2009 Nephrology Research Abstracts

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Section 1

Renal Transplantation
Role of Natriuretic Peptides in Solid Organ Transplantation Associated Acute Kidney Injury: A Systematic Review and Meta-Analysis

Sagar U. Nigwekar, Sankar D. Navaneethan, Charuhas V. Thakar
Rochester General Hospital; Cleveland Clinic, Cleveland, OH; University of Cincinnati

Acute kidney injury (AKI) after solid organ transplantation is associated with significant morbidity and mortality. Randomized controlled trials (RCTs) involving natriuretic peptide administration in solid organ transplantation have shown inconsistent effects for renal endpoints. We aimed to systematically review these RCTs to ascertain the role of natriuretic peptides in solid organ transplantation associated AKI.

MEDLINE, CENTRAL, Google Scholar and reference lists of retrieved articles were searched for the relevant articles. Outcomes analyzed were AKI requiring dialysis (AKI-D), duration of dialysis requirement, AKI incidence (defined as per the Acute Kidney Injury Network criteria), 30-day mortality, post-transplantation creatinine clearance, and adverse events. Results were expressed as relative risks (RR) and weighted mean difference (WMD) for dichotomous and continuous outcomes respectively, with 95% confidence intervals (CI). Statistical heterogeneity was analyzed using I² test.

Seven RCTs (3 liver transplantation trials, 3 renal transplantation trials and 1 heart transplantation trial) involving 238 participants met the inclusion criteria. Pooled analysis showed reduction in AKI-D in the natriuretic peptide group (RR 0.60, 95% CI 0.37 to 0.98, I²=0%) and reduction in the duration of dialysis requirement (WMD -44.0 hour, 95% CI -60.5 to -27.5 hours) without any difference in 30-day mortality. Sufficient data were not available from individual studies to compute the AKI incidence; however, natriuretic peptide use was associated with a trend towards improvement in post-transplantation creatinine clearance (WMD 5.5 ml/min, 95% CI -1.3 to 12.2 ml/min). Natriuretic peptides were not associated with any adverse events in this setting. Methodological quality of the included studies was noted to be low.

In conclusion, natriuretic peptides may confer benefits in AKI associated with solid organ transplantation. An appropriately powered high quality trial is needed to confirm these results. Future studies should report data on renal function in a consistent manner to compute the AKI incidence.
Mycophenolic Acid Level and BK Viremia in Renal Transplant

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Undetected BK viremia (BKV) may lead to graft loss. Intensity of immunosuppression is a consistent correlate of BKV. Hypothesis: Higher mycophenolic acid trough levels (MPA C\textsubscript{0}) correlate with increased risk for BKV and BK nephropathy (BKVAN).

We examined adult first or repeat solitary kidney transplants between Jan 2006 and Dec 2008 at our center. Cases had at least one positive BKV(PCR) or biopsy proven BKVAN at any time and MPA trough (C\textsubscript{0}) within 3 mo of BK. Controls had no BKV but had MPA\textsubscript{C\textsubscript{0}}. We compared BKV rates and graft survival between cases and controls across MPA\textsubscript{C\textsubscript{0}} demographics, donor type, HLA mismatches, induction and maintenance regimens, cumulative doses and troughs of immunosuppressants at the time of BK and averaged within 3 mo of BK.

Of 455 transplants performed, 50 Cases and 50 matched controls were selected.

Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases Mean(Std)</th>
<th>Controls Mean(Std)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(yr)</td>
<td>53.6 (12.4)</td>
<td>54.3 (12.2)</td>
<td>0.76</td>
</tr>
<tr>
<td>Cumulative steroid dose within 3months of BK (mg)</td>
<td>1.4 (1.2)</td>
<td>1.0 (0.9)</td>
<td>.10</td>
</tr>
<tr>
<td>Mean MPA C\textsubscript{0} averaged for 3 months prior to BK</td>
<td>2.6 (1.6)</td>
<td>2.6 (1.2)</td>
<td>0.92</td>
</tr>
<tr>
<td>Mean MPA C\textsubscript{0} at the time of BK</td>
<td>3.2 (2.7)</td>
<td>2.7 (2.1)</td>
<td>0.24</td>
</tr>
<tr>
<td>Mean FK C\textsubscript{0} averaged for 3 months prior to BK</td>
<td>8.6 (3.8)</td>
<td>8.5 (3.7)</td>
<td>0.87</td>
</tr>
<tr>
<td>Mean FK C\textsubscript{0} at the time of BK</td>
<td>8.3 (5.7)</td>
<td>8.5 (4.4)</td>
<td>0.8</td>
</tr>
<tr>
<td>Mean CsA* C\textsubscript{0} averaged for 3 months prior to BK</td>
<td>9.5 (47.2)</td>
<td>2.0 (14.1)</td>
<td>0.28</td>
</tr>
<tr>
<td>Mean CsA C\textsubscript{0} at the time of BK</td>
<td>9.2 (52.4)</td>
<td>1.9 (13.3)</td>
<td>0.34</td>
</tr>
<tr>
<td>Cumulative SRL dose averaged for 3 months prior to BK (mg)</td>
<td>24.9 (72.1)</td>
<td>20.7 (72.8)</td>
<td>0.77</td>
</tr>
<tr>
<td>Mean SRL trough averaged for 3 months prior to BK</td>
<td>1.6 (4.0)</td>
<td>1.2 (3.6)</td>
<td>0.61</td>
</tr>
<tr>
<td>Mean SRL trough at the time of BK</td>
<td>1.5 (4.3)</td>
<td>1.1 (3.4)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

No significant difference was found between the groups with respect to any of the selected covariates. Cumulative doses and C\textsubscript{0} for MPA, and other immunosuppressants did not differ among cases and controls. Allograft survival was inferior with 9 failures with BKV and one failure in those without BKV. Patient survival was no different.

MPA\textsubscript{C\textsubscript{0}} did not correlate with BKV/BKVAN. Inferior graft survival with BKV emphasizes early recognition and intervention regardless of immunosuppressive regimen.
Section 2

Renal Disorders
Undergoing Non Emergent Percutaneous Coronary Intervention

Praveen Kandula, Ravish Shah, Nishith Singh, Nishant Bhensdadia, Stephen J. Markwell, Sankar D. Navaneethan
Internal Medicine, Southern Illinois University, Springfield, IL; Statistics and Research Consulting, Southern Illinois University, Springfield, IL; Nephrology and Hypertension, Cleveland Clinic, Cleveland, OH

Aim: Oxidative stress and ischemia are suggested as possible mechanisms of contrast induced nephropathy (CIN). Statins may offer renoprotection in both acute and chronic kidney disease due to their antioxidant and anti-inflammatory properties. We investigated whether use of statins prior to non-emergent percutaneous coronary intervention (PCI) reduces incidence of CIN. Methods: We retrospectively evaluated 540 consecutive adult patients who underwent non-emergent PCI over a three-year period. CIN was defined as 25% or 0.5 mg/dl increase from baseline creatinine at 48-72 hours. We also classified patients based on Mehran score for risk of developing CIN and analyzed effect of statins. Results: 353 patients met inclusion criteria. 239 patients were on statins prior to PCI and 114 were not. Baseline characteristics were similar for both groups. CIN occurred in 75 patients (21.2%). There was higher incidence of CIN among patients on statins (24.7% vs. 14%; 95%CI: 1.09-3.67; p =0.02). However, propensity based adjustment for receipt of statins revealed no significant differences in CIN between both groups (OR: 1.6; 95%CI: 0.87-3.22; p=0.12). There were no significant differences in CIN between the groups when categorized on Mehran score. Multivariate adjustment of significant predictors revealed only Mehran Score to be predictive of CIN.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate OR</th>
<th>Multivariate OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.1</td>
<td>0.7</td>
</tr>
<tr>
<td>CHF</td>
<td>2.0</td>
<td>0.8</td>
</tr>
<tr>
<td>PVD</td>
<td>1.8</td>
<td>1.2</td>
</tr>
<tr>
<td>CKD</td>
<td>1.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Hypotension</td>
<td>5.1</td>
<td>1.8</td>
</tr>
<tr>
<td>Diuretic</td>
<td>2.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Mehran Score</td>
<td>1.2</td>
<td>1.2*</td>
</tr>
</tbody>
</table>

*p<0.05

No patient required dialysis following PCI. Conclusions: Statin use prior to non emergent PCI is not associated with reduction in CIN. Further randomized controlled trials based on proper risk adjustment for development of CIN are needed.
Preoperative Risk Calculator for ARF after Non-Cardiac Surgery

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Purpose: To construct a practical, novel risk calculator for predicting Acute Renal Failure (ARF) after non-cardiac surgery (NCS)

Methods: Electronic record data of 8,475 patients whose preoperative estimated glomerular filtration rates (eGFR) by the 4-variable MDRD equation was $\geq$60 ml/min/1.73m$^2$ and underwent NCS at Cleveland Clinic between 2003-2005 were analyzed. We created a logistic regression model (LRM) with 30 baseline variables chosen for their theoretical association with ARF and ease of use. The full model was reduced using stepdown method suggested by Harrell. In this method, full model is fit in order to obtain the linear predictor, which is then used as outcome for an ordinary least squares (OLS) regression using same variables. The variables are ranked according to their importance by determining their impact on the correlation coefficient in OLS mode which is then used to find LRM model that has the best accuracy in terms of the bootstrap corrected concordance index.

Results: 1,385 (16.3%) patients developed ARF according to the RIFLE Criteria (Creatinine increase $\geq$50% or eGFR decrease of $>$25%) within 7 days of surgery. Final model contained 12 preoperative variables: age, statin, thiazolidinedione, weight, systolic blood pressure, diuretic, diabetes, hypertension, peripheral vascular disease, creatinine, eGFR, and surgical risk. The bias corrected concordance index using 1000 bootstrap samples was 0.65 and the model appears to be well calibrated. A beta version of an electronic calculator is available for use with personal computer or smart phone at http://simpal.com/RCC/links/RANCS.html.

Conclusion: We created a novel, practical and accurate ARF calculator in NCS patients with normal baseline kidney function
Non Invasive Dynamic Measure of Renal Function in a Rat Acute Injury Model

Hazelwood, MO; Martin Debreczeny Consulting, Danville, CA; Nephrology and Hypertension, Cleveland Clinic, Cleveland, OH

A simple, reliable measure of renal function that is both sensitive and precise remains an unmet medical need for detection and monitoring of kidney function. With the injection of a fluorescent tracer that is freely filtered by the kidney (glomerular filtration agent), renal function can be determined from the elimination rate constant (terminal half life) measured with an optical probe over the skin. We hypothesize that a series of fluorescent tracer injections and non invasive terminal half life measurements can provide a sensitive measurement of renal function capable of showing dynamic changes over time. Several terminal half life measurements and serum creatinine measurements were made in 5/6 nephrectomy rats in order to show the dynamic changes in renal function over time after acute kidney injury (AKI). Four hours after AKI in rats, serum creatinine levels increased 3 fold and continued to increase to a maximum 4 fold over baseline by 24 hours. In contrast, the maximum change in the terminal half life occurred at 4 hrs and showed significant recovery by 12 hours. The dynamic changes in terminal half life of the fluorescent tracer suggests that after initial injury, the remaining viable kidney begins to recover or compensate for reduced function much earlier than suggested by serum creatinine levels. A series of fluorescent tracer injections followed by non invasive terminal half life measurements provide a sensitive method for monitoring acute changes in renal function over time.
Terlipressin Therapy for Hepatorenal Syndrome: A Systematic Review and Meta-Analysis

Mirela A. Dobre, Sevag Demirjian, Sankar D. Navaneethan
Huron Hospital; Glickman Urological and Kidney Institute, Cleveland Clinic Foundation

**Background:** Hepatorenal syndrome (HRS) is a common complication in patients with cirrhosis or fulminant liver failure. Several therapeutic agents, especially vasopressors are being used in patients with HRS while they await liver transplantation, though there is no consensus regarding the best approach. We systematically reviewed the benefits and harms of using terlipressin in patients with HRS.

**Methods:** We searched MEDLINE (1966- Jan. 2009), SCOPUS (Jan. 2009), and abstracts from nephrology, gastroenterology and hepatology conference proceedings for relevant randomized trials comparing terlipressin with placebo or another vasoconstrictor or no treatment, in adult subjects with HRS type 1 or type 2. Analysis was conducted using random-effects model in Cochrane RevMan.

**Results:** Eight trials (320 participants) were included. When compared with placebo, terlipressin significantly improved HRS reversal (4 trials, 234 patients; odds ratio [OR], 7.47; 95% confidence interval [CI], 3.17 to 17.59), mean arterial pressure (3 trials, 91 patients; weighted mean difference [WMD] 11.26 mmHg; 95% CI, 1.52 to 21), and urine output (3 trials, 94 patients; WMD 558.46 ml; 95% CI, 224.44 to 892.48). There was a significant increase in gastrointestinal and cardiac adverse events with terlipressin when compared to placebo (OR 8.80, 95% CI 1.89, 41.02). There was mild to moderate heterogeneity in these analyses. There was no significant difference between terlipressin and noradrenaline in HRS reversal (2 trials, 62 patients; OR, 1.23; 95% CI, 0.43 to 3.54), mean arterial pressure, and urine output. We could not ascertain whether terlipressin had better side effect profile compared with noradrenaline.

**Conclusion:** In patients with HRS, terlipressin improves HRS reversal and other surrogate outcome measures compared with placebo. But no significant differences for these outcomes were noted while comparing terlipressin and noradrenaline. Terlipressin is a potential therapeutic option for HRS but larger trials comparing terlipressin to other commonly used vasopressors are warranted prior to terlipressin being used as a first-line agent for HRS.
Section 3

Dialysis
Middle-Molecule Clearance at 20 ml/kg/hr and 35 ml/kg/hr CVVHDF

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Background: Of five clinical trials testing dose-response of CRRT in AKI, two showed a benefit, two showed none, and one was reported as negative, but showed separation in the Kaplan-Meier curves. However, blood-membrane interactions may dominate macromolecule transport in CVVHDF, reducing the association of prescribed dose and delivered clearance for middle molecules. The ATN Study may have delivered similar clearances for middle molecules, despite excellent dose separation for urea.

Methods: We examined middle molecule clearance in the two CRRT dosing arms of the ATN study. Citrated bovine blood spiked with a polydisperse macromolecular probe was subjected to 26.6 or 46.6 ml/min of balanced 1:1 predilution CVVHDF at a blood flow of 200 ml/min. Clearance of tracers between 10-100 kilodalton (kD) molecular weight was measured during six hours of therapy.

Results: Middle molecule clearance (10-100kD) differed by less than 2 ml/min between the two dosing arms tested (Figure 1).

Conclusion: The CRRT prescription used in the ATN Study appears to have achieved the targeted dose separation for small molecules, but middle molecule clearance was nearly identical between the two arms. This effect might contribute to similar survival curves in the ATN study, and suggests subsequent trial designs.
Is CRRT Effluent Useful for Therapeutic Drug Monitoring in the ICU?

Michael J. Connor, Christina L. Hofmann, William H. Fissell
Nephrology and Hypertension, Cleveland Clinic, Cleveland, OH; Biomedical Engineering, Cleveland Clinic, Cleveland, OH

Dose adjustments for acute renal failure and dialysis are based on pharmacokinetic parameters that may not be appropriate for critically ill patients receiving continuous dialysis. Therapeutic drug monitoring in plasma can require expensive sample preparation and multiple phlebotomies. Effluent is cell- and protein free, and simple to prepare for HPLC. As infections are a leading cause of death in acute renal failure, we explored whether CRRT effluent could be used to monitor antibiotic levels in critically ill patients. In an IRB-approved protocol, paired plasma and effluent samples were obtained before antibiotic dose, after antibiotic dose, and before the next antibiotic dose for patients receiving any of six antimicrobial agents. Five patients receiving piperacillin/tazobactam were enrolled and samples obtained. Plasma free and total drug levels, as well as drug levels in CRRT effluent were measured by HPLC. Effluent levels were compared to plasma free and total drug levels. With the exception of two outlying data points, effluent levels predicted free and total drug levels well. This suggests that CRRT effluent may be useful for therapeutic drug monitoring in critically ill patients.
Hemodialysis Patient Preference for Type of Vascular Access: Predictors and Variation across Countries in the DOPPS

R. B. Fissell, D. S. Fuller, H. Morgenstern, B. W. Gilespie, D. C. Mendelssohn, H. Rayner, Bruce M. Robinson, H. Kawanishi, R. L. Pisoni
Cleveland Clinic, Cleveland, OH; Arbor Research Collaborative for Health; Univ of Michigan; Humber River Regional Hospital, Canada; Birmingham Heartlands Hospital, UK; Tsuchiya General Hospital, Japan

Morbidity and mortality are associated with type of vascular access (VA) used for hemodialysis (HD). Understanding factors influencing patient (pt) VA preference and facility VA use may improve VA and HD outcomes.

We examined VA preference reported by 3554 HD pts in 12 countries participating in DOPPS III (2005-08). Logistic regression, adjusted for country, was used to test associations between pt VA preference and pt factors.

Pt preference for VA type varied greatly across countries (Figure). Catheter (CATH) preference was indicated by 1% of HD pts in Japan vs. 42-45% in Belgium and Canada, and among pts using a CATH, 72-92% preferred CATH in Sweden, Germany, Canada and Belgium. Preference for CATH vs. arteriovenous (AV) access was associated with age (odds ratio (OR) per 10 yrs=1.1; 95% CI=1.0-1.2), female sex (OR=1.9; 95% CI=1.5-2.3), diabetes (OR=1.4; 95% CI=1.1-1.7), time with ESRD (OR per 3 yrs=0.91; 95% CI=0.84-0.97), albumin (OR per 1 g/dl=0.71; 95% CI=0.55-0.91), and the proportion of CATH use in the pt’s facility (OR for 10% more=1.4; 95% CI=1.3-1.5). In the US, the odds of preferring CATH vs. AV access was 2.0-fold higher for females but did not differ by diabetes status.

Remarkable variation is seen in pt VA preference across countries; its strong associations with pt factors and facility CATH use may influence pt preference for CATH. Country variation in CATH use suggests opportunities to change patient choice and facility culture to improve VA outcomes.

**Patient’s Indication of Most Preferred Access, by DOPPS 3 country**

<table>
<thead>
<tr>
<th>Access Type</th>
<th>All patients*</th>
<th>Patients currently using catheter*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CATH</td>
<td>42%</td>
<td>50%</td>
</tr>
<tr>
<td>AV</td>
<td>58%</td>
<td>50%</td>
</tr>
</tbody>
</table>

*Legend: JP=Japan, ANZ=Australia, IT=Italy, GE=Germany, FR=France, UK=UK, SP=Spain, US=US, SW=Sweden, BE=Belgium, CA=Canada

N facilities*: 59 J, 14 A, 13 I, 19 G, 10 F, 8 U, 10 S, 19 S, 14 B, 14 C
Atrial Fibrillation (AF) in Hemodialysis (HD) Patients: Stroke Risk Stratification and Use of Anticoagulation in the Dialysis Outcomes and Practice Patterns Study (DOPPS)

Bruce M. Robinson, L. Tong, B. Bieber, T. Hasegawa, R. Fissell, V. Wizemann
Arbor Research, Ann Arbor, MI; Georg Haas Dialysezentrum, Giessen, Germany; Showa U., Tokyo, Japan; Cleveland Clinic, Cleveland, OH

Use of warfarin in HD pts with AF is controversial. The study purpose is to evaluate [1] the predictive value of CHADS2, a stroke risk stratification scheme used in the general population, & [2] stroke risk according to use/non-use of warfarin. Data included 3,298 pts (1996-2004) with history of AF in the DOPPS, an observational HD study in North America [NA=US/Canada], Japan [JP], Australia/New Zealand [ANZ], and 7 European [EU] countries. Pts with mechanical heart valves were excluded. Median f/u=1.28 yrs. Cox models stratified by country, accounted for facility clustering, & adjusted for pt. case-mix & study phase.

Results: AF prevalence rose with age, from 4 to 21% (NA), 5 to 26% (EU), and 3 to 9% (JPN) at <55 and 75 yrs, respectively. HD pts with AF had incr. risk for mortality (hazard ratio, HR=1.16 [1.08-1.26]), hospitalizations (HR=1.01 [0.96-1.07]), & stroke (HR=1.28 [1.01-1.63]). CHADS2 score effectively stratified AF pts, identifying equal-sized groups with low (CHADS2 2; rate 2/100 pt-yrs) & higher (CHADS2 3; rate 4/100 pt-yrs) stroke rates. (Figure 1). Warfarin use in AF [1] varied from 4% (JP) to 9% (ANZ/EUR) to 25% (NA); [2] did not vary by CHADS2 score; [3] was associated with incr. stroke risk in pts with CHADS2 3 (HR=1.99 [1.21-3.28]) & 75 yrs (HR=2.38 [1.17-4.84]).

Conc: CHADS2 score can identify HD pts with AF who are at low CVA risk, providing further support for decisions to not anti-coagulate these pts. For pts with higher CHADS2 score, anti-coagulation risks may still outweigh benefits and treatment decisions should be individualized.

Figure 1: CVA Event Rates among HD Patients with AF, by CHADS2 Score
* CHADS2 Score derived among patients in general population with these characteristics. As in the general population, distinctions are not made between paroxysmal, persistent, and permanent AF.
** CHADS2 scores (0-6) = sum of prior CVA or transient ischemic attack (2 pts), age ≥ 75 (1 pt), hypertension (1 pt), diabetes (1 pt), congestive heart failure (1 pt).
Aspirin (ASA) Responsiveness in a Sample of Hemodialysis (HD) Patients as Measured by the Point-of-Care Platelet Function Assay (POC assay)

Yin Ping Liew, Qi Che, Rachel Fissell, Deepak L. Bhatt, Kandice Kottke-Marchant, Robert J. Heyka
Renal Services, RIPAS Hospital, Bandar Seri Begawan, Brunei Darussalam; Cleveland Clinic, Cleveland, OH; Brigham and Women’s Hospital, Boston, MA

Data on ASA resistance using platelet function assays are not available for the HD population. The present observational study examines a sample of HD patients taking ASA, to determine ASA responsiveness using the POC assay.

Methods: Adult patients who were stable on thrice weekly HD and taking ASA 81mg or 325mg daily for at least 2 weeks were studied. Patients were excluded if they took other medications affecting platelet function, experienced acute bleeding, or had platelet counts <150 or >450 K/uL, or hemoglobin (Hb) <10 g/dl. The POC assay (VerifyNow) was used to determine ASA responsiveness. Assays were performed at week 1 and week 2 of the study enrollment period. An aspirin reaction unit (ARU) 550 indicates ASA resistance.

Results: The present sample includes 28 patients: 16 (57%) males, 23 (82%) blacks, mean age 60 10 yrs. Main causes of End-Stage Renal Disease (ESRD) were diabetes mellitus and/or hypertension, 16 (57%). Fourteen (50%) patients had a history of cardiovascular disease. The majority (24/28, 86%) were on ASA 81mg daily, the others were on ASA 325mg daily. Mean Hb was 11.3 0.8g/dl; mean platelet count was 243 71K/uL; The overall mean ARUs were 484 66, week 1 mean ARUs were 479 67, week 2 mean ARUs were 488 66. Overall, 7/28 (25%) had ASA resistance by the assays, one of them was on ASA 325mg daily. Only one patient had ASA resistance on 2 consecutive weeks. The majority of patients (86%) with ASA resistance by the POC assay reported non-compliance with ASA intake.

Conclusion: This study shows a rate of ASA resistance similar to previous literature using the POC assay in the cardiology population. However, the majority of study subjects with ASA non-responsiveness in this study were also non-compliant with ASA intake. This finding suggests that ASA resistance found in the HD population may be more attributable to non-adherence to a medication regimen, than to ASA resistance.
A Microfluidic Bioreactor for Studying Renal Epithelial Cells under Shear Stress

Nicholas J. Ferrell, Ravi R. Desai, Aaron J. Fleischman, William H. Fissell
Biomedical Engineering, Cleveland Clinic, Cleveland, OH; Cleveland Clinic Lerner College of Medicine, Cleveland, OH; Nephrology and Hypertension, Cleveland Clinic, Cleveland, OH

We have developed an optically transparent bilayer microfluidic perfusion bioreactor for long term study of renal epithelial cells exposed to well-controlled shear stress. The bioreactor consists of apical and basolateral fluidic chambers with a transparent microporous membrane fixed between the two layers. The apical chamber contains microfluidic channels to provide controlled, physiologically relevant shear stress over the apical surface of the cells. The basolateral chamber provides a reservoir for fluid transport across the cell layer and provides support for the membrane. The area for cell growth totals 10 cm$^2$. The microfluidic systems were fabricated from polydimethylsiloxane (PDMS) using standard microlithographic techniques. The membrane was sealed between the chambers by printing a thin layer of medical grade epoxy onto both PDMS surfaces. Bioreactors were characterized by optical and scanning electron microscopy. The bioreactor’s ability to sustain long term viability and differentiated cell function under shear stress conditions was evaluated using human renal epithelial cells (HREC). After seeding and attachment under static conditions, cells were exposed to 1 dyne/cm$^2$ shear for periods of > one week. Immunofluorescence for ZO-1 tight junction protein and acetylated -tubulin (HREC central cilia) were used to evaluate cell organization and differentiated function without need to remove the cells from the bioreactor. The bioreactor provided leak-free flow over the duration of the perfusion experiments. HREC cells showed positive staining for ZO-1 and acetylated -tubulin. This bioreactor design provides a novel platform for studying kidney epithelial cell behavior under shear stress. This novel bioreactor has applications in development of artificial kidneys and the study of cellular response to mechanical forces and ciliary function.
Section 4

Chronic Kidney Disease (CKD)
Urinary Albumin Excretion, Insulin Sensitivity and Adiponectin Levels Following Bariatric Surgery

Nephrology and Hypertension, Cleveland Clinic, Cleveland, OH; Pathobiology, Cleveland Clinic, Cleveland, OH; Bariatric and Metabolic Institute, Cleveland Clinic, Cleveland, OH

Background: Albuminuria portends an increased risk for renal and cardiovascular disease in diabetes. We examined the effect of weight loss induced by two types of bariatric surgery on urinary albumin excretion in severely obese type 2 diabetic subjects.

Methods: 15 consecutive diabetic patients (BMI >25 kg/m²) undergoing either Roux-en-Y gastric bypass (RYGB) (n=9), or gastric restrictive (GR) (n=6) surgery underwent determination of random urine albumin:creatinine ratio (UACR), adipokines and insulin sensitivity (using Matsuda Index) during a mixed meal tolerance test performed 2 weeks prior to and 6 months following surgery.

Results: Six-months after RYGB, there was a significant decrease in BMI (-4.74 kg/m²), fasting glucose, total cholesterol and leptin levels. Insulin sensitivity, High Molecular Weight (HMW) adiponectin ([1296.63 kg/m²: 596.68 ng/ml, p=0.02]) increased significantly along with a significant reduction in UACR (median 36 mg/g (7-94) vs 27 mg/g (5.5-42.5), p=0.01). The reduction in UACR following RYGB was inversely correlated with insulin sensitivity (r=-0.74, p=0.02) and HMW adiponectin (r=-0.67, p=0.04). In contrast, despite reduction in BMI following GR, there was no significant improvement in insulin sensitivity, UACR and HMW adiponectin levels. In patients with pre-existing microalbuminuria there was a significant decrease in UACR (median 65 mg/g (61-126) vs 39 mg/g (27-56), p=0.04) with 4n patients regressing from microalbuminuria to normoalbuminuria. In patients with normoalbuminuria, there was no significant change in UACR was noted. Serum creatinine levels reduced markedly following both surgery types. However, no changes in serum cystatin C levels were noted.

Conclusion: RYGB in severely obese diabetic subjects is associated with reduction in albuminuria that is correlated to the improvement in insulin sensitivity and HMW adiponectin. Larger benefits were seen in patients with microalbuminuria. Further larger studies are warranted to confirm these findings.
Risk Calculator for ARF in CKD Patients Undergoing Non Cardiac Surgery

Saira Noor, Ali Usmani, Anitha Rajamanickam, Brian Wells, Martin Lasceno, Preethi Patel, Ajay Kumar, Changhong Yu, Amir Jaffer, Martin Schreiber
Hospital Medicine, Cleveland Clinic, Cleveland, OH; Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH; Nephrology and Hypertension, Cleveland Clinic, Cleveland, OH; Hospital Medicine, University of Miami, Miami, FL

Purpose: To create a calculator for predicting risk of postoperative acute renal failure after noncardiac surgery (NCS) in patients with Chronic kidney disease (CKD)

Methods: We evaluated Electronic Medical Records data of 1,726 patients with CKD (eGFR < 60 ml/min/1.73m² according to the 4-variable MRDR equation.) who underwent NCS at Cleveland Clinic between 2003-2005. A logistic regression model (LRM) with 30 baseline variables was selected to assess their theoretical association with ARF. The full model was reduced using the step down method suggested by Harrell. The full model is fit in order to obtain the linear predictor, which is then used as the outcome for an ordinary least squares (OLS) regression using the same variables. The variables are ranked according to their importance by determining their impact on the correlation coefficient in the OLS model. The variable ranking is then used to find the LRM model that has the best accuracy in terms of the bootstrap corrected concordance index.

Results: The median GFR in the cohort was 49.5 ml/min/1.73m², 43.4% of the patients were male, and 89.5% were Caucasian, 302 patients developed ARF within 7 days of surgery according to the RIFLE criteria (50% increase in creatinine or >25% decrease in GFR). The bias corrected concordance index using 1,000 bootstrap samples was 0.62 and the model appears to be well calibrated. A beta version of an electronic calculator is available for use with personal computer or smart phone at: http://simpal.com/RCC/links/RANCS_CKD.html

Conclusion: We pioneered a simple and accurate online calculator for predicting the risk of ARF after non-cardiac surgery in patients with CKD. The online version of this calculator may be useful for estimation of patient specific risk of ARF and to enhance physician-to-patient communication regarding this risk preoperatively
Prevalence and Predictors of Sexual Dysfunction in Chronic Kidney Disease: A Systematic Review of Observational Studies

Sankar D. Navaneethan, Maria-Cristina Vecchio, Antonio Nicolucci, Giusi C. Graziano, Fabio Pellegrini, Giovanni F. M. Strippoli
Nephrology and Hypertension, Cleveland Clinic Foundation, Cleveland, OH; Department of Clinical Pharmacology and Epidemiology, Mario Negri Sud Consortium, Santa Maria Imbaro, Italy; Diaverum Medical Scientific Office, Lund, Sweden

Sexual dysfunction (SD) is an under-recognized problem in chronic kidney disease (CKD) and several factors have been proposed to predict it. We conducted a systematic review to assess the prevalence and predictors of SD in CKD.

We searched MEDLINE for relevant observational studies. Prevalence rates were pooled using an inverse of variance method. Continuous variables were expressed as weighted mean difference (WMD) with 95% confidence intervals (CI) using a random effects model. Subgroup analysis and meta-regression were performed to explore the influence of various covariates on the prevalence rates.

Forty-six studies (8050 patients) were included in this review. The prevalence of any level of erectile dysfunction (ED) was 69% (95% CI 61%-77%, p<0.001). Prevalence of mild, mild to moderate, moderate and severe ED was 23.7%, 19.5%, 32.8% and 24.7% respectively. There was a significantly lower overall score of the Female Sexual Function Index questionnaire (WMD -6.93, CI 95% -9.01 to -4.78) in CKD compared to healthy controls. Differences in the reported prevalence rates of ED could be attributed to age, comorbid conditions, stage of CKD and type of study tool used. Predictors of SD were assessed in 20 studies and old age, diabetes mellitus and depression were the most frequently reported predictors.

Various forms of SD are highly prevalent in both male and female CKD patients especially in dialysis. Larger studies enrolling different ethnic groups, using validated study tools and analyzing the influence of various factors on development of SD are needed.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Event rate and 95% CI</th>
<th>Relative weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ali 2005</td>
<td>0.827 0.724 0.697 0.512 0.000 62 / 75</td>
<td>4.84</td>
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</tr>
<tr>
<td>Arslan 2002</td>
<td>0.807 0.740 0.650 0.730 0.000 151 / 167</td>
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<td></td>
</tr>
<tr>
<td>Cappuccio 2002</td>
<td>0.900 0.850 0.705 1.734 0.003 69 / 119</td>
<td>5.24</td>
<td></td>
</tr>
<tr>
<td>Cummings 2003</td>
<td>0.907 0.507 0.501 0.507 4 / 16</td>
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<tr>
<td>El-Behassy 2008</td>
<td>0.918 0.518 0.518 0.518 0.000 143 / 400</td>
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<tr>
<td>Espinoza 2006</td>
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<tr>
<td>Icck 2008</td>
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<tr>
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<td>Jorgensen 2006</td>
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<td>Naya 2002</td>
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<tr>
<td>Neto 2002</td>
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<td>5.00</td>
<td></td>
</tr>
<tr>
<td>Rabk 2003</td>
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<td>5.34</td>
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<td>Rosso 2001</td>
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<td>Russo 2004</td>
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<tr>
<td>Tian 2008</td>
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<td>Turk 2004</td>
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<tr>
<td>Zim 2003</td>
<td>0.806 0.510 0.779 4.246 0.000 104 / 146</td>
<td>5.25</td>
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</tr>
</tbody>
</table>

Test for heterogeneity: P=0.95, P<0.001
Mehran Score and Statins for Prevention of Contrast Induced Nephropathy in Patients Undergoing Non Emergent Percutaneous Coronary Intervention

Praveen Kandula, Ravish Shah, Nishith Singh, Nishant Bhensdadia, Stephen J. Markwell, Sankar D. Navaneethan
Internal Medicine, Southern Illinois University, Springfield, IL; Statistics and Research Consulting, Southern Illinois University, Springfield, IL; Nephrology and Hypertension, Cleveland Clinic, Cleveland, OH

Aim: Oxidative stress and ischemia are suggested as possible mechanisms of contrast induced nephropathy (CIN). Statins may offer renoprotection in both acute and chronic kidney disease due to their antioxidant and anti-inflammatory properties. We investigated whether use of statins prior to non-emergent percutaneous coronary intervention (PCI) reduces incidence of CIN.

Methods: We retrospectively evaluated 540 consecutive adult patients who underwent non-emergent PCI over a three-year period. CIN was defined as a 25% or 0.5 mg/dl increase from baseline creatinine at 48-72 hours. We also classified patients based on Mehran score for risk of developing CIN and analyzed effect of statins.

Results: 353 patients met inclusion criteria. 239 patients were on statins prior to PCI and 114 were not. Baseline characteristics were similar for both groups. CIN occurred in 75 patients (21.2%). There was higher incidence of CIN among patients on statins (24.7% vs. 14%; 95%CI: 1.09-3.67; p=0.02). However, propensity based adjustment for receipt of statins revealed no significant differences in CIN between both groups (OR: 1.6; 95%CI: 0.87-3.22; p=0.12). There were no significant differences in CIN between the groups when categorized on Mehran score. Multivariate adjustment of significant predictors revealed only Mehran score to be predictive of CIN.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate OR</th>
<th>Multivariate OR</th>
</tr>
</thead>
<tbody>
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<td>Age</td>
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</tr>
<tr>
<td>Diabetes</td>
<td>2.1</td>
<td>0.7</td>
</tr>
<tr>
<td>CHF</td>
<td>2.0</td>
<td>0.8</td>
</tr>
<tr>
<td>PVD</td>
<td>1.8</td>
<td>1.2</td>
</tr>
<tr>
<td>CKD</td>
<td>1.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Hypotension</td>
<td>5.1</td>
<td>1.8</td>
</tr>
<tr>
<td>Diuretic</td>
<td>2.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Mehran Score</td>
<td>1.2</td>
<td>1.2*</td>
</tr>
</tbody>
</table>

*p<0.05

No patient required dialysis following PCI. Conclusions: Statin use prior to non emergent PCI is not associated with reduction in CIN. Further randomized controlled trials based on proper risk adjustment for development of CIN are needed.
Hepcidin Dysregulation Induced by Iron and LPS Results in ESA Hypo-Responsiveness in a Mouse Model of CKD

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GUKI, Cleveland Clinic, Cleveland, OH; Cell Biology, Cleveland Clinic, Cleveland, OH; BME, Cleveland Clinic, Cleveland, OH

ESA hypo-responsiveness has been associated with increased mortality, but the underlying mechanisms involved have not been elucidated. An elevated plasma level of hepcidin might contribute by limiting iron availability, but the role of hepcidin in CKD is not understood. We have investigated the hemoglobin (Hgb) response to Epo and ferric gluconate (FG) in CKD mice with and without LPS-induced inflammation. Hgb response, hepcidin expression, and reticuloendothelial (RE) non-heme iron were determined in C57Bl/6 mice. CKD was induced surgically. Mice were divided into 6 groups: control; no treatment (CKD); CKD + i.p. Epo 10 units, 3x week (CKD+Epo); Epo + i.p. iron 18 g FG, 1x week (CKD+Epo+FG); Epo + i.p. LPS 1.5 g/g, 1x week (CKD+Epo+LPS), and Epo + FG 18 g and LPS 1.5 /g, 1x week (CKD+EPO+FG+LPS). At sacrifice, livers and spleens were snap-frozen, RNA was isolated, and hepcidin mRNA was analyzed by Northern blot and non-heme iron by BPhen. After 3 weeks, CKD mice developed anemia and a 64% decrease in hepcidin vs. control. Reversal of anemia by Epo did not restore hepcidin expression; it decreased even further by 79% of control. The low hepcidin seen in CKD and CKD+Epo was associated with a decrease in spleen RE iron to 78% and 46% of controls respectively. The same pattern of lower hepcidin and RE iron content was observed in the CKD+Epo+FG but, resulted in larger Hgb increase vs. CKD+Epo mice (1.1 vs. 2.2 g/dL). Mice treated with both FG and LPS had opposite effects, a blunted Hgb response of 0.7 g/dL and a 40% increase in hepcidin and RE iron especially in the liver (62% increased) vs. controls. Interestingly, LPS alone (CKD+Epo+LPS) did not alter Hgb and hepcidin response. Our findings suggest that, downregulation of hepcidin, and consequent RE iron release, is necessary for Epo response. Concomitant inflammation and iron therapy, but not inflammation alone, may negatively alter this response by up-regulating hepcidin and preventing RE iron release resulting in ESA hypo-responsiveness. The consequences of the additive effects of iron and inflammation and its impact on human CKD anemia need to be investigated.
Intervention for Male and Female Sexual Dysfunction in Chronic Kidney Disease: A Meta-Analysis of Randomized Trials

Mariacristina Vecchio, Valeria Saglimbene, Sankar D. Navaneethan, Antonio Nicolucci, Giovanni F. M. Strippoli Farmacologia Clinica ed Epidemiologia, Mario Negri Sud Consortium, S. Maria Imbaro, CH, Italy; Nephrology, Cleveland Clinic, Cleveland, OH; Diaverum Medical Scientific Office, Lund, Sweden; Centre for Kidney Research, NHMRC Centre for Clinical Research Excellence in Renal Medicine, Sidney, Australia; Cochrane Renal Group, Sydney, Australia

Background: Sexual dysfunction is highly prevalent in chronic kidney disease (CKD). We analyzed the benefits and harms of any intervention for sexual dysfunction in CKD.

Methods: MEDLINE (1966-Dec 2008), EMBASE (1980-Dec 2008) and the Cochrane Trial Registry (2008 issue) were searched for trials of any sexual dysfunction treatments in male and female CKD patients. Data were pooled by random effects model meta-analysis; results are given as weighted mean differences (WMD) and relative risks (RR) with 95% confidence intervals (CI).

Results: Thirteen trials (8 parallel, 5 cross-over, n=278) were included. Sildenafil compared with placebo significantly increased the overall International Index of Erectile Function-5 (IIEF-5) score (2 RCTs, 42 patients, WMD 1.81, CI 95% 1.51 to 2.10) and all its individual domains. One trial using the complete 15 item IIEF tool also found a significant increase in the overall score with sildenafil vs placebo (21 patients, WMD 2.42, CI 95% 0.85 to 3.99). Sildenafil caused a consistent improvement of other unvalidated measures (e.g. ‘overall global sexual performance efficacy’ and other as defined by authors. Testosterone levels were not significantly increased by addition of zinc to dialysate (2 RCTs, 22 patients, WMD 0.82, CI -6.82 to 8.46) while oral zinc significantly increased them (1 trial, 20 patients, WMD 2.20, CI 1.06 to 3.34). There was no difference in plasma testosterone, luteinizing and follicle stimulating hormone level at the end of study period with neither agent.

Conclusions: Sildenafil and zinc are promising but unproven interventions for treating sexual dysfunction in CKD. There is an unmet need for trialling interventions for both male and female sexual dysfunction in CKD, considering the significant burden.
Development of Electronic Medical Record Based CKD Registry: Application of eGFR and ICD-9 Code Criteria

Sankar D. Navaneethan, James Simon, Benjamin Strom, Anil Jain, Michael Kattan, Joseph V. Nally
Nephrology and Hypertension; Quantitative Health Sciences; Medicine, Cleveland Clinic, Cleveland, OH

National Kidney Foundation guidelines classifies patients with estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m² twice at three months apart as chronic kidney disease (CKD). Although widely used, this definition is under debate as the implementation of eGFR without adjustment for the effects of aging and gender might result in an over estimation of CKD.

We constructed a CKD registry within the Cleveland Clinic that included patients who had an outpatient encounter with a physician and met the following criteria: a) eGFR <60 ml/min/1.73m² twice at three months apart and/or b) patients who were billed for or had various CKD diagnoses in the problem list during two outpatient visits (defined as ICD-9 code criteria). Dialysis patients and renal transplant recipients were excluded.

Our registry included 39,748 CKD patients. 82.1% of patients met the eGFR criteria alone, 10% of patients met the ICD-9 code criteria alone (e.g. PCKD with eGFR >60 ml/min/1.73m²) and 7.9% of patients met both criteria. We categorized the entire group into 18-49, 50-64, 65-74 and ≥75 year age-groups. Number of patients included in this registry based on eGFR criteria alone increased from the 18-49 year age-group to ≥75 years age-group in both genders but more so in females while the number of patients who met the ICD-9 code criteria alone decreased from 18-49 year age-group to >75 year age-group.

In our registry elderly patients and females were more likely to be identified as CKD based on the eGFR criteria alone whereas in younger adults, there was a greater use of ICD-9 code criteria. These results also highlight the lack of identification of CKD by clinicians warranting provider education efforts.

<table>
<thead>
<tr>
<th>Age in years</th>
<th>Met eGFR Criteria alone (%)</th>
<th>Met ICD 9 code Criteria alone (%)</th>
<th>Met both eGFR and (%) ICD-9 code criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-49</td>
<td>1243 (52.8)</td>
<td>719 (30.6)</td>
<td>391 (16.6)</td>
</tr>
<tr>
<td>50-64</td>
<td>6007 (74.6)</td>
<td>936 (11.6)</td>
<td>1109 (13.8)</td>
</tr>
<tr>
<td>65-74</td>
<td>9663 (82.6)</td>
<td>597 (5.1)</td>
<td>1430 (12.2)</td>
</tr>
<tr>
<td>&gt; 75</td>
<td>17774 (85.3)</td>
<td>789 (3.8)</td>
<td>2274 (10.9)</td>
</tr>
</tbody>
</table>

Table 1. Number of patients included in the CKD registry based on different inclusion criteria

<table>
<thead>
<tr>
<th>Age in years</th>
<th>Met eGFR Criteria alone (%)</th>
<th>Met ICD 9 code Criteria alone (%)</th>
<th>Met both eGFR and (%) ICD-9 code criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-49</td>
<td>720 (56.4)</td>
<td>184 (14.4)</td>
<td>372 (28.1)</td>
</tr>
<tr>
<td>50-64</td>
<td>3440 (79.8)</td>
<td>480 (11.1)</td>
<td>389 (9.0)</td>
</tr>
<tr>
<td>65-74</td>
<td>5571 (87.2)</td>
<td>575 (9.0)</td>
<td>240 (37.6)</td>
</tr>
<tr>
<td>&gt; 75</td>
<td>10899 (89.6)</td>
<td>929 (7.6)</td>
<td>339 (2.8)</td>
</tr>
</tbody>
</table>

Table 2. Number of female patients included in the registry based on different inclusion criteria

<table>
<thead>
<tr>
<th>Age in years</th>
<th>Met eGFR Criteria alone (%)</th>
<th>Met ICD 9 code Criteria alone (%)</th>
<th>Met both eGFR and (%) ICD-9 code criteria</th>
</tr>
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<tbody>
<tr>
<td>18-49</td>
<td>523 (48.6)</td>
<td>207 (19.2)</td>
<td>347 (32.3)</td>
</tr>
<tr>
<td>50-64</td>
<td>2567 (68.6)</td>
<td>629 (16.8)</td>
<td>547 (14.6)</td>
</tr>
<tr>
<td>65-74</td>
<td>4092 (77.1)</td>
<td>855 (16.1)</td>
<td>357 (6.8)</td>
</tr>
<tr>
<td>&gt; 75</td>
<td>6875 (79.3)</td>
<td>1345 (15.5)</td>
<td>450 (5.2)</td>
</tr>
</tbody>
</table>

Table 3. Number of male patients included in the registry based on different inclusion criteria
Section 5

Blood Pressure Disorders
Ambulatory Blood Pressure Levels in Patients with Restless Legs Syndrome

Qi Che, Nancy Foldvary-Schaefer, Noah Andrews, Michelle Garcia, Martin Schreiber, Mohammed Rafey

Nephrology and Hypertension, Glickman Urological and Kidney Institute, Cleveland Clinic Foundation, Cleveland, OH; Sleep Disorders Center, Cleveland Clinic Foundation, Cleveland, OH

Objective: Restless legs syndrome (RLS) is associated with an increased risk for hypertension and heart disease in epidemiological studies. Preliminary data showed transient, nocturnal elevations of blood pressure in patients with RLS and periodic limb movements (PLMS). We evaluated the prevalence of sustained high blood pressure or abnormal diurnal patterns of blood pressure in otherwise young healthy individuals with RLS.

Methods: Healthy individuals aged 18 to 50 years with symptoms of RLS were screened based on International Restless Legs Syndrome Study Group criteria. OSA was ruled out by an overnight ambulatory polysomnograph (PSG). Blood pressure (BP) was measured with 24 hour blood pressure monitor (ABPM).

Results: 6 patients with RLS (4 women, mean age 35.6 +/- 14.6 years) and 6 controls (4 women, mean age 36.5 +/- 7.2 years) were analyzed. Median duration of RLS symptoms was 7.25 years (range 1.5 to 20 years). Two (25%) had family history of RLS. 6/6 RLS patients had PLMS, while none of the controls did (PLMS index median 12.3 (5.7-49) in RLS patients vs. 0 (0-4) in controls, P<0.05). There was no significant difference in age, race, gender, BMI, family history of hypertension between RLS patients and controls. 24 hr ABPM showed no significant difference in 24 hr average BP (116 +/- 70 in RLS vs 113 +/- 70 mmHg in controls), daytime or nighttime systolic (SBP) or diastolic BP, pulse pressure, mean arterial pressure (MAP) in the 2 groups. Absence of the normal dipping pattern of SBP was comparable in both groups (2/6 non-dipper in RLS vs. 2/6 in controls, P>0.05). Ambulatory arterial stiffness index (AASI), a novel early indicator of arterial stiffness was not different in RLS patients vs controls (0.38 +/- 0.11 vs. 0.43 +/- 0.24, P>0.05).

Conclusions: Our pilot study reaffirms that most RLS patients have PLMS (on PSG) as documented in the literature. RLS patients did not show sustained high blood pressure or abnormal diurnal blood pressure patterns on 24 hr ABPM when compared to controls.