively. Immunosuppression was based on steroids, tacrolimus (n = 71), or ciclosporine A (n = 26), with or without mycophenolate mofetil (n = 32). In addition, 85% of patients had induction therapy with either antithymocyte globulins (29%) or anti-CD25 monoclonal antibodies (56%). Acute renal failure (ARF) was defined as having, during the first month of post-transplantation, at least one value of serum creatinine (sCr) greater than 180 µmol/L. In addition, we recorded the need for hemodialysis for the first month post-OLT.

Thirty-two patients developed ARF: of these 13 required at least one dialysis session. Univariate analysis factors that were significantly associated with ARF were the number of OLT (>1), pre-op sCr (>75 µmol/L), pre-op creatinine clearance (CC) (<80 ml/min), the number of blood transfusions during OLT, post-op diuresis (<120 cm³/h), the requirement for post-op vasopressive drugs, the time to aspartate aminotransferase (ALT) peak (>12 h), the time on mechanical ventilation (>1 d), the time in ICU (>13 d), the requirement for post-op salperatomy, and the transient stop of CNIs.

In multivariate analysis, independent factors associated with ARF were the time to alanine aminotransferase (ALT) peak (>12 h) (OR 4.2 [1.1-16.5]; p = 0.04), the need for post-op salperatomy (OR 4.4 [1.4-12.1]; p = 0.01), post-op diuresis (<120 cm³/L) (OR 4.7 [1.6-15.5]; p = 0.005), and the need for post-op vasopressive drugs (OR 4.7 [1.6-15.5]; p = 0.01). The independent factors associated with the need for post-OLT hemodialysis were pre-op sCr (>75 µmol/L) (OR 4.58 [1.98-909]; p = 0.002), post-op salperatomy (OR 20.8 [1.7-252]; p = 0.01), and the time to ALT peak (>18 h) (OR 8.4 [1.1-64.5]; p = 0.04).

We conclude that a requirement for ARF requiring or not hemodialysis is quite common after OLT. Its independent factors are mainly related to perioperative events.

# EARLY DETECTION OF PATIENTS AT RISK OF ACUTE RENAL FAILURE AFTER NATURAL DISASTERS

Parta Hatamizadeh, Iraj Najafi, Houshang Sanadogl, Shiva Seyrafian, Shahnaz Atabak, Farid Rashid Farrokh, Ahmad Moomari, Sami Magham, Behrooz Broumand, Raymond Vanholder, Norbert Lameire, Mehran Ira, Tarhan, Iran; Zahedan, Iran; Isfahan, Iran; Tehran, Iran; Kerman, Iran; Tehran, Iran; Bandar-Ahs, Iran; Tehran, Iran; Ghent, Belgium; Ghent, Belgium

Crush syndrome, a common problem after natural disasters, may lead to acute renal failure (ARF), particularly if appropriate prophylactic measures are not performed. Thus, timely detection of patients at risk of developing ARF by the limited available resources during disaster aftermath is essential. On Friday 26 December 2003, a devastating earthquake with a magnitude of 6.6 on the Richter Scale, struck Bam (southeastern Iran), killed more than 26,000 people and injured tens of thousands of the others. To evaluate the nephrological problems, a questionnaire was sent to the hospitals which have accepted the victims. At the time of data analysis for the present study, data of a total of 2086 patients (1079 males, mean age =29.0±15.6 years) from 15 centers who had been hospitalized in the first 10 days after the earthquake was collected. However, due to the chaotic circumstances of the quake aftermath, some of the questionnaires contained only partial information. Therefore, the cases that underwent any of the statistical analyses, were those about whom the relevant information for that particular analysis was available. ARF was defined as at least two daily serum creatinine values equal to or above 1.6 mg/dL and/or need for dialysis. Student’s t-test or Mann-Whitney test and Chi-square or Fisher’s exact test were performed as appropriate.

ARF was associated with longer time under the rubble (6.2±4.1 vs. 2.1±3.9 hours), and higher levels of the following parameters on admission: systolic and diastolic blood pressures (127.2±23.0 vs. 113.8±17.1 mmHg and 79.0±12.3 vs. 71.7±10.5 respectively), serum levels of muscle enzymes (15277.1±19550.0 vs. 3976.4±4760.5 IU/l for creatine phosphokinase[CK]), 2866.2±1766.0 vs. 896.0±610.1 IU/L for lactate dehydrogenase[LDH] and 259.0±204.6 vs. 113.8±111.8 IU/l for aspartate aminotransferase[AST]), BUN (102.0±64.9 vs. 23.3±18.8 mg/dL), creatinine (4.4±2.3 vs. 0.8±0.2 mg/dl) and potassium (5.6±2.1 vs. 4.3±0.5 meq/l) and lower level of serum sodium (132.9±5.3 meq/l) along with lower urine output during the first 24 hours after hospitalization (0.8±1.2 vs. 2.5±1.8 L/24hr). Likewise, higher proportions of ARF patients had positive urine taste test results for blood (91.7% vs. 50.5%) and protein (61.8% vs. 18.2%) on admission. (P<0.001 for all comparisons).

Therefore, simple evaluation of injured victims by estimation of the time under the rubble, blood pressure measurement and urine test tape, that can be easily performed in the field of catastrophe, can help early detection of patients at risk of ARF. Measurement of daily urine output, muscle enzymes, BUN, creatinine, sodium and potassium are useful complementary assessments after hospitalization.

# PREDICTIVE FACTORS FOR ACUTE RENAL FAILURE (ARF) AFTER ORTHOTOPIC LIVER TRANSPLANTATION (OLT)

Joelle Guittard1, Nassim Kamar1, Olivier Cointault1, Laurence Lavayssiere1, Bertrand Sour1, Karol Barange2, David Ribes1, Dominique Durand1, Lionel Rostaing1,2 (Nephrology, Dialysis, and Transplantation, CHU Rangueil, Toulouse, France; 3Gastroenterology, CHU Purpan, Toulouse, France)

In this retrospective study, we reviewed the charts for 97 liver transplantations from 91 patients in order to determine the predictive factors for acute renal failure (ARF). The mean age of the patients was 52 ± 10 years: 69.2% were men. End-stage liver disease, leading to orthotopic liver transplantation (OLT), was related to alcohol (n = 33), hepatitis C virus (n = 23), or to other causes (n = 35). In addition, 33 cirrhotic patients had hepatocarcinoma lesions. At transplantation, the Child-Pugh stages A, B, or C were found in 21%, 25%, and 54% of patients, respectively. Immunosuppression was based on steroids, tacrolimus (n = 71), or ciclosporine A (n = 26), with or without mycophenolate mofetil (n = 32). In addition, 85% of patients had induction therapy with either antithymocyte globulins (29%) or anti-CD25 monoclonal antibodies (56%). Acute renal failure (ARF) was defined as having, during the first month of post-transplantation, at least one value of serum creatinine (sCr) greater than 180 µmol/L. In addition, we recorded the need for hemodialysis for the first month post-OLT.

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We conclude that a requirement for ARF requiring or not hemodialysis is quite common after OLT. Its independent factors are mainly related to perioperative events.

Patients with (Group 1) or without (Group 2) gadolinium induced nephrotoxicity

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>Age</th>
<th>Baseline CrCl (ml/min/1.73m²)</th>
<th>DM (%)</th>
<th>DN (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>12 (7M/5F)</td>
<td>67.08 ± 8.41*</td>
<td>17.50 ± 0.66*</td>
<td>50</td>
</tr>
<tr>
<td>Group 2</td>
<td>61 (35M/26F)</td>
<td>54.52 ± 17.11*</td>
<td>33.50 ± 15.70*</td>
<td>16.3</td>
</tr>
</tbody>
</table>

DM: Diabetes mellitus, DN: Diabetic nephropathy, * Mean values ± SDs. 

# Author declined to present
ROLE OF HYALURONAN AND CD44 IN INFLAMMATION AFTER ACUTE ISCHEMIA/REPERFUSION INJURY

Anne Emile Declèves 1, Nathalie Caron 2, Gérard Toubeau 2, Denis Nonclercq 3, Alexandre Legrand 2, Bruno Flamion 1.

Hyaluronic acid (HA) has been shown to accumulate in the renal cortex (C) in I/R injury while its major receptor, CD44, considered as an adhesion molecule, is up-regulated. We hypothesized that HA and CD44 could be considered as suitable candidates involved in the inflammatory processes as well as in renal regeneration. To address this point, the localization and expression of HA, CD44, monocytes/macrophages (M/M) and PCNA-positive (regenerative) cells were characterized by immunocytochemistry at different time-points after I/R injury in uninephrectomized rats in C, outer and inner stripes of outer medulla (OS, IS), and inner medulla (IM). Co-expression of CD44 and monocytes/macrophages was analyzed by double-labeled immunofluorescence method. Renal function was also evaluated by measuring creatininemia, which significantly increased within 12 h, was maximal at 48 h and tended to return to control at day 15. In uninjured kidneys, HA was mainly localized in the interstitium of IM and IS but was virtually absent of C. After I/R, HA staining progressively increased in C and OS from 12 h to day 7, and decreased but did not normalize at day 15. In controls, CD44 was mainly present on basolateral membranes of collecting ducts in IS. After I/R, CD44 appeared in C and OS at 24 h and reached maximal expression at day 7. It was then detected on the apical pole of collecting duct and proximal tubule cells and in the interstitium. In IS, the increase in CD44 staining was maximal at 48 h. The expression of CD44 decreased at day 15 and was restrained to degenerative areas. No significant changes were detected for HA and CD44 staining in IM at any stages after I/R. The amount of M/M increased in the interstitium of C, OS and IS at 48 h, and was maximal at day 7. In the IM area, M/M were observed only at days 7 and 15 in the interstitium. Moreover, CD44 and M/M were partially co-expressed in some interstitial areas and granulomas throughout the kidney. Proliferation in tubules was mainly detected at 24 h and 48 h, while in the interstitium, the staining was maintained until day 7. In conclusion, our results demonstrate that, after renal I/R, interstitial HA appeared first, and CD44 followed closely within 24 h, while the presence of M/M was detected later. HA and CD44 remained elevated for at least 7 days and thereafter seemed to be attenuated, in correlation with the evolution of renal function. Therefore, HA and CD44 might play a role in the processes of inflammation and regeneration related to I/R, as further suggested by the co-expression of CD44 and M/M staining.
incidence of primigravida (p=0.02) and a longer gestational age at the on-
set of HELLP (p=0.01) than those in the non-ARF group. The recovery time of
HELP in the ARF group was much longer than that in the non-ARF group (p=0.01). In the ARF group, the serum AST concentration was higher
(p=0.01) and the nadir blood platelet counts were lower (p=0.02). The incidence of disseminated intravascular coagulation (DIC) was signif-
ically higher in the ARF group than in the non-ARF group (p=0.00). There
was no significant deference in the incidence of pulmonary edema, abrupt-
tio placentae, eclampsia, and fetal death between the two groups. There was
no maternal mortality in either groups. Only one patient in the ARF group
diagnosis. In all ARF patients, the renal impairment fully recovered
within a median of 5 days (range: 2-32 days) after the onset of ARF. In con-
clusion, the clinical factors associated with ARF in HELLP syndrome were
primigravida, gestational age, serum AST level, blood platelet counts, and
DIC. The ARF in HELLP syndrome fully recovered without progression to
permanent renal impairment.

**SP082** THE INVESTIGATION OF HYPERBARIC OXYGEN THERAPY’S ROLE IN CISPLATIN INDUCED NEPHROTOXICITY IN RATS

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Cisplatin (CP) is an effective chemotherapeutic agent used in the treatment of various solid tumours. The most frequently observed side effect with the use of CP is nephrotoxicity. Recently, evidence has been demonstrated that reactive oxygen species forming in the tubular epithelium play an impor-
tant role in CP-linked nephrotoxicity. The aim of the study was to observe the effect of hyperbaric oxygen (HBO) therapy on CP nephrotoxicity, a subject which has not been studied previously. Wistar rats were treated with CP (a single intraperitoneal [IP] dose of 0.6 mg/kg) alone and in combination with HBO (60 mins every day for seven days at 2.5 atmo-
spheric pressure). Effects of the treatment on renal functions and histology were determined. In analyses at the end of the study it was observed that the serum urea, creatinine and daily urinary protein excretion levels of the CP group were higher than at the start of the study, and that the creatinine clearance level had fallen (p < 0.05). There was no significant difference between the CP+HBO group and HBO group serum urea, creatinine, creat-
inine clearance and daily urinary protein excretion levels at the beginning and end of the study (p > 0.05). At histopathological examination, in the CP group, the necrosis score in the proximal tubule epithelial cells and average apopitic cell numbers were higher than those in the CP+HBO and HBO groups (p < 0.05). There was no statistical difference between the CP+HBO group and the HBO group in terms of necrosis score in the prox-
imal tubule epithelial cells and the percentage of distal tubules containing hyaline casts in the lumen. In conclusion, in this study it was observed that in the prevention of experimental CP nephrotoxicity the synchronous application of HBO therapy with CP prevents kidney damage.

**SP083** EFFECTS OF PRECONDITIONING WITH CYCLOSPORIN A ON EXPRESSION OF THE HEAT SHOCK PROTEIN 47 IN GENTAMICIN-INDUCED NEPHROTOXICITY

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Heat shock protein 47 (HSP47) is a collagen-binding protein, thought to play an essential role in the assembly and processing of procolla-

gen and it was strongly expressed in the tubular cells and interstitial cells in gentamicin-induced nephrotoxicity (GIN). Preconditioning with cy-
closporin A (CsA) is protective against renal injury by cholesterol accumu-
lation or induction of reno-protective heat shock protein. We hypothesis that preconditioning with CsA would ameliorate renal injury and whether regulates expression of HSP47. Sprague-Dawley rats were given vehicle (control), gentamicin (100mg/kg/day for 7 days, IP/GM) and CsA (10mg/kg, 24 hour before GM therapy for 7 days, SQ/CsA). BUN, creatinine, creatinine clearance were mea-
sured 7 days after gentamicin therapy. And the left kidney was obtained 7
days after gentamicin therapy and processed for histological, immunohis-
tochemical, immunofluorescent and molecular analyses for HSP47.

Preconditioning with CsA significantly improved renal function and struc-
tural injury in model with GIN. The immunohistochemical and immunoflu-
orescent expression density for HSP47 in CsA group was significantly
lower than those in GIN group but it was higher than those in control group. These data demonstrate that preconditioning with CsA have protective ef-
fect on renal function and structure in GIN. And the reduction of HSP47 overexpression by preconditioning with CsA may play a role in the inhibi-
tion of development and progression of GIN. Further investigation of the role of preconditioning with CsA in GIN is in progress.

**SP084** RISK FACTORS FOR DEATH IN ACUTE RENAL FAILURE REQUIRING DIALYSIS IN CRITICALLY ILL PATIENTS

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Acute renal failure (ARF) is common in critical care patients, and is asso-
ciated with increased morbidity and mortality, especially in its more severe
form, that requires renal replacement therapy. The aim of our study is to
recognize the risk factors for death in the patients with ARF that require
dialysis in our Unit. We recorded all patients dialized for ARF between
October 1994 and October 2004. For intermittent hemodialysis we use a Fresenius 4008E machine and polysulfone dialyzers. For continous ther-
apies (CRRT) we first used a DM 08 Fresenius machine, and since 2001, a Diapact-CRRT Braun machine with polysulfone hemofilters.

A total of 179 patients were treated, 64% males, mean age 60.4 ± 20.4 years
(range 15-92, median 65), APACHE II score at admission was 21.6 ± 5.4
points. Overall mortality rate was 45.2%. In a univariate analysis, factors
significantly associated with increased risk of death (p < 0.05) were: age 70
years or older (OR 1.40), APACHE II score at admission higher than
20 (OR 1.43), the need of mechanical ventilation (OR 2.76), the presence of
sepsis (OR 1.45), and the treatment with CRRT (OR 1.40). There was
no significant association with gender, surgery as a primary diagnosis of
admission, use of contrast or nephrotoxins, use of vasoactive drugs and
the presence of oliguria. Multivariable analysis using step-forward variable
selection (model acceptance criterion, p<0.05) showed that only age older
than 70 and the use of mechanical ventilation independently correlated
with death. The availability of better technology and better understanding
of the use of CRRT also impact on death risk. Before 2001, 70.5% of
patients treated with CRRT died (OR 1.60 compared with IHD). In contrast,
since 2001, patients treated with CRRT had 45.7% mortality rate (OR 1.28
compared with IHD).

In conclusion, in the patients we dialize for ARF, the risk of death is higher
in those who are older than 70, mechanically ventilated, septic patients. The
results with CRRT are improving, due to better knowledge and technology,
expanding its use.

**SP085** FACTORS AFFECTING OUTCOME IN ACUTE RENAL FAILURE (ARF) TREATED WITH HEMODIALYSIS (HD) IN INTENSIVE CARE UNIT (ICU)

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ARF in the critical patient on ICU bears a high mortality rate, in partic-
ular when dialysis is necessary. In order to identify the main predictive
outcome factors, we have analysed all the ARF cases needing HD we followed up in one adult ICU (not including heart surgery patients) of the Policlinico S. Orsola-Malpighi. Out of 129 cases (93 M, 35 F; 63.4±15 years; intermittent dialysis (ID) in 85 and continuous (CD) in 44) the overall mortality was 40.6% (30.9% in ID, 60.4% in CD). Multivariate logistic regression with both forward and backward variable selection was used to assess the weight of different variables related to outcome at two different moments, the ICU entry (T1) and at the moment of HD need. Access to ICU was due to medical causes in 41.7% of the cases, with a 54% mortality rate, and in the remaining cases due to surgical reasons (32% emergency and 26.3% first-choice treatment, with a mortality of 48.3% and 29.2%, respectively). The aetiology of ARF was multifactorial in 64.8% of the cases. Diuresis upon entry was < 200 ml/die in 23 patients, 16 of whom (69.6%) subsequently died. No differences emerged between survivors (S) and non-survivors (nS) in terms of age, the presence of major concomitant pathologies (APACHE), the number of hospitalisation days, the overall number of dialysis sessions and the number of days elapsing between ICU entry and the delivery of the first HD.

At univariate analysis, variables with the highest significant association with mortality were: miocardial insufficiency (p=0.0001, Odds Ratio, OR, 1.8 at T1 and 2.36 at T2), respiratory insufficiency (RI) requiring assisted mechanical ventilation (p=0.001, OR 3.76), and sepsis as the etiologic factor of ARF (p=0.009, OR 2.93). At multivariate analyses, RI at T2, rather than myocardial insufficiency, was the strongest predictive factor, followed by the APACHE score, sepsis and diuresis at T2.

Table 1. Multivariate regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>P value</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>RI at T2</td>
<td>0.006</td>
<td>6.08</td>
<td>2.16-17.1</td>
</tr>
<tr>
<td>Sepsis at T1</td>
<td>0.0027</td>
<td>5.19</td>
<td>1.77-15.25</td>
</tr>
<tr>
<td>Diuresis at T2</td>
<td>0.033</td>
<td>0.21</td>
<td>0.74-0.89</td>
</tr>
<tr>
<td>APACHE at T2</td>
<td>0.0065</td>
<td>1.12</td>
<td>1.03-12.1</td>
</tr>
<tr>
<td>Myoc. Insuff. at T1</td>
<td>0.02</td>
<td>3.1</td>
<td>1.22-8.68</td>
</tr>
<tr>
<td>Sepsis at T2</td>
<td>0.033</td>
<td>2.99</td>
<td>1.1-8.2</td>
</tr>
</tbody>
</table>

Post-surgical ARF and a pre-existing renal dysfunction which were found significant at the univariate analysis (p=0.07 and 0.04, respectively) did not turn out to be relevant predictive outcome factor at the multivariate analysis.

In conclusion, prolonged respiratory insufficiency proved as the factor absolutely most closely linked to outcome, even more than myocardial failure; the septic state, contraction of the urinary volume and the APACHE score are other factors highly critical for the survival probability.

**SP086**

**THE PROMETHEUS (P) SYSTEM: AN EXTRACORPOREAL SUPPORT IN COMBINED LIVER AND KIDNEY INSUFFICIENCY**

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The appearance of ARF in patients with end-stage liver disease (ESLD) is generally a factor with a fatal prognosis. For those on waiting list for the organ allocation, with creatinine and bilirubin having a leading role, the importance of such a system is expected to be growing, offering the chance to patients otherwise rejected from the Tx program and with a fatal prognosis to wait for the new organ.

was 57.3±17, uric acid 55.2±9.5, phosphate 51.6±11%. A significant reduction was observed in the circulating level of the soluble receptor for Interleukin 2 (-15.5%, p=0.002); Interleukin 8 and TNF as well showed an important reduction (-53.4% and -29.6%, respectively), even though not significant. Five patients received LTx, 3 died. The P system proved able to control the metabolic derangements of both kidney and liver insufficiency. The ability to remove some cytokines raises the possibility that P might reduce the splanchnic vasodilatation typical of ESLD. In the MELD era (model for ESLD) for the organ allocation, with creatinine and bilirubin having a leading role, the importance of such a system is expected to be growing, offering the chance to patients otherwise rejected from the Tx program and with a fatal prognosis to wait for the new organ.

**SP087**

**NEW RISK FACTORS OF CONTRAST INDUCED NEPHROPATHY**

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Contrast-induced nephropathy (CIN) is a common cause of hospital-acquired acute renal failure. Contrast-related risk factors include excess doses of contrast volume and the use of ionic and high osmotic agents. Patient-related risk factors include pre-existing renal insufficiency, diabetes mellitus, advanced age, congestive heart failure, concomitant administration of drugs that interfere with the regulation of renal perfusion and any condition associated with decreased effective circulation volume. The aim of this present study was to assess the possible new risk factors of contrast nephropathy.

We studied 1323 patients who underwent coronary angiography and 207 of them was included to the study. We excluded in this study all the well known contrast-related and patient-related risk factors. A relative increase in the serum creatinine concentration of at least %25 from the baseline value was defined CIN. All patients were evaluated for possible risk factors for CIN such as metabolic syndrome, pulmonary hypertension, mild anemia, multi-vessel coronary stenosis, smoking, left ventricle diastolic dysfunction, hyperalbuminemia and chronic ACE inhibitors administration. Metabolic syndrome diagnosed using the ATP III criteria., pulmonary hypertension by doppler echocardiography when the pulmonary artery pressure is over 30 mmHg, diastolic dysfunction diagnosed when E/A in echocardiography, Multi-vessel coronary stenosis diagnosed when two or more coronary vessel involved over %70. Serum albumin level below 3.5 g/dl was defined as hyperalbuminemia. Hemoglobin level between 14-12 g/dl in males, 13-11 g/dl in females were defined as mild anemia. Chronic ACE inhibitor usage defined at least 6 months administration of any ACE inhibitors. Smoking was diagnosed from history of the patients (Smoking at least 1 packet a day for 20 years). Twenty patients (%9.6) developed CIN. This study demonstrates a high incidence of MS (p=0.003), mild anemia (p=0.029), multi vessel-coronary involvement (p=0.000) and hyperalbuminemia (p=0.006) in patients who developed CIN compared with non developed CIN.

Metabolic syndrome, mild anemia, multi-vesselcoronary involvement and
hypoalbuninemia are new risk factors for CIN in patients underwent coronary angiography. Pulmonary hypertension, smoking, left ventricle diastolic dysfunction and chronic ACE inhibitor administration are not risk factors for CIN.

**SP088** IS N-ACETYL CYSTEINE EFFECTIVE ON PREVENTION OF CONTRAST NEPHROPATHY IN PATIENTS WITH LOW CREATININE CLEARANCE (CCr) LEVEL?

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Contrast nephropathy is a common cause of renal dysfunction after cardiac angiography. There are controversies in preventive effect of N acetyl cysteine (NAC) on contrast nephropathy (CN) after imaging. Some studies have shown the preventive effect of NAC in patients with CCr less than 60 ml/min. In order to evaluate the effect of NAC in prevention of CN in patients with decreased CCr level a controlled study was designed. The study group consisted of 120 subjects (53% males and 47% females). Eligible patients were candidates for cardiac angiography with creatinine clearances between 30-50 (42.55±7.4) ml/min calculated by cockcroft gault equation. Patients were randomized to two groups. Group I were patients who assigned to receive NAC orally 600 mg every 12 hour plus normal saline infusion 100 cc per hour from the day before procedure to the day after for 48 hours. Group II received just IV saline infusion same as group one. We defined end point as 0.5 mg/dl increase in serum creatinine level within day 1 and 2 after procedure.

There were no significant differences between baseline characteristics of two groups (NAC+ vs.NAC-) including serum creatinine level (1.52±0.33 vs.1.56±0.24, p = 0.45), CCr(42.85±7.4v.s.42.34±7.4 p=0.713), age (62.22±7.1 vs. 63.20±8.3 Yrs.), number of diabetic patients, duration of angiography and mean volume of dye infused. CN by definition developed in 8.3% of subjects, 10% in NAC group and 6.7% in control group (P=NS). The independent predictors of CN risk were diabetes and higher serum creatinine level in our patients. In our study NAC was not effective on prevention of CN after cardiac angiography in patients low CCr.

**SP089** ROLE OF AMINOPHYLLINE IN THE MANAGEMENT OF NEONATAL ACUTE RENAL FAILURE - A PROSPECTIVE STUDY

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Acute Renal Failure(ARF) in the neonate is a challenging problem. Practical difficulties in undertaking dialysis add to the woes. Any simple drug therapy which can avoid dialysis and improve the outcome would be a boon. Elegant experimental studies have shown the usefulness of Aminophylline in ARF, through its anti-adenosine effect. Intra renal Adenosine appears to be causally involved in the early stages of vasomotor nephropathy. Adenosine causes renal vasoconstriction by itself and by potentiat- ing Angiotensin II but decreases post-glomerular tone independant of An- giotensin II. But clinical studies to prove the efficacy of Aminophylline are few and far apart.

A prospective study was undertaken to analyze the role of Aminophylline in neonatal renal failure. Consecutive cases of neonatal ARFs were included in the study. Prerenal azotemia, neonates who died within 48 hrs, renal failure due to congenital anomalies and obstruction, and those associated with other serious cardiac and other systemic congenital problems were excluded. Alternate cases were allotted to the Aminophylline limb.

Aminophylline infusion was infused - bolus of 5 mg/kg over 2 hrs followed by 0.3mg/kg/hr. It was stopped at the end of 48 hrs, in case of no response (if urine output did not increase to > 1 ml/kg/hr). The other group was treated with fluid resuscitation, diuretics and other standard measures for ARF. PD was undertaken in case of persistant oliguria, fluid excess, hyperkalemia or significant uremia.

Total 50 cases. Etiology of ARF included Asphyxia neonatorum and Septicemia.

**SP090** EFFECTS OF DIFFERENT AGENTS ON RADIOGRAPHIC CONTRAST AGENT-INDUCED NEPHROPATHY

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Radiographic contrast agents are used at an increasing rate for several diagnostic applications due to development in imaging technologies. Therefore, radiographic contrast agent-induced nephropathy (RCAIN) is seen frequently in clinical practice. Because of effectiveness of different agents in the prevention of RCAIN is incompatible, we wanted to investigate the efficacy of N-acetylcysteine, theophylline, nimodipine and misoprostol in the prevention of RCAIN in subjects without renal disease.

Eighty-six subjects, in whom radiographic imaging with contrast agents were planned for non-renal causes, were divided into the five groups (group I, only hydrated with 2000 ml saline, n=18; group II, misoprostol 400 mg a day was used and hydration, n=19; group III, nifedipin 30 mg a day and hydration, n=11; group IV, theophylline 200 mg a day and hydration, n=18; group V, N-acetylcysteine 600 mg a day and hydration, n=20). Non-ionic radio-contrast agents including iomeprol 61.2g/100ml and iopamidol 61.2g/100ml (100 ml) were given for the studies. All preventive measures were used in previous day of the procedure, procedure day and next day. In previous and next days, measurements of blood pressures, blood urea nitrogen, serum creatinine, sodium, potassium, plasma renin activity, aldosterone, urine and plasma osmolality, urine sodium were performed. Urine outputs were recorded. In addition, estimation of creatinine clear-
THE CHANGING FACE OF ARF IN THE INTENSIVE CARE UNIT: DATA FROM THE CASEMIX PROGRAMME

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The Case Mix Programme (CMP) is a national comparative audit of adult, general Intensive Care Units (ICUs) in England, Wales and Northern Ireland co-ordinated by the Intensive Care National Audit & Research Centre. The programme collects information about patients in the first 24 hours of admission to ICU, and their subsequent outcome.

Data were extracted for 276,731 admissions over an 8 year period to 170 adult, ICUs. ARF was defined as a serum creatinine ≥ 300 μmol/L and/or serum urea ≥ 40 mmol/L in those not requiring RRT prior to admission.

Sub-groups of oliguric and non-oliguric ARF were determined by a urine output of ≤ 0.5 ml/kg/hour, and ICU and hospital survival were recorded.

ARF occurred in 17.3% of admissions (6.3%), mean age was 63.2 ± 1.5 years and 66.4% were male. The source of admission was non-surgical in 83.7%. Sepsis was present in 43.7%, ventilation was required in 59.6%, and ARF was non-oliguric in 63.9% of cases. All ARF mortality in the CMP unit was 43.3% rising to 58.6% at hospital discharge. Median CMP LOS for ARF was 4.1 days for survivors and 2.0 days for non-survivors versus 1.7 and 2.0 days respectively for all admissions. Median hospital LOS for ARF was 31 days for survivors and 8 days for non-survivors versus 16 and 9 days respectively for all admissions. Oliguria was associated with longer lengths of stay for survivors and shorter lengths of stay for non-survivors.

The following factors were associated with increased odds of mortality: increasing age, male sex, presence of past medical history conditions, CPR during the 24 hours prior to admission to the CMP unit, mechanical ventilation during the first 24 hours after admission to the CMP unit, oliguria, hospital stay of at least one week prior to admission to the CMP unit, low pH, abnormal serum sodium, high serum potassium, low serum albumin, high haematocrit, low white blood count, and low Glasgow Coma Score. Surgery during one week prior to admission or during the first week in the CMP unit and sepsis were both associated with decreased odds of mortality.

The aetiology of ICU ARF is now predominantly non-surgical and the mean age of ICU ARF is increasing reflecting population trends. ARF accounts for nearly 10% of all ICU admissions and their subsequent outcome. The mean age of ICU ARF is increasing reflecting population trends.

Moreover, we have examined a possible influence of angiotensin con-

ting treatment, plasmapheresis, blood transfusions, antibiotic and steroids therapy (iv boluses) followed by oral steroids (prednisone 1 mg/kg/die), achieved complete clinical recovery and improved renal function even if the nephritic syndrome persisted.

The peculiarity of this case report is the association of multicentric hyline vascular type CD with thrombotic microangiopathy. In general, kidney involvement in reported case of CD is most frequently represented by various histological lesions, ranging from all kinds of glomerulonephritis (membranoproliferative, minimal changes, membranous, mesangial, crescentic and fibrillar) to secondary AA amyloidosis.

Another interesting aspect of our case is the favourable prognosis with complete recovery of renal function thanks to only corticosteroid ther-apy, an effective alternative treatment of multicentric CD with systemic symptoms and renal involvement.

SP093 ACUTE TUBULAR TOXICITY OF CYTOSTATIC THERAPY IN CHILDREN WITH CANCER

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Nephrotoxicity is a well known side effect of cytostatic therapy. We have investigated proximal tubular function impairment of cytostatic agents frequently used in childhood cancer therapy. A possible protective role of dexrazoxane on anthraclycin-induced tubular lesion was also observed. Moreover, we have examined a possible influence of angiotensin convertase enzyme (ACE) insertion/deletion (ID) polymorphism on tubular toxicity.

Proximal tubular function was assessed by urinary N-acetyl-b-D-glucosaminidase activity normalized to urinary creatinine concentration (NAGi) and microalbuminuria (MA) in 1381 urine samples obtained from 94 children with cancer (boys:girls = 58:36, age: 8.5yrs, range: 1-26 yrs, median: 7.5 yrs) treated at Department of Pediatrics of the Medical and
The aim of the survey was to evaluate, through a retrospective phase and a subsequent prospective phase, the incidence and management of ARF in three Italian regions considering Nephrology departments (ND) and ICU. 79 centres were included. In the first phase a logistic-epidemiological questionnaire was sent to all centres regarding staff, availability of different dialysis modalities, incidence of ARF and management of dialysis treatment during 2002. The same centres were prospectively monitored for 3 months (April-June 2003); each centre filled a case report form for each case of ARF. 26 nephrology centres out of 33 and 27 ICU out of 46 responded to the first phase. 21,556 hospitalisations were monitored (12,253 in nephrology and 9,303 in ICU) and the incidence of ARF was 14.17% (median 11.02%); the incidence in the nephrology department 16.31% (median 12.5%), and in the ICU 11.93% (median 10%). The majority of centres described an incidence of ARF requiring dialysis between 10 and 20% (for both nephrology and ICU). The most utilized technique for patients with severe ARF was CRRT in ICU and intermittent haemodialysis (IHD) in the ND. 36 centres responded to the second phase (40% ICU and 53% ND) 994 hospitalisations in the ND and 2164 in the ICU were monitored. In the ND the mean hospitalisation time was 10.37 days (if ARF was present 14.26 days), in ICU 5.72 days and 14.71 days if ARF was present. The incidence of ARF in Nephrology departments was 30.87% (median 31.58) and 11.61% (median 9.30) in ICU; in the Nephrology Department the mortality was 4.99% but if ARF was present increased to 9.66%; in the ICU 13.64% and 36.21% if ARF was present. From our data it seems that ARF was underestimated in retrospective analyses.

Critical care nephrology appears to be more and more a multidisciplinary field where various specialists are involved in the process of diagnosis and management.

**Rhabdomyolysis and acute renal failure - report of 10 cases**

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More than 100 conditions have been reported to lead to rhabdomyolysis. Among the different clinical entities complicating the syndrome, acute renal failure (ARF) seems to be the most severe and, often, fatal one. We report 10 cases of rhabdomyolysis complicated by ARF. In two of them certain infectious agents (staphylococcus hominis, enterococcus) were isolated in blood cultures, suggesting the direct implication of bacteremia in the pathogenesis of rhabdomyolysis via acute bacterial invasion in muscle tissue. Both presented with CK > 5000 U/L and a 20-fold increase in aminotransferases, although by day 5 CK dropped significantly below 5000 U/L and ARF developed. One of those patients was also an intravenous drug abuser with prolonged periods of muscle pressure during his unconscious state. In three other cases, the patients had a long history of alcohol abuse, another well-known risk factor for acute muscle tissue damage. The proposed mechanisms include inadequate calcium and carbohydrate metabolism, cell membrane ATPase malfunctioning and concurrent electrolyte disturbances. CK levels rose well above 5000 U/L by day 5 with ARF development and 5-fold increased aminotransferase levels. By day 8, both CK levels and ARF resolved. However, in one of them Streptococcus sanguis was isolated from blood cultures due to septic arthritis. Three other cases included patients who presented with acute muscle pain and weakness after intensive muscle activity. On admission CK levels were above 5000 U/L with only 2-fold increase in aminotransferases and mild ARF with rapid resolution by day 5. Finally, two patients presented with diabetic ketoacidosis due to respiratory and urinary tract infections respectively. In the latter case E. coli was isolated from blood cultures. On day 3 painful muscle convulsions and a CK rise above 4000 U/L indicated rhabdomyolysis with subsequent development of ARF and 4-fold rise in aminotransferases, which resolved gradually over 15 days.

Mechanisms incriminated in the pathogenesis of ARF in rhabdomyolysis are: myoglobin cylinder formation and renal tubule obstruction, direct nephrotoxicity of muscle cell components, tissue hypoxia and circulation regulatory disturbances. In our cases the severity of ARF, as indicated by serum creatinine, was corresponding to the severity of the rhabdomyolysis.
itself. The concurrent rise in white blood cell, lactic dehydrogenase and aminotransferase was also directly associated with rhodobacterolysis extent. In all cases CK clearance was rapid and irrelevant of renal function, while none of the patients was in need of dialysis. All patients were treated conservatively with active fluid replacement, urine alkalization and close monitoring of fluid-electrolyte balance.

Concluding, rhodobacterolysis should be recognized early, using a high level of suspicion. Prompt treatment of the syndrome itself, as well as of the, frequently fatal, complication of ARF results in remission of symptoms and complete restoration of the patients' health.

**SP097 Proliferation and Differentiation of 5-Fluorouracil-Resistant Cells in Uranyl Acetate-Induced Acute Tubular Injury in Rats: Possible Progenitor Cells in Proximal Tubules**

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We previously reported that tubular cells in the distal zone of S3 segment of the proximal tubules (PTs) may be slow-cycling cells and responsible for the repair of the entire S3 in uranyl acetate (UA)-induced acute renal failure in rats. Progenitor cells are known to have characteristics of slow-cycling, a large capacity for proliferation and ability to produce daughter cells. It is reported that daughter cells divided from the progenitor cells are sensitive for 5-fluorouracil (FU), but progenitor cells are not. In this study, we examined characteristics of the PT cells in the distal zone of S3 in response to acute tubular injury induced by UA, and tested whether the target cells are FU resistant and have a capacity for proliferation and differentiation after stopping FU. PT injuries in the S3 segment were induced by i.v. injection of UA (4mg/kg) into rats. The initially regenerating PT cells in the distal zone of S3 were labeled at days 2, 2.5 and 3 after UA injection by [3H]-thymidine. Kidneys were examined at days 3, 5, 7 and 9 by autoradiography. Other UA-treated rats were injected with FU or its vehicle daily from days 0 to 4, and were labeled at days 2, 2.5 and 3 by bromodeoxyuridine (BrdU). Kidneys were examined at days 5, 7 and 9 for immunohistochemistry of BrdU, Ki67, cyclin D1 and megalin. Autoradiography revealed that the number of PT cells with > 40 grains/nucleus was significantly higher in the distal 1/4 of S3 than in other 1/4 zones at day 3. The PT cells with diluted number of grains (5 to 10 grains/nucleus) were found only occasionally at day 3. The PT cells with 5 to 10 grains/nucleus were distributed increasingly throughout the entire S3 by day 7, but those with > 40 grains/nucleus remained in significantly higher number in the distal 1/4 of S3 than in other 1/4 zones until day 9. In other experiments with FU-treatment, rats treated with vehicle showed that BrdU positive/Ki67 positive PT cells were found in the distal 3/4 of S3 at day 5 and distributed in the almost entire S3 by day 7. Most of BrdU positive PT cells were not stained with megalin at day 5, but some of them became megalin positive at day 7. Rats treated with FU showed BrdU positive/Ki67 negative PT cells restrictedly in the distal 1/4 of S3 at day 5. Some of BrdU positive PT cells showed cyclin D1 positive at day 5, suggesting G1 arrest. After stopping FU at day 4, BrdU positive/Ki67 positive PT cells were distributed towards the proximal direction in S3 after day 7. BrdU positive cells showed megalin negative at day 5 and some of BrdU positive cells became megalin positive at day 7. In conclusions, the PT cells in the distal zone of S3 have a large capacity for proliferation and ability to produce daughter cells, being the main source of tubular regeneration. Those cells can arrest cell cycle at G0/G1 by FU-treatment but can enter cycling, proliferate, migrate and differentiate to matured PTs. The data suggest that PT cells in the distal zone of S3 may have some characteristics of progenitor cells.

**SP098 Caveolin-1 Expression and Cell Cycle Progression of Regenerating Tubular Cells in Gentamicin-Induced Acute Renal Failure in Rats**

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Caveolin-1 is a principal component of caveolae membrane and compartmentalizes signaling molecules, mediating cell cycle arrest. However, it is not known whether caveolin-1 involves in regenerating tubular cells after acute tubular injury. The present study was designed to determine the spatial and temporal correlation between immunoreactive caveolin-1 and cell cycle related molecules in regenerating proximal tubules (PTs) after gentamicin-induced acute renal failure in rats where PTs in the cortex are mainly damaged. Subcutaneous injection of gentamicin (400 mg/kg/day, for 2 days in divided doses every 8 hours) in rats induced cortical PT damage as early as day 0, which peaked at day 6 after last gentamicin injection. Ki67-positive proliferating PTs were first found at day 3 and peaked in number at day 6, then decreased. Cyclin-dependent kinase inhibitor p21 was found in regenerating PT, peaked in number at day 10. Immunoreactive caveolin-1 was not expressed in normal PTs. The regenerating PTs showed cytoplasmic caveolin-1 expression weakly at day 4 and strongly at days 6 to 8. Coarse granular cytoplasmic pattern of caveolin-1 staining was found in the PTs after day 10. Megalin as differentiated phenotype of PT was found in some regenerating PTs at day 8 in almost all PTs by day 12. Immunoelectron microscopy showed that caveolin-1-positive caveolae were found on the free and basal cell membranes as well as in the cytoplasm of PTs at days 4 to 8, and caveolin-1 positivity was found only in the endocytic structures after day 10. Western blot analysis showed that caveolin-1 levels markedly increased in the cortex after induction of acute renal failure and peaked at day 6. In conclusions, the regenerating PT transiently expressed caveolin-1, which peaked in association with peaked PT proliferation and disappeared from the cell membranes with cell cycle arrest/differentiation. The data suggest that caveolin-1 expression mediates cell cycle arrest of regenerating PTs possibly by inhibiting growth signaling molecules in gentamicin-induced acute renal failure.
Preconditioning with 1,25 (OH)2 vitamin D3 epoetin alfa (EPO) does not modify acute preconditioning with VitD3 decreased ERK and JNK expression. With VitD3 improved not only renal function but also tubular necrosis. In conclusion, these preliminary data demonstrate that acute inhibition of p21-Ras at time of IR prevents to a great extent both the acute and chronic damage following this oxidative stress, opening new perspectives for a possible role of Ras inhibition to prevent IR in renal transplantation.

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The actions of vitamin D3 (VitD3) include the maintenance of calcium homeostasis, but recent its diverse action such as immunomodulatory effects and anti-inflammatory effects were reported. Induction of heat shock protein 70 (HSP70) is effective in preventing ischemia/reperfusion (IR) injury. In this study we examined the possible role of VitD3 as an inducer of HSP70, and effect of preconditioning with VitD3 on IR injury in rat kidneys. In the first study, we observed the effect of VitD3 on HSP70 expression. Adult male Sprague-Dawley rats on a low calcium diet (0.4%) were treated daily for 7 days with vit D (0.5 ug/kg in saline). In the first study, we observed that HSP70 expression was gradually increased at days 3, and maximal increase of HSP70 was observed at days 7. Vitamin D receptor (VDR) was also increased in rat kidneys with VitD3 treatment. In the second study, VitD3 was treated for 7 days based on study 1, and then IR injury was induced by clamping both renal arteries for 45 min. Rats were sacrificed 24h later. The effect of VitD3 on IR injury was evaluated with renal function, tubular injury and the expression of ERK or JNK for preconditioning with VitD3 on subsequent IR injury. In conclusion, these findings suggest that VitD3 is a non-toxic inducer of HSP70, and this effect may be associated with renoprotective effect of VitD3 on subsequent IR injury.

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Heme oxygenase-1 (HO-1), an inducible heat shock protein, is known to have cytoprotective effects against ischemic injury. Cobalt chloride (COC) has hypoxia-mimetic effects by inhibiting degradation of HIF-1α, which is a master regulator of genes activated by low oxygen tension. This study evaluated the efficay of COC in a bilateral renal ischemia-reperfusion (I-R) injury model of male Sprague-Dawley rats. I-R renal injury was induced by 45 min clamping of both renal arteries. Rats in the sham(n=6) and I-R control groups(n=8) had been drinking tap water, whereas rats in the sham(n=8) and COC treated I-R groups(n=9) had been drinking water containing 2 mM COC from day -14 to day 1. The serum levels of creatinine, AST, LDH, and the renal tubular necrosis score based on light microscopic examination in each group were measured 24 hrs after surgery. The levels of renal gene expressions of HO-1, TGF-β, MCP-1, TNF-α, endothelin-1, iNOS, Bcl-2 and Fas were measured by competitive RT-PCR. The serum level of creatinine 24 hrs after surgery was 2.6±0.1(mean±SD) mg/dL in I-R COC treated group, significantly lower than that in I-R control group(4.2±1.6 mg/dL, p<0.05). The level of Bcl-2 gene expression of kidneys in COC treated I-R group measured by Western blot analysis was also significantly higher than that of I-R control group(p<0.05). The expressions of TGF-β, MCP-1, TNF-α, endothelin-1 and Fas genes in the kidneys of COC treated I-R rats were significantly lower than those of I-R control rats(all, p<0.05). The level of Bcl-2 gene expression of kidneys in COC treated I-R rats was significantly higher than the level of I-R control rats (p<0.05).

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Numerous studies have now been reported demonstrating that Epoetin (EPO) administered at the time of or up to 24 hours prior to ischemia, has attenuated the degree of resultant acute renal failure (ARF). All such reports have used male animals. We have examined the effects of EPO at different dosages, given either SC or IV, on the development of ARF in female Sprague-Dawley (SD) rats. Two models of ischemic ARF were used. Model A involved a unilateral right nephrectomy followed by clamping of the left renal pedicle for 50 minutes one week later. Model B was similar, apart from the left renal pedicle clamp being applied 3 weeks post nephrectomy. Female SD rats (200-250g) were given either Vehicle or EPO, SC or IV, for Model A and IV (only) for Model B. EPO doses were 100 or 500U/kg immediately before ischemic injury alone or 1000U/kg immediately before ischemia with a further 1000U/kg at reperfusion. Renal function was monitored by serum creatinine over 7 days.

ARF was readily achieved, with a change in serum creatinine from baseline peaking at 24 hours for Model A (0.05±0.01 – 0.21±0.11 mmol/L, mean±SD) and at 48 hours for Model B (0.05±0.01 – 0.55±0.35 mmol/L). There were no significant differences in serum creatinine at the time of injury, nor at 24, 48, 96 or 168 hours post injury between those treated with vehicle or EPO (any dose) for either model. Similarly, no differences were noted in body weight or serum potassium. Haemoglobin concentrations ([Hb]) were higher in Model A at day 4 for EPO treated animals compared to vehicle. No differences were seen in [Hb] for Model B. Immuno-histochemical analysis at day 7 also demonstrated no differences in myofibroblast (alpha SMA) or monocyte-macrophage (ED-1) accumulation, fibrosis (Collagen III) or tubular cellular proliferation (PCNA). These data suggest that, although the use of EPO has previously been shown to attenuate renal ischemic injury in male rats, it may not have the same effect in female rats nor, possibly, in more severe models of ARF.
Acute renal failure — experimental, toxic nephropathies

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SP103 RENAL ADENOSINE TRIPHOSPHATE IN SEPSIS: A NEW TECHNIQUE FOR MEASUREMENT

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Acute renal failure (ARF) affects 5% to 7% of all hospitalised patients. Sepsis and particularly septic shock are important risk factors for ARF in the wards and remain the most important trigger for ARF in Intensive Care Units (ICU) with high mortality up to 70%. Understanding of the pathogenesis of septic ARF is poor. Renal ischaemia, due to a decrease in renal blood flow (RBF), has been proposed as central to the pathogenesis of septic ARF. However, models of hyperdynamic sepsis fail to show either decreased global renal blood flow or decreased medullary flow, suggesting that during hyperdynamic sepsis, global renal ischaemia may not occur. Bioenergetic failure (a decrease in adenine triphosphate) might occur despite adequate blood flow; however, this has not yet been studied in large animals. We now report the measurement of ATP over a prolonged period of time in kidneys of time in kidneys of animals. We now report the measurement of ATP over a prolonged period of time in kidneys of large mammals receiving continuous invasive blood pressure monitoring during experimental septic shock and induced circulatory arrest. An implantable coil was placed around the left kidney of three adult Merino ewes, designed to fit snugly around the main body of the kidney without causing superficial ischaemia. Isoflurane anaesthesia was maintained with an oxygen/air mix. Fractional inspired oxygen was altered to maintain PaO2 ~100 mmHg and ventilation controlled to maintain PaCO2 ~40 mmHg. Haemodynamic parameters were recorded continuously. Following a 2-hour observation period, sepsis was induced by intravenous bolus injection of 1.2 ml of 3 x 109 colony forming units of live E. coli in 50 ml normal saline. Sustained septic shock was achieved after the administration of E. coli with the onset of significant hypotension. The sheep became hypotensive within 30 min (mean arterial pressure dropped from 75 mmHg to 45 mmHg). The 31P spectra obtained at baseline, after 2 hours of sustained septic shock and following euthanasia demonstrate a relatively limited (18%) change in ATPβ signal, which contrasts with a prominent fall in the phosphoester/phosphodiester (PME/PDE) peak ratio (~50%). Compared to the control animal, relative preservation of high energy phosphate levels occurred despite a significant decrease in kidney perfusion pressure. In summary, the results provide provocative insights into the mechanisms of ARF by showing minimal changes in tissue ATP and early variability of the phosphoester ratio - a different pattern to that induced by ischemia. These observations suggest that bioenergetic failure does not play a significant role in sepsis-induced ARF.

SP104 PRECONDITIONAL INDUCTION OF HIF BY CARBON MONOXIDE AMELIORATES ISCHEMIC ACUTE RENAL FAILURE

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Hypoxia is an important pathophysiological mechanism in ischemic acute renal failure (iARF), due to various effects of inadequate energy supply on cytoskeletal architecture, membrane physiology and protein synthesis. There is also evidence that the cellular consequences induced by sublethal hypoxia may protect tissues against a subsequent, second insult, a phenomenon termed "ischemic preconditioning". Although the molecular mechanisms responsible for this protective effect remain incompletely understood, the generation of oxygen radicals due to a sequence of ischemia and reoxygenation appears of crucial importance. Since recently there is renewed interest in cellular effects of hypoxia following the discovery of widespread system of hypoxia-inducible gene expression, mediated by hypoxia-inducible transcription factors (HIF). HIF-target genes include among others EPO, VEGF, glucose transporters, glycolytic enzymes and heme oxygenase-1 and have the potential to confer adaptation and reduced sensitivity to hypoxia. In contrast to those conditions previously described to induce "ischemic preconditioning" HIF is mainly induced by continuous, non-ischemic hypoxia. In this study we have tested the hypothesis that induction of HIF by severe functional anaemia, induced by systemic exposure to carbon monoxide (CO) protects against iARF in a rat model. The right kidney was removed before clamping the left renal artery for 40 minutes. To induce HIF animals were exposed to 0.1% CO for 10 hours before onset of iARF, untreated (UnT) animals with iARF and sham operated (sham) rats served as controls (n=10 per group).

Following pretreatment with CO, HIF-1 accumulated in proximal tubules and collecting ducts and HIF-2 in interstitial cells and this induction was parallel by upregulation of target genes, as determined by RNase protection and immunohistochemistry. S-crea (Table) and urea (not shown) were significantly lower in the CO group compared to UnT. Morphological changes were less severe in the CO group, as determined blindly using a scoring system, and the number of infiltrating macrophages and apoptotic cells was reduced.

In summary these data provide first proof of principle that preconditional activation of the HIF pathway by CO protects against iARF. Pharmacological induction of HIF therefore appears as a highly attractive strategy for renoprotection.

SP105 ATORVASTATIN IMPROVES RENAL OUTCOME IN RAT ISCHEMIC ACUTE RENAL FAILURE

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HMG-CoA-reductase inhibitors (statins) are considered to cause pleiotropic effects, e.g. by improving nitric oxide (NO)-metabolism. Regulation of NO-dependent renal hemodynamics and glomerular function is disturbed in ischemic acute renal failure (iARF). Here we analysed the impact of atorvastatin (ATO) on the recovery in the course after iARF, with particular emphasis on functional parameters, regulation of NO-synthases and active tubular transport mechanism.

In a rat model renal arteries were bilaterally clamped for 45 min to induce iARF. Animals received either saline or ATO orally (50 mg/kg bw) immediately after clamping. Expression of inducible and endothelial NO-synthases (iNOS/eNOS) was analysed. Changes in serum creatinin, BUN and potassium accumulation were monitored. Glomerular filtration rate (GFR) and renal plasma flow (RPF) were measured. Glomerular filtration rate (GFR) and renal plasma flow (RPF) were measured. PAH net secretion was determined to analyse active tubular transport mechanism.

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Hypertension – clinical

**ROLE OF KIDNEYS IN METABOLISM OF ADIPONECTIN. STUDIES IN PATIENTS WITH UNILATERAL RENAL ARTERY STENOSIS**

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Patients with chronic renal failure are characterized by elevated plasma adiponectin concentration. It is also known that successful kidney transplantation is followed by a significant reduction of plasma adiponectin concentration. To date, renal extraction of adiponectin has not been reported. Therefore the aim of the study was to estimate extraction of adiponectin by the kidney, by measuring its concentration in aorta and both renal veins, in patients with unilateral renal artery stenosis.

In 8 subjects (M=1, F=7; age 42 ± 12 years; body mass index 27.1 ± 4.4 kg/m²; plasma creatinine concentration 88 ± 22 µmol/l) with unilateral renal artery stenosis plasma adiponectin (ELISA) was measured in blood samples withdrawn from aorta, both renal veins and vena cava inferior below the orifices of renal veins.

Plasma adiponectin concentrations in renal veins (both from kidney with renal artery stenosis and from contralateral kidney) were significantly (p<0.05) lower than measured in aorta (16.7 ± 7.8; 16.2 ± 7.5; 17.7 ± 8.3 µg/ml respectively).

Renal adiponectin fractional extraction was 6 ± 5% in kidney with renal artery stenosis and 8 ± 6% in contralateral “normal” kidney. Differences in plasma adiponectin concentration in renal veins and renal adiponectin fractional extraction from kidney with renal artery stenosis and from contralateral kidney did not reach statistical significance (p=0.31; p=0.31, respectively).

The highest values of plasma adiponectin concentration was observed in vena cava inferior below the orifices of renal veins (18.5 ± 8.7 µg/ml; p<0.05 vs plasma adiponectin in aorta).

Human kidneys are an important organ in the adiponectin extraction and elimination.

**HOMOZYGOUS 677TT AND DOUBLE HETEROZYGOUS 677CT/1298AC MTHFR GENE MUTATIONS IN: a) PATIENTS WITH PRIMARY MALIGNANT HYPERTENSION AND b) HYPERTEINVEOUS PATIENTS WITH FIBROMUSCULAR DYSPLASIA (FMD) OF THE RENAL ARTERIES AND SUPERADDED THROMBOSIS LEADING TO RENAL INFARCTS**

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**Background:** The homozygous 677TT and the double heterozygous 677CT/1298AC mutations of the MTHFR gene lower the enzyme activity to 35–45% and ~42% respectively and are pathophysiologically linked to venous thromboses (DVT) and also arterial atherosclerotic events of the coronary, carotid and peripheral arteries. Studies in our dept have shown a significantly increased incidence of these mutations in CRF patients with hypertensive nephrosclerosis. We now present our MTHFR findings in a) patients with primary malignant hypertension and b) patients with fibromuscular dysplasia (FMD) and superadded thrombosis leading to renal infarcts.

**Material, methods and results:** a) All 6 patients with primary malignant hypertension between 1995 and 2004 had their MTHFR C677T and A1298C genotypes analysed by PCR of genomic DNA in 2004. There were 4 men and 2 women aged 18–58 at presentation. All had presented with significant diastolic hypertension, headaches, blurred vision and papilloedema, renal insufficiency and LVH. Four patients have progressed to ESRD and 3 have been successfully transplanted. 1 patient is on dialysis. Three of the patients are homozygous 677TT and three are double heterozygote 677CT/1298AC. b) Four patients with FMD, 3 females and 1 male, who had superadded thromboses and renal infarcts, one leading to a nephrectomy, were investigated for thrombophilia in 2004. The only abnormality was the finding in all 4 patients of significant MTHFR mutations: One homozygous 677TT and 3 double heterozygotes, 677CT/1298AC.

**Conclusions:** The MTHFR findings in the 6 patients with primary malignant hypertension reveal for the first time a possible genetic link in this puzzling disease and may help explain the accelerated atherosclerosis and fibrinoid necrosis in these patients. The similar MTHFR findings in some patients with FMD, may also help explain the occurrence of thrombotic episodes in some of these patients. In both situations, therapeutic possibilities in the form of aspirin and folic acid supplements become a distinct possibility.

**PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY OF RENAL ARTERY STENOSIS – THE ULM EXPERIENCE**

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**Objective:** Controversy still exists on whether renal artery stenosis (RAS) should be treated by antihypertensive medication alone or whether RAS should be dilated by percutaneous transluminal angioplasty (PTA) in addition. It is our clinical impression that many individuals with RAS benefit from PTA in both, blood pressure control and renal function.

**Patients and Methods:** We retrospectively analysed all cases with renal artery stenosis (RAS ≥ 70%) who have been treated by PTA at our hospital between years 1991 and 2000. PTA was performed by the standard transfemoral approach, and stated successful if the remaining stenosis was < 50%. Improvement of blood pressure was assumed if the need for antihypertensive medication could be reduced. Differences between individual creatinine values were tested for statistical significance by the nonparametric Dixon and Mood sign test.

**Results:** A total of 57 cases were recorded, 43 men and 14 women. Mean age was 57 years ranging from 20 to 78 years. Mean follow-up was 41 months ranging from 1 week to 11 years. PTA could be performed in only 49 cases, and in 14 cases a stent was placed (29%). PTA was successful in 44 cases (90%), but complicated by renal artery occlusion after the intervention in 3 cases (6%). Haemodialysis was needed in 4 cases within 7 days after PTA and in a further 3 cases on the long run. Cholesterol embolism was diagnosed in 2 patients by kidney biopsy. Long-term blood pressure improved in 27 of 37 evaluable cases (73%). In the 16 cases with primarily impaired renal function, mean creatinine was 283 µmol/l (±187) and significantly improved to 262 µmol/l (±229) immediately after PTA (p = 0.04, sign test). Renal function deteriorated again in 8 of 16 patients. Overall mean serum creatinine was 210 µmol/l (±173)