KDIGO Controversies Conference

Blood Pressure in Chronic Kidney Disease Stage 5D

Celebrating Five Years 2003–2008

Abstracts

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BP MEASUREMENT, INTERDIALYTIC HYPERTENSION AND THE ROLE OF SALT

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The management of hypertension in hemodialysis patients is complicated by difficulties in making an accurate diagnosis of hypertension in these patients. It is now well recognized that blood pressures obtained in the dialysis unit before and after dialysis are inaccurate, imprecise and biased estimates of interdialytic ambulatory blood pressure recording [1]. Dialysis unit BPs also correlate poorly with left ventricular hypertrophy [2]. On the other hand, the mean or the median of all dialysis unit blood pressure measurements obtained during a dialysis treatment correlate best with interdialytic ambulatory blood pressures [3]. Thus, if dialysis unit blood pressures are to be used for clinical decision making, it appears that it may be better to use the median intradialytic blood pressure instead of pre or post-dialysis BP.

Self-measured home blood pressures obtained 2-3 times daily over 4 days after a mid-week dialysis are much better in predicting interdialytic ambulatory blood pressure, target organ damage and all-cause mortality [4-6]. Home blood pressure recordings will correctly diagnose hypretension 89% of the time when interdialytic ambulatory blood pressure recordings are used as the reference standard [4]. Thus, home blood pressure monitoring should become the standard of care when managing hypertension in hemodialysis patients [7]. I advocate the use of blood pressures obtained before and after dialysis to ensure hemodynamic stability whereas home blood pressures for managing hypertension in hemodialysis patients. When using an automatic, validated, oscillometric device (such as HEM 705CP, Omron HealthCare, Bannockburn, IL), home blood pressures averaging 150 mmHg or more carries 80% sensitivity and 84% specificity in diagnosing hypertension [4].

Interdialytic ambulatory BP monitoring remains a useful tool because it strongly correlates with measures of arterial stiffness such as pulse wave velocity [8]. Increasing pulse wave velocity is associated with higher mean interdialytic ambulatory systolic and blood pressure as well as higher pulse pressure. Increasing sodium intake, and consequently increased interdialytic weight gain, on the other hand is associated with greater interdialytic slopes of blood pressure.

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PETER J. BLANKESTIJN, MD

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HYPERACTIVITY OF THE RENIN AND SYMPATHETIC NERVOUS SYSTEM IN CKD STAGE V PATIENTS

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Multiple lines of evidence indicate that volume overload and enhanced activities of the renin system and the sympathetic nervous system are important in determining hypertension in CKD stage 5 (review in 1). Epidemiological studies in dialysis patients show a relationship between sympathetic activity and cardiovascular morbidity and mortality (2,3). Therefore, treatment should be aimed at addressing these pathophysiological mechanisms. As a consequence the combination of volume correction and ACE inhibitor / AngII antagonist is the cornerstone of treatment.

Several uncertainties exist.
1] ACEi/ARB in usual dosage reduces but not normalises sympathetic activity (4). Higher than usual dosage may be necessary to obtain full vascular protection. Alternatively, the addition of another sympatholytic agent to the ACEi/ARB treatment may be beneficial. Some data indeed suggest that the addition of a betablocker or combining ACEi with ARB might improve outcome in dialysis patients (5).
2] It is very well possible that the enhanced activities of the renin and sympathetic system decrease or cease to exist in the course of "dialysis life" as a result of progressive destruction of kidney tissue. No data exist on how to identify patients who will especially benefit of pharmacological (as addition to volume correction) treatment.
3] Frequent dialysis / high dosage hemodialysis lower sympathetic overactity (6). The mechanism(s) is (are) unknown. It is not known whether patients on intensive dialysis schedules benefit of pharmacological treatment.

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THE LAG-PHENOMENON OF HYPERTENSION CORRECTION IN HEMODIALYSIS PATIENTS: A REAPPRAISAL

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The lag phenomenon is the delay that is observed between the reach of dry weight and the plateau of normal predialysis blood pressure [1, 2]. It has been reported in incident hemodialysis (HD) patients receiving 8-hour dialysis 3 times a week and in which the dry weight method was applied [3]. This phenomenon is also described with thiazide therapy in hypertensive patients [4]. One of the strong hypotheses to understand these findings is that the lag phenomenon is related to the correction of the cardiovascular remodeling associated with the extracellular volume (ECV) overload [5]. Guyton's experiment in nephrectomized dogs fed with salty food has shown that after 2 weeks the animals present with sustained hypertension and increased peripheral resistances [6]. Peripheral resistances are often reported increased in hypertensive HD patients [7-9], whereas they were found low in Tassin normotensive patients [8] Uncontrolled studies have shown an improvement of cardiovascular remodeling by strict volume control in HD patients [10, 11]. The mechanisms of vascular remodeling have been recently reviewed [5] including the role of ECV expansion on ouabaïn-like compounds acting as Na-K-ATPase inhibitors, the role of high sodium intake on nitric oxide imbalance and altered endothelial metabolism. In conclusion, the existence of this lag phenomenon in HD patients stresses the importance of the physiopathology of sodium imbalance and ECV overload in dialysis patients. It highlights the fact that sustained correction of hypertension is more than short term ECV correction. Is a prolonged negative sodium balance the answer? New tools are needed to follow not only the ECV but also the hemodynamic consequences of its expansion.

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CONTROL OF BLOOD PRESSURE IN CHRONIC KIDNEY DISEASE STAGE 5D

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Hypertension is a common problem in dialysis patients. Approximately 50-60 % of hemodialysis patients and nearly 30 % of peritoneal dialysis patients are hypertensive. Although the etiology of hypertension is multifactorial in dialysis patients, extracellular volume expansion is the major factor in the pathogenesis. Thus, the basic principles of hypertension treatment in these patients are an achievement of dry body weight, proper dialysis prescription with respect to dialysis time and intra-dialytic sodium balance, and dietary sodium and water restriction. Achieving low-normal blood pressure levels (systolic blood pressure between 100 and 130 mm Hg) with strict volume control and salt-restricted diet has a beneficical effect on survival in hemodialysis patients (1). Regarding the pharmacological treatment of hypertension, drugs inhibiting the renin-angiotensin system may have a survival benefit independent of blood pressure control in dialysis patients (2,3). These drugs may also help preserve residual renal function. The general recommendation for the target blood pressure is a predialysis blood pressure of less that 140/90 mm Hg and a postdialysis blood pressure of less than 130/80 mm Hg (4). However, the target blood pressure should be based upon individual patient characteristics. Home blood pressure monitoring may improve hypertension detection and may have a prognostic value in hemodialysis patients (5,6).

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Misinterpretation of Guidelines for HTH in CKD

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Guideliners must be careful about the conclusion from a referred study. For example, K/DOQI guideline states "..in the dialysis population, a blood pressure of 140/90 mm Hg minimized the occurrence of LVH and death". A physician who read that statement simply thinks higher blood pressures are associated with LVH and death, which may not be true. Because authors of the mentioned study concludes "…higher blood pressure levels were associated with the presence of concentric LV hypertrophy on repeat echocardiography ($P = 0.02$), while lower blood pressure levels were associated with death following admission for cardiac failure ($P = 0.0001$) and overall mortality ($P < 0.0001$)…" So death comes from lower blood pressure.

Traeatment algorithm for hypertensive hemodialysis patients offered by K/DOQI guidelines is taken from the JNC guidelines with little modification. It begins with lifestyle modifications and may lead to misinterpretation of the recommendation. Lifestyle changes includes high K and Ca diet along with weight reduction for the general hypertensive population. Since high K and Ca in the diet of a dialysis patient is not justified and reduction of dry weight might be associated with increased mortality, these measures might be harmful to the dialysis population.

A recent study published in NDT from Izmir tested two strategies to control the blood pressure: salt restriction and medication. The groups had similar blood pressure levels, but salt restriction group had beter cardiovascular consequences. Na restriction seems most important choice in the management of the hypertension in dialysis.

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BP CONTROL IN UK DIALYSIS PATIENTS – DATA FROM THE UK RENAL REGISTRY REPORTS 1997-2006

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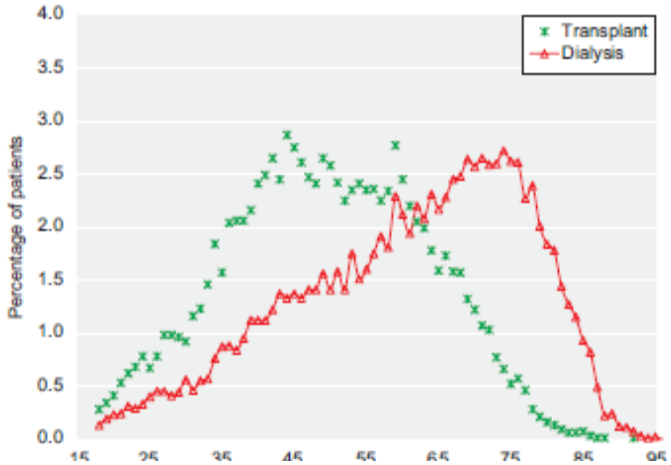
UK Renal Registry (UKRR)

- Established in 1997
- 100 % coverage of England and Wales expected by 2007
- Fully electronic data extraction from clinical information system
- Quarterly biochemical and clinical data on all patients on renal replacement therapy (RRT)

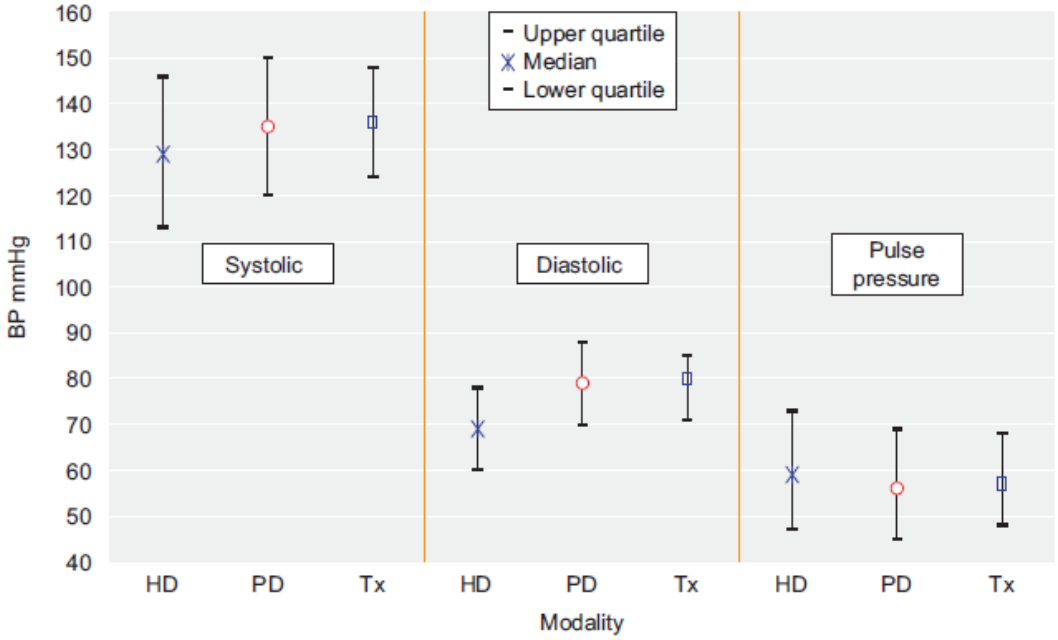
43,901 adult patients receiving renal replacement therapy in the UK at the end of 2006: 18,835 on HD, 4,715 on PD and 20,351 transplanted

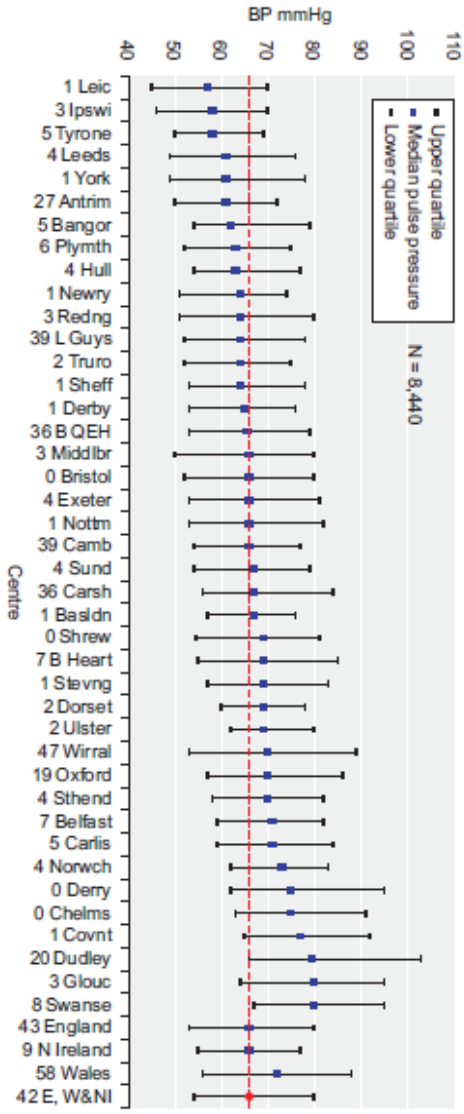
Comparing the age distribution of dialyzed and transplanted patients (prevalent):



Over the period 1997 – 2006 there was no significant change (improvement or deterioration) in the BP levels achieved in dialysis patients. The 3rd but not the 4th set of Clinical Practice Guidelines had included a BP target (< 140/90 mm Hg pre-dialysis and < 130/80 mm Hg post-dialysis). The 4th set of CPG sensibly did away with these arbitrary targets as there was no evidence underpinning their adoption.

Overall, in 2006, this was the outcome for the 43,901 patients :





This figure lists the individual centres which contributed data to the UK RR, and shows the pre-dialysis Pulse Pressure (SBP-DBP) for each centre.

Unlike anaemia, dialysis adequacy, phosphate control, where there have been large improvements in the direction of optimal standards / suggested guidelines, over the period 1997-2006, there has been no change in achieved BP values. The reasons for this need careful consideration. “Not trying at all” is not likely to be credible. “Not trying hard enough” may explain some lack of progress, but is unlikely given the progress in other clinical parameter domains. “Not having the tools to do the job” is the likely explanation here. “Not treating patients with BP medicine” is not credible (although the UK RR does not collect drug utilization, other large audit data sets, eg Pan Thames Audit for 2005/2006 with 2500 patients, suggest that 65-75% of HD patients are routinely using 2-3 antihypertensive medications.

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ENDOTHELIAL DYSFUNCTION IN ERYTHROPOIETIN-INDUCED HYPERTENSION IN RENAL FAILURE

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Background/Aims: In a previous study, we demonstrated that recombinant human erythropoietin (EPO) enhances the expression of the endothelial ETB receptor in normal rats without any modification in blood pressure and in vascular endothelin-1 (ET-1) concentrations. The current study was designed to evaluate the effect of EPO on blood pressure and on the vascular expression of the ET-1 and the ETB receptor in uremic rats.
Methods: Renal failure was induced by a two-stage 5/6 nephrectomy followed by a 3-week stabilization period. Rats were divided into three groups: control + vehicle (veh), uremic (Nx) + veh and Nx + EPO (100 u/kg, s.c., three times per week) for three weeks. Systolic blood pressure was recorded by the tail cuff method before the treatment period and weekly thereafter. Hematocrit and serum creatinine were measured prior to treatment and at the end of the study. Creatinine clearance and proteinuria were determined at the end of the protocol. The expression of ET-1 and of the ETB receptor was assessed by real time RT-PCR.
Results: The animals who underwent the 5/6 nephrectomy developed uremia, anemia and hypertension. The administration of EPO corrected the anemia, but aggravated hypertension ($p < 0.05$). Serum creatinine and proteinuria were significantly higher ($p < 0.01$) in the two uremic groups. EPO therapy induced a further increase in serum creatinine ($p < 0.01$). In contrast to normal rats, EPO caused a significant increase in thoracic aorta ET-1 expression in uremic rats ($p < 0.01$) without any significantly increase in the ETB receptor expression.
Conclusion: The results of this study suggest that EPO induces an increase in ET-1 vascular expression that is not compensated by an increase of the ETB receptor vascular expression, which may account, at least in part, for EPO-induced hypertension in uremic rats.

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WHAT IS KNOWN FROM CLINICAL TRIALS ABOUT OPTIMAL DRUG MANAGEMENT OF HYPERTENSION IN CKD STAGE V – THE ROLE OF BETA BLOCKERS, AND VARIOUS FORMS OF INHIBITION OF THE RAAS?

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Hypertension is highly prevalent and highly recognized in HD patients. In 2005 KDOQI guidelines suggested a pre dialysis blood pressure target of less than 140/90 and a post-dialysis value of less than 130/80. However, the strength of this recommendation was weak. This has two main reasons. First, many associations studies were not able to demonstrate a clear relationship between hypertension and increased mortality or cardiovascular risk, probably because of the known "reverse" epidemiology of the dialysis population. Indeed, hypertensive patients are more likely to be relatively healthy, well-nourished and on dialysis from a shorter time. Conversely, those with normal or low blood pressure values have often already developed hearth failure. Second, large interventional studies assessing the effect of lower blood pressure values are lacking.
In addition to this, little is known about the role of single antihypertensive agents, given the paucity of randomized clinical trials.
ACE inhibitors have not consistently shown survival benefits in a single RCT, in which 397 patients were randomized to fosinopril (5-20 mg/day) or placebo plus conventional therapy for 24 months. After adjustment for risk factors, trends were observed suggesting fosinopril may be associated with a lower risk of cardiovascular events. The use of ACE inhibitors was not associated with better survival in observational studies. Beta-Blockers showed mortality benefit in one cohort study and in an RCT of patients with congestive heart failure. After myocardial infarction they seem as effective as in patients without chronic kidney disease. Data from observational studies also indicate that calcium channel blockers were o be associated with a lower risk of mortality among ESRD patients.
In conclusion the present evidence about benefits of single antihypertensive agents is weak in the dialysis population; RCTs, as well as well-designed observational studies are needed.

HOW TO BEST CONTROL SALT OVERLOAD IN HYPERTENSION? ALIGNING DIALYSATE SODIUM WITH PATIENT'S SERUM SODIUM

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From the beginning of the dialysis era, the most appropriate composition of the dialysate has been one of the central topics in the delivery of dialysis treatment. Sodium balance is the cornerstone of intra-dialysis cardiovascular stability and good inter-dialysis blood pressure control. Hypernatric dialysis carries the risk of positive sodium balance, with the consequent possibility of the worsening sense of thirst and hypertension. Conversely, hyponatric dialysis may lead to negative sodium balance, with the possibility of intra-dialysis cardiovascular instability and 'disequilibrium' symptoms including fatigue, muscle cramps and headache. The goal is to remove with dialysis the exact amount of sodium that has accumulated in the inter-dialysis interval. The conductivity kinetic model is applicable on-line at each dialysis session and has been proved to be able to improve intra-dialytic cardiovascular stability in hypotension-prone patients. Therefore, it should be regarded as a promising tool to be implemented in everyday clinical practice. The prescription of dialysis fluid is moving from a pre-fixed, standard dialysate solution to individualization of electrolyte and buffer composition, not only during the dialysis session, but also within the same session (profiling) in order to provide patients with an optimal blood purification coupled with a high degree of tolerability and avoiding a pathological increase of blood pressure values.

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ABSTRACT: DR C AMIRA- MSC THESIS: RISK FACTORS FOR ATHEROSCLEROSIS IN BLACK SOUTH AFRICAN PATIENTS ON HAEMODIALYSIS

Supervisor: Dr S Naicker

ABSTRACT: Atherosclerosis in HD patients

The risk of cardiovascular disease in patients with ESRD is far greater than in the general population. Amongst patients with ESRD, the prevalence of coronary artery disease (CAD) and congestive heart failure is approximately 40% compared with 5-12% in the general population. The excess risk is caused by multiple traditional and non-traditional risk factors for ischaemic heart disease present in these patients. There is little information on CAD and its risk factors in black haemodialysis patients as most of these studies were carried out in the white population. This study is therefore aimed at determining the risk factors for atherosclerosis in Black and non-black (White and Indian) South African patients on haemodialysis (HD).

METHODS: Fifty-eight black patients and twenty-six non-black patients on HD were recruited, together with sixty three age and sex matched controls. Fasting venous blood samples were drawn for measurement of C-reactive protein, homocysteine, Lp (a), serum lipids and adiponectin. Carotid intima-media thickness and plaque occurrence was measured by B-mode ultrasonography. Echocardiography was used to determine LVH.

RESULTS: HD patients had significantly lower total cholesterol, LDL cholesterol and triglycerides compared with controls ($p<0.001$; $p= 0.042$). Hs-CRP, adiponectin and homocysteine levels were significantly higher in patients compared with controls ($p< 0.001$). The prevalence of plaques was significantly higher among HD patients (32%) compared with controls (7%) $X^2 = 60.72$ $p< 0.001$. LVMI was significantly higher among HD patients ($194.25\pm 7.69 gm/m^2$) compared with controls (93.21 ± 3.27 gm/m^2) $p < 0.001$. Patients had higher CIMT (0.65 ± 0.02mm) compared with controls (0.61 ± 0.02mm) but this was not significant $p= 0.137$. Risk factors associated with CIMT on regression analysis were total cholesterol, LDL-cholesterol, age, Hs-CRP, family history of CKD. Risk factors associated with plaque occurrence on logistic regression analysis were age, systolic blood pressure, male gender, smoking, calcium phosphate product and serum phosphate.

CONCLUSION

HD patients have a high prevalence of traditional and non-traditional risk factors for atherosclerosis. Traditional risk factors like lipids were much lower in ESRD patients. HD patients showed a high prevalence of atherosclerosis as measured by increased carotid intima-media thickness and plaque occurrence in carotid arteries.

ABSTRACTS: DR JAMES CHABU'S PHD THESIS "FACTORS IMPACTING ON LVH IN HD PATIENTS"

Supervisors: Drs Sarala Naicker and Gavin Norton

Abstract 1: Multiple blood pressure measurements vs 24 Hour ABPM in HD

The value of multiple pre- and post-dialysis BP measurements in chronic renal failure is uncertain. This study assessed whether 24-hour BP predicts target organ changes better than pre-, post- and averaged dialysis BP in 79 patients without diabetes mellitus receiving MHD for an average of ~49 (3-300) months. 3 Pre- and 3 post-dialysis BPs were determined over 3 sessions of dialysis per week for 4 weeks and the average calculated from the mean of these measurements. Pulse wave analysis performed at the carotid, femoral and radial artery was employed to determine carotid-femoral PWV and AIc. Echocardiography was performed to determine LVM which was indexed to body surface area (LVMI). Using multivariate regression analysis with adjustments for potential confounders, pre- ($p \leq 0.005$), post- ($p<0.05$) and averaged dialysis ($p < 0.015$) systolic BP were associated with LVMI and PWV. Neither 24 hour ($r = 0.260$, $p < 0.05$), day ($r = 0.25$, $p< 0.05$), nor night ($r= 0.24$, $p <0.05$) systolic BP were more closely associated with LVMI than the averaged dialysis systolic BP ($r = 0.27$, $p < 0.02$). Moreover, neither 24 hour ($r = 0.41$, $p = 0.0003$), day ($r=0.400$, $p = 0.0005$), nor night ($r =0.41$, $p< 0.0005$) systolic BP were more closely associated with PWV than the post-dialysis systolic BP ($r=0.39$, $p=0.0001$). In conclusion, these results indicate that the average of multiple pre- and post-dialysis BP measurements are equally effective in predicting cardiovascular target organ changes (LVMI and PWV) as 24-hour ambulatory BP values in patients receiving HD.

Abstract 2: Relationship between aortic stiffness and function and LVM in HD

The relationship between aortic stiffness and function and LVM in patients on HD is uncertain. This study assessed whether large artery function is associated with LVMI in 94 non-diabetic patients receiving MHD for an average of ~49 (3-300) months. Pulse wave analysis performed at the carotid, femoral and radial arteries was employed to determine carotid-femoral PWV and AIc. Echocardiography was performed to determine LVM which was indexed to body surface area (LVMI). Despite relations noted between systolic blood pressure and LVMI ($r=0.36$, $p<0.0005$) and pulse pressure and LVMI ($r=0.44$, $p<0.0001$), on univariate analysis no relationship between either PWV ($r=-0.08$), or AIc ($r=-0.10$) and LVMI was noted. Further, despite significant relations noted between systolic blood pressure and the mean of LV posterior and septal wall thickness (LV mean wall thickness-MWT) ($r=28$, $p<0.01$) and pulse pressure and LV MWT ($r=0.27$, $p<0.02$), on univariate analysis no relationship between PWV ($r=-0.11$), or AIc ($r=0.03$) and LV MWT was noted. Adjustments for potential confounders did not reveal a relationship between large artery function and either LVMI, or LV MWT. In conclusion, these results suggest that large artery dysfunction plays little role in contributing toward LVM or wall thickness in patients receiving chronic HD.

Abstract 3: Volume status and LVH in HD

Although volume status contributes toward cardiovascular target organ changes in chronic renal failure, the relative contribution of blood pressure (BP)-dependent and -

independent mechanisms has not been determined. This study assessed whether IVCD, an index of volume status was associated with LVM and geometry and large artery dysfunction independent of multiple pre- and post- dialysis BP measurements and 24-hour BP in 94 non-diabetic patients receiving maintenance haemodialysis for an average of ~49 (3-300) months. Pulse wave analysis performed at the carotid, femoral and radial artery was employed to determine carotid-femoral PWV and AIc. Echocardiography was performed to determine LVM which was indexed to body surface area (LVMI) and LV geometry and IVCD was determined using ultrasound techniques. After adjustments for a number of potential confounders as well as the average of pre- and post-dialysis systolic BP (SBP) values or 24-hour SBP, IVCD was independently associated with LVMI (partial r adjusted for average dialysis SBP=0.27, p=0.014; partial r adjusted for 24-hour SBP=0.29, p=0.013), and LV mean wall thickness ($p<0.01$), but not with either LV relative wall thickness (p=0.18), or LV end diastolic diameter (p=0.88). Moreover, after adjustments for a number of potential confounders as well as the average of pre- and post-dialysis systolic BP (SBP) values or 24-hour SBP, an association between IVCD and AIc (partial r adjusted for average dialysis SBP=0.21, $p<0.05$), but not PWV was noted. These data support the notion that in patients receiving HD, volume-overload produces effects on cardiovascular target organs that are not predicted by BP effects alone.

Abstract 4: Natriuretic peptides and LVH in HD

Increased plasma concentrations of natriuretic peptides are associated with both increases in cardiac preload and in LVM. In chronic renal failure, there is uncertainty as to whether plasma natriuretic peptide concentrations predict volume status independent of LVMI. The association between natriuretic peptides and IVCD independent of LVM was assessed in 94 non-diabetic patients receiving MHD for an average of ~49 (3-300) months. Echocardiography was performed to determine LVM which was indexed to body surface area and IVCD was determined using ultrasound techniques. ANP, NT-proANP, BNP and NT-proBNP were measured in blood samples taken on the same interdialytic day as echocardiographic measurements. On univariate analysis, natriuretic peptides were correlated with LVMI and IVCD. On multivariate analysis, adjusting for age, sex, BMI, smoking, number of antihypertensive agents and IVCD, both NT-proANP and NT-proBNP were independently associated with LVMI ($p<0.0001$). Neither NT-proANP nor NT-proBNP were associated with IVCD independent of LVMI and additional confounders, although a trend effect for NT-proANP was still noted (partial r=0.22, p= 0.074, n=76). These findings suggest that plasma natriuretic peptide concentrations are closely associated with LVMI after adjusting for volume status in patients receiving HD.

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CONTROL OF BLOOD PRESSURE IN PATIENTS ON CAPD WITH AN ANGIOTENSIN RECEPTOR BLOCKER

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Hypertension has been considered to contribute to morbidity and mortality in patients with chronic kidney disease stage 5. In patients receiving hemodialysis, mild to moderate hypertension is well tolerated. In contrast, hypertension is a significant risk factor in kidney transplant recipients. The association of blood pressure levels and cardiovascular morbidity and mortality in patients on CAPD has been reported in a few studies. Previous data indicate that in patients on CAPD preservation of residual renal function contribute to reduce left ventricular hypertrophy (LVH) which directly relates with carediovascular disease in general population. However, in patients on CAPD, data are scant regarding prevention and/or reduction of LVH. Recently our data have shown that in patients with hypertension starting CAPD therapy, an ARB slowed the decline in residual renal function and reduce LVH(1, 2). We would like to discuss the role of ARBs in hypertensive patients on CAPD for reduction of cardiovascular morbidity and mortality based on data obtained from a single center in Saitama, Japan.

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MECHANISMS OF ERYTHROPOIETIN (EPO) -INDUCED HYPERTENSION (HTN) IN CHRONIC KIDNEY DISEASE (CKD)

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In addition to erythroid progenitor cells many other cells express functionally active EPO receptor. This accounts for un-intended consequences when high EPO doses are used to treat anemia in patients with CKD or cancer. For instance EPO can lead to development or exacerbation of HTN in CKD patients within several weeks following the onset of therapy.[1,2] Since the rise in arterial pressure (BP) in EPO-treated patients frequently coincides with that of hematocrit, the associated HTN was initially attributed to amelioration of anemia. This conclusion was based on the following erroneous assumptions: I- The rise in hematocrit toward normal levels would raise blood viscosity, hence systemic vascular resistance (SVR) and BP. This supposition was incorrect since blood viscosity-hematocrit relationship remains flat within a wide range of hematocrit from subnormal to normal values. II- The rise in hemoglobin (HB) could raise SVR and BP by diverting endothelium-derived nitric oxide (NO) away from the vessel wall. This assumption was wrong since unlike free HB which irreversibly binds NO, reaction of NO with HB in intact erythrocyte leads to formation of S-nitrosohemoglobin which serves as an NO carrier to peripheral tissues. III- Increase in erythrocyte mass could raise BP by expanding blood volume. This supposition was baseless since anemia correction reduces cardiac output[3] which is a main determinant of BP. These contradictions prompted the author to undertake a series of experiments designed to isolate the effect of anemia correction from that of EPO on BP [4,5]. To this end, iron-sufficient and iron-deficient CKD (5/6 nephrectomized) rats were randomized to placebo-treated, EPO-treated (100 units/kg, twice weekly for 6-weeks) and transfusion-treated (multiple rat red cell transfusions through tail vein to simulate the effect of EPO) groups. The study revealed marked HTN of similar magnitudes with EPO therapy in both iron-sufficient and iron-deficient CRF rats (despite persistent anemia in the latter) and no increase in BP, despite anemia correction, in the transfused rats[4,5]. In a separate study, we found no change in BP when severe anemia was corrected with iron repletion in a group of iron-deficient ESRD patients.[6] Together; these observations provided irrefutable evidence that EPO as opposed to anemia correction causes HTN. Moreover, EPO was shown to cause HTN by: a- increasing cytosolic $[Ca^{2+}]_i$ and expanding sarcoplasmic calcium stores in vascular smooth muscle cells, b- raising endothelin-1 production and increasing thromboxane / prostacyclin ratio in the vascular tissue and c- activation of tissue renin-angiotensin system (reviewed in 1,2). In addition to HTN, high doses of EPO can cause thrombotic complications (by promoting thrombocytosis, platelet hyper-activity and endothelial cell activation[7,8,9]), vascular remodeling, proliferative retinopathy and blood access failure [10,11]. For these reasons EPO should be used judiciously and its overzealous use in pursuit of arbitrary HB targets should be avoided. Finally, evaluation and management of HTN in CKD patients should include careful examination of the concurrent EPO therapy.

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VOLUME STATE AND BLOOD PRESSURE (BP) IN HEMODIALYSIS (HD) PATIENTS

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Achievement of normotension in HD patients via correction of fluid status or antihypertensive drugs or a combination of both is an undisputed goal. However, the lack of an objective tool to measure fluid status in HD patients made the possible association of fluid imbalances and BP nearly uninterpretable. Recently a bioimpedance spectroscopy method was validated in healthy and in HD patients by isotope reference methods and was shown to allow a reliable measurement and quantification (in liters) of hydration state (HS).

In 5oo middle –European HD-patients HS and BP sys.pre-HD were measured. When plotted five regions could be identified:
A central region (normal HS and BP) was defined with data from 1247 healthy Caucasian controls.46 % of the HD patients were in this acceptable region.
15% of the HD patients could be identified as clearly overhydrated (>2.5 kgs pre-HD) and hypertensive (BPsys > 150 mmHg),5% were dehydrated and still hypertensive and 10% were clearly overhydrated and had a normal or low BP. Another 5% were dehydrated even before dialysis and had a normal or low BP.
Our data were confirmed by identical results in 600 check HD Patients who were measured by the same bioimpedance method.

This study illustrates a wide variability in BPsys regardless of the degree of hydration state. It is hypothesized that a hydration plot allows a differential treatment of hyper/hypotension in HD patients on a more objective choice of therapeutical strategies. Further studies are required to assess the impact on outcome of such a therapy.