“Home Nocturnal Hemodialysis: Have we found our Holy Grail?"

The New York Society of Nephrology
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Christopher T Chan MD FRCPC
Toronto General Hospital
University Health Network
University of Toronto

YES!

Objectives

- Why do we need a new renal replacement therapy modality?
- Does NHD modify morbidities of ESRD patients?
- Future Directions

Possible solutions for poor ESRD Rx outcomes

- ***Higher dialysis dose***
  - ***Hemo study – no benefit***
  - ***ADEMEX study – no benefit***
- ***Alternative schedules***
  - ***Daily (quotidian HD)***
  - ***Intermittent long HD***
- ***Alternative modalities***
  - ***Hemo(dia)filtration***
  - ***Sorbents***
  - ***Other***
- ***Address the co-morbidities → RETURN TO NORMAL PHYSIOLOGY***

Daily nocturnal home hemodialysis (NHD)

- Form of home hemodialysis
  - Done by the patient or a family member
  - Partner not required
- 8 hours 5-6 times per week nightly during sleep
- Low blood flow (typical 250 ml/min)
- Low dialysate flow (typical 300 ml/min)
- Dialysate
    - HCO_3 28-35 mEq/L / (mmol/L)
    - Ca 3.0-4.5 mEq/L / 1.5 – 2.25 mmol/L
    - P 0-4.5 mg/dL / 0 – 1.5 mmol/L

Nocturnal Hemodialysis

- 5 - 6 sessions / week
- 8 – 10 hrs / treatment
- 3 x normal dialysis dose
- Enhanced middle molecule clearance, including:
- Moderate fluctuations in volume and biochemical status

Conventional Hemodialysis

- 3 sessions / week
- 3 – 4 hrs / treatment
- Less solute clearance
- Less middle molecule clearance
- Large fluctuations in volume and biochemical status

ESRD affects every organ system!

- CVS (leading cause of death)
  - Hypertension
  - Autonomic dysfunction
  - Elevated arterial stiffness
  - PTH/Ca/Pi
  - Impaired vascular responsiveness
  - Abnormal LV geometry and function
  - Inflammation
- Anemia
- Endocrinopathies
  - Vit D
  - Lipid
  - Bone/Osteoporosis
  - Reproduction
- Cognition
- Improvement → Correction

Impact of long term NHD on LVMI, blood pressure, and anti-hypertensive therapy

Measurements	CHD (n=13)		NHD (n=28)	
	Initial	Final	Initial	Final
LVMI (g/m^2)	142 ± 33	150 ±56	147 ± 42	114 ± 40*
SBP (mmHg)	136 ± 25	131 ± 20	146 ± 20	122 ±13*
DBP (mmHg)	82 ± 13	80 ± 15	84 ± 15	74 ± 12*
PP (mmHg)	54 ± 22	51 ± 17	61 ± 12	49 ± 12*
Anti-BP Meds	1.5	1.5	1.8	0.3*

* denotes $p < 0.05$

Chan CT et al, *Kidney Int* 61:2235-2239., 2002

Effect of Frequent Nocturnal Hemodialysis vs Conventional Hemodialysis on Left Ventricular Mass and Quality of Life

A Randomized Controlled Trial

Table 2. Outcomes for LV Mass, Blood Pressure, Anemia, and Mineral Metabolism[a]

Characteristic	Nocturnal Hemodialysis[b] (n = 26)	Conventional Hemodialysis[b] (n = 25)
LV mass, mean (SD), g		
Baseline	177.4 (51.1)	181.5 (92.3)
Exit	163.6 (45.2)	183.0 (84.2)
Change	−13.8 (23.0)	1.5 (24.0)
LV mass, mean (SD), g/m^2		
Baseline	92.4 (26.6)	101.8 (50.6)
Exit	85.3 (23.2)	102.8 (46.1)
Change	−7.1 (12.4)	1.0 (14.1)
Blood pressure, mean (SD), mm Hg		
Systolic		
Baseline	129 (23)	135 (19)
Exit	122 (23)	139 (20)
Change	−7 (29)	4 (17)
Diastolic		
Baseline	75 (14)	77 (16)
Exit	68 (16)	75 (12)
Change	−7 (16)	−2 (12)

Culleton et al – JAMA 2007

Regression of LVH with NHD

- ? Improved ECFV
- ? Vasculature
- ? Both

Vascular effects of NHD

	CHD	NHD - 1 month	NHD - 2 months
Resting systolic BP, mm Hg	140±5	124±3*	119±3*
Resting diastolic BP, mm Hg	82±3	75±3*	71±3*
Cardiac output, L/min	4.9±0.4	5.3±0.4	5.5±0.5
Stroke volume, mL	63±5	64±5	68±6
Heart rate, beats/min	78±3	75±3	80±4
Total peripheral resistance, dyne -s-cm-5	1967±235	1647±185*	1499±191*

Chan et al Hypertension 42(5):925-31 2003

Vascular effects of NHD

	CHD	NHD 1 month	NHD 2 months
Norepinephrine, nmol/L	2.66±0.4	1.82±0.4*	1.91±0.2*
Antihypertensive medications (per patient)	2.5	0.6*	0.2*
Brachial artery responses			
Change after hyperemia, %	(-2.7±1.8)	4.7±1.7*	8.0±1.0*
Change after GTN, %	6.9±2.8	8.8±1.4*	15.7±1.6*

Chan et al Hypertension 42(5):925-31 2003

The natural history of coronary calcification progression in a cohort of nocturnal haemodialysis patients

Darren Yuen[1], Andreas Pierratos[2], Robert M.A. Richardson[1] and Christopher T. Chan[1]

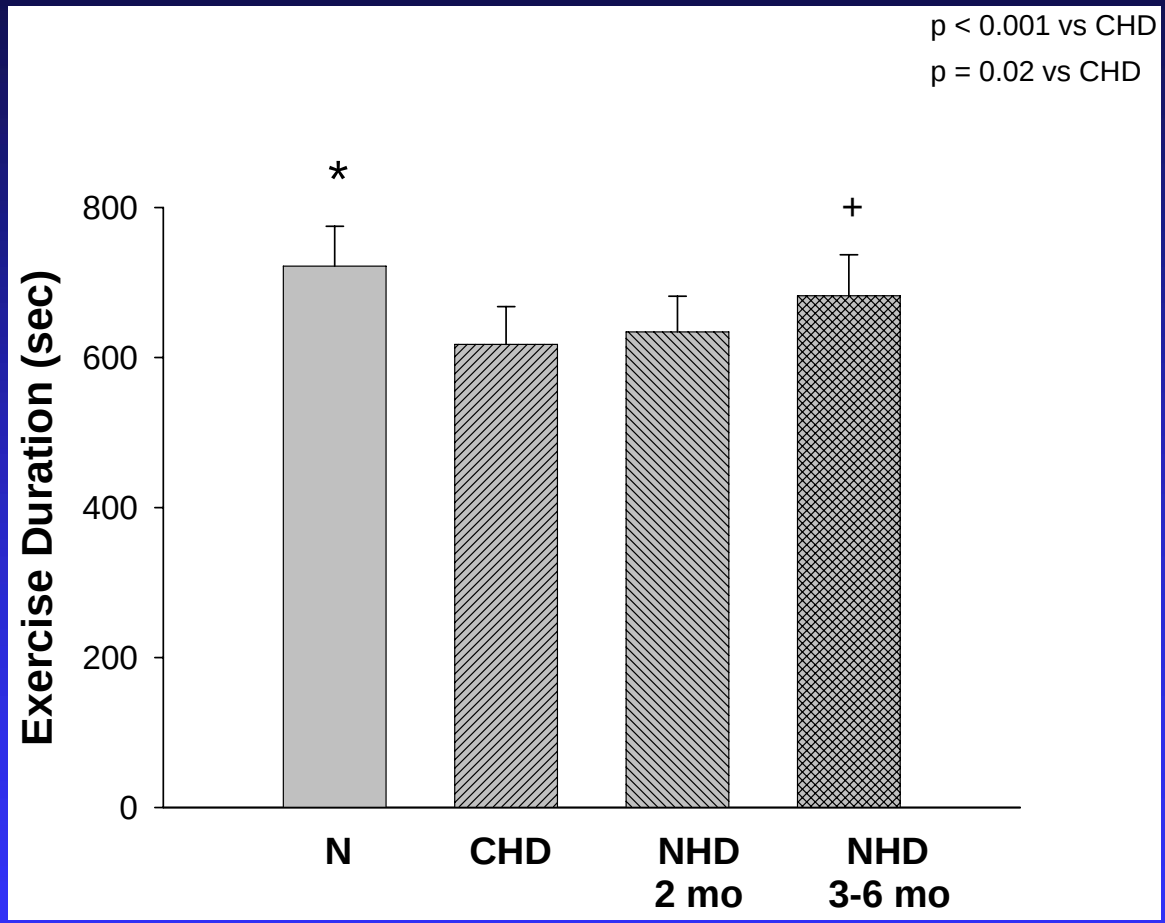
Table 1. Changes in CACS before and after conversion to NHD ($n=38$)

Variables	All Patients	Baseline CACS ≤10	Baseline CACS >10
Mean baseline CACS (range)	691 ± 295 (0–8217)	0.7 ± 0.5 (0–10)	1874 ± 697 (112–8217)
Mean follow-up CACS (range)	765 ± 316 (0 to 8356)	6 ± 4 (0–71)	2066 ± 739 (179–8356)
ΔCACS per year	64 ± 38	5 ± 3	164 ± 98
1 year standardized CACS[a]	755 ± 315	6 ± 3	2038 ± 740
Percentage change in CACS over 1 year	9%	762%	9%

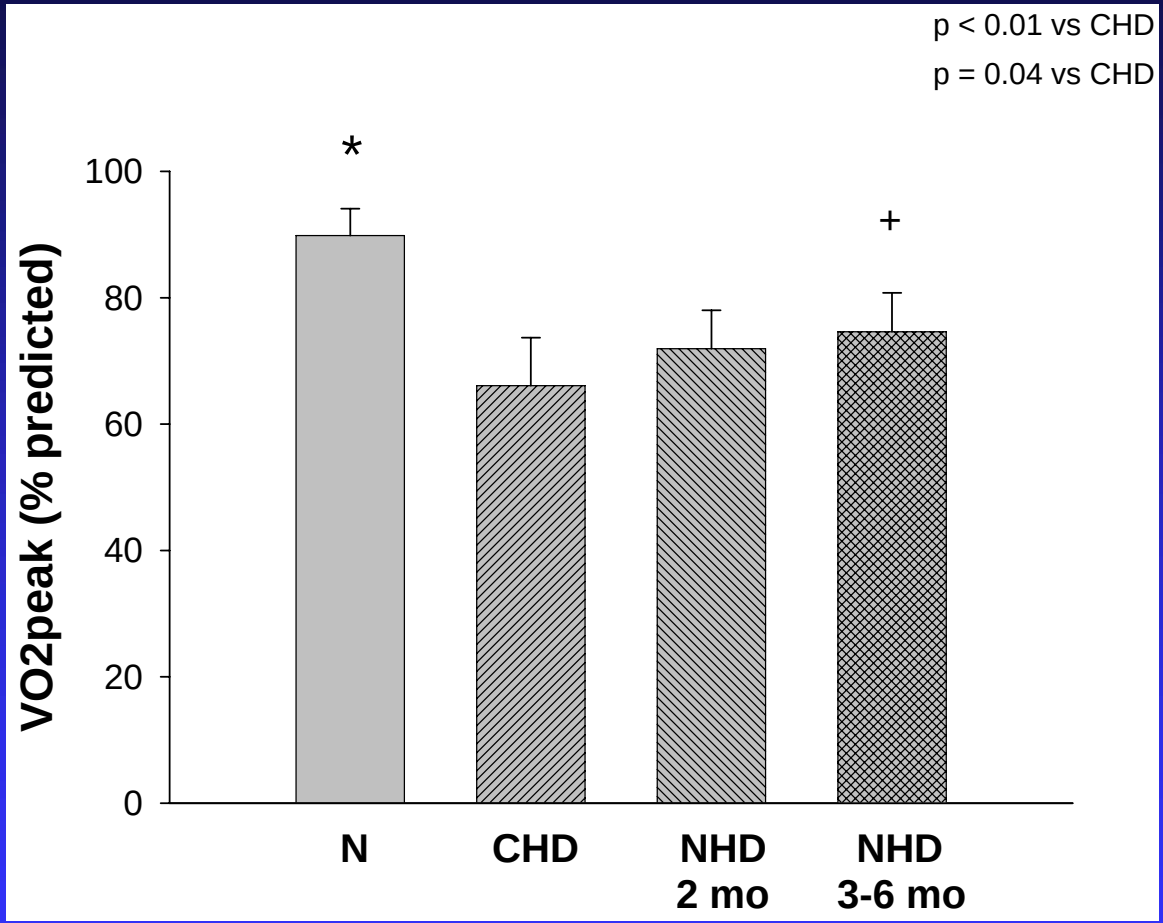
Results are expressed as mean ± SEM, median (range).
[a]1 year standardized CACS refers to the change in CACS adjusted for a 1 year interval assuming a linear rate of CACS change (see Methods section).

Yuen et al : NDT: 2006

Improvement in exercise capacity after conversion to NHD



Chan et al - NDT



Chan et al - NDT

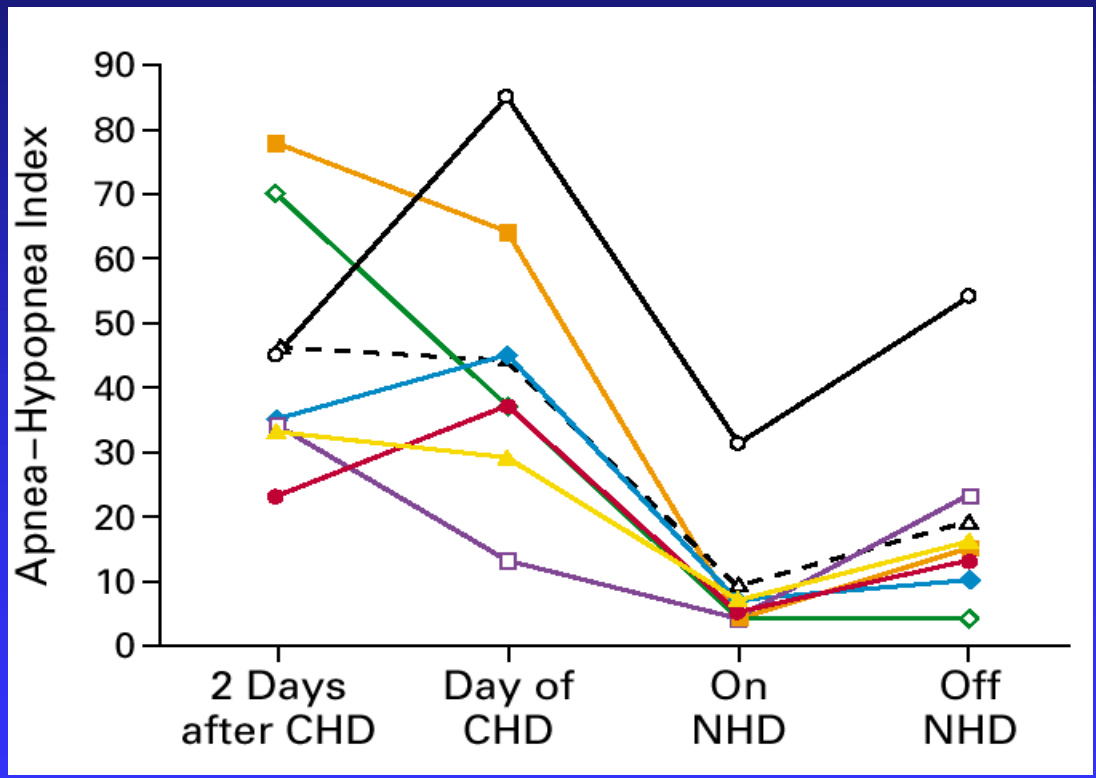
Sleep related breathing disorder in uremia

- Common in ESRD
- Nocturnal hypoxemia
  - Development of LVH
  - Pathogenesis of HTN
  - Independent predictor of incident adverse CVS events
- Recurrence of hypoxemia and hypercapnia ± profound changes in cardiac loading conditions
- Net result: increase in SNS outflow to the heart and periphery

Correction of Sleep Apnea with NHD

Hanly P, Pierratos A. NEJM 2001

The first 14 patients of the Nocturnal Hemodialysis project in Toronto. 8 patients had sleep apnea (AHI>15/hr)



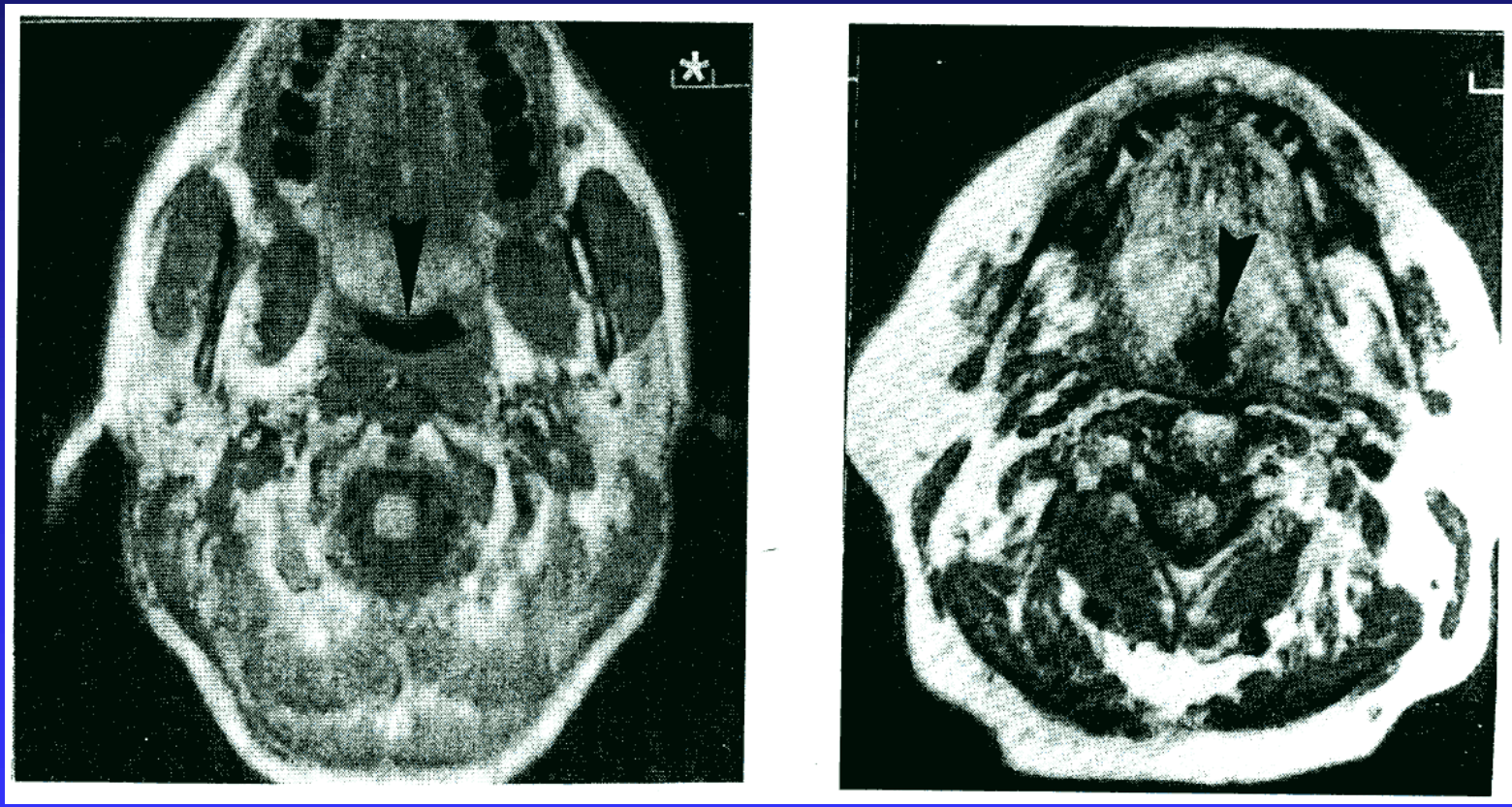
AHI decreased from 46±19 to 9±9 p=0.006

Minimum O_2 sat increased from 89.2±1.8 to 94.1±1.6 p=0.005

Why would NHD correct sleep apnea?

ECF volume vs. Uremia or Both?

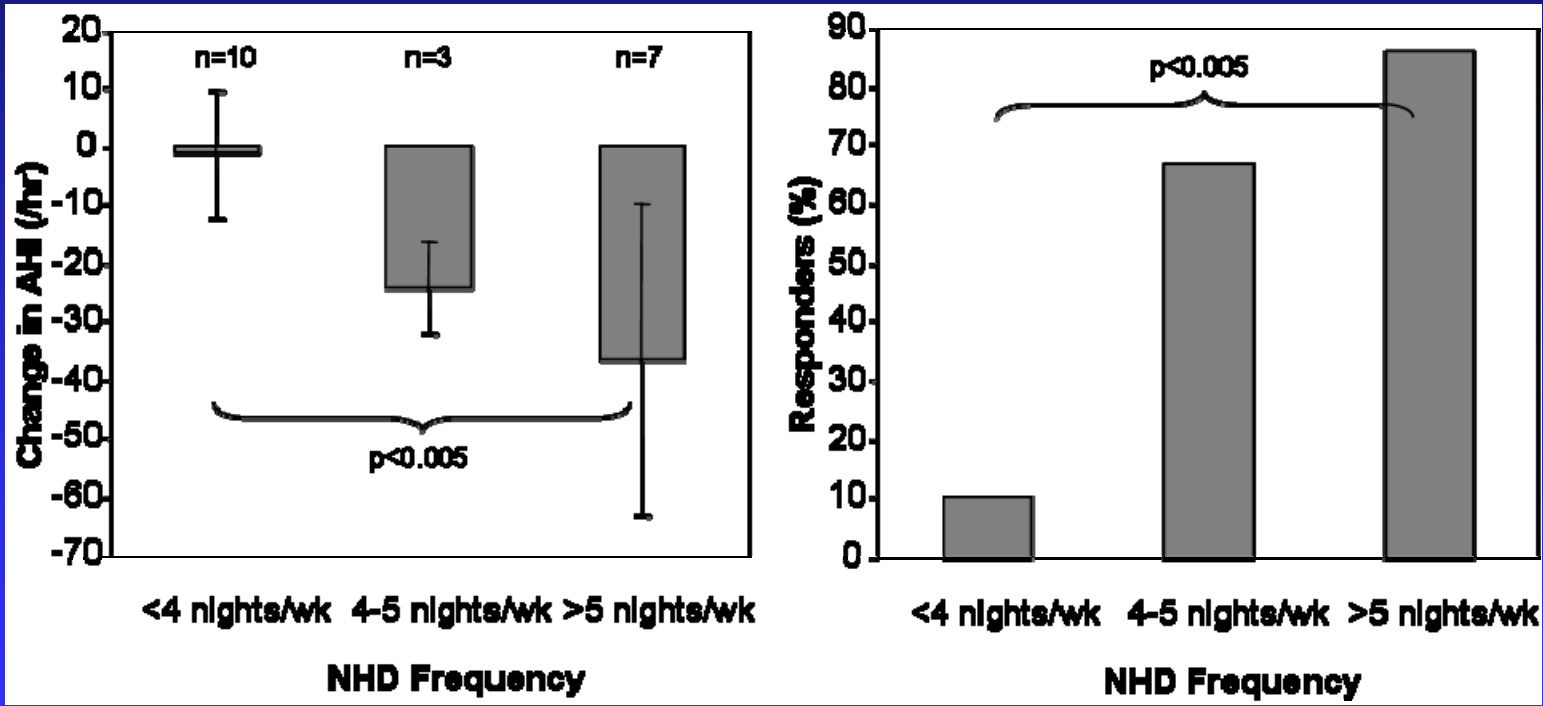
ECF volume overload: upper airway edema?



Normal Subject

Sleep Apnea

The Impact of Nocturnal Hemodialysis on Sleep Apnea is Dose-dependent



Beecroft J et al ATS 2006

Impact of NHD on EPO responsiveness

	Initial (CHD)	6 mos	12 mos	**p**
NHD				
Hb (g/L)	115 ± 2.3	122 ± 2.5	124 ± 2.3*	0.03
EPO dose (u/week)	10400 ± 1400	8500 ± 1300	7600 ± 1100	0.03
EPO free (%)	19	24	24*	NS
CHD				
Hb (g/L)	110 ± 2.2	115 ± 2.7	115 ± 2.2	NS
EPO dose (u/week)	8300 ± 1100	8100 ± 1300	8600 ± 1000	NS
EPO free (%)	13	13	9.4	NS

Schwartz et al: Clin Nephro, 2005

Inflammation and NHD

Variables	CHD (n=14)	NHD (n = 14)
Hb (g/L)	120 ± 4	124 ± 4
Ferritin (ng/ml)	482 ± 73	413 ± 123
EPO dose (u/wk)	11643 ± 1258	6877 ± 1482*
hsCRP (mg/L)	8.4 ± 1.8	4.6 ± 1.3
IL – 6 (pg/ml)	6.5 ± 0.8	3.9 ± 0.7*

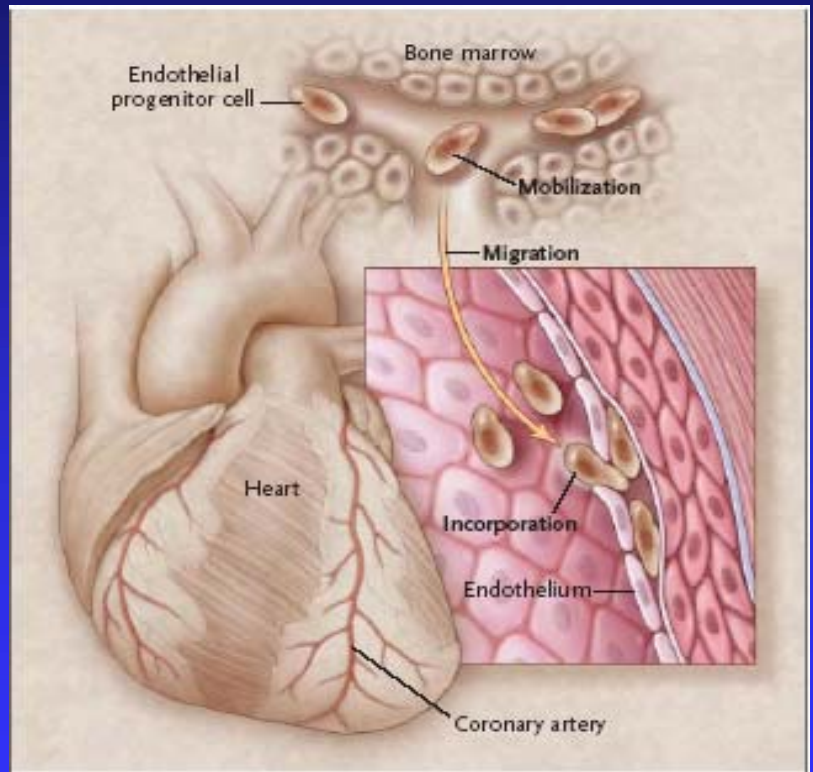
Yuen et al – ASAIO J 2005

Uremia and Cardiovascular disease

- Why does uremia pose such a malignant course for CVD?
- Risk factors +++
- ? Capacity for vascular and cardiac repair ?

Role of EPCs

- Endothelium maintenance
- Neovascularization
  - Substrate for angiogenesis and vasculogenesis
- Normal cardiovascular homeostasis:
- Balance of **injury vs. repair**



Three Stages in the Movement of Endothelial Progenitor Cells from Bone Marrow to Vascular Endothelium.

Rosenzweig: NEJM, 2003

Research questions

- Does uremia control modulate EPCs number and function?
- Does augmentation of uremia control (NHD) improve EPCs?

Methods

- Cross sectional study
- Subjects:
  - Normal: age + gender matched , no symptomatic CVD, n=10
  - CHD: n = 12, no symptomatic CVD
  - NHD: n = 10
- EPC number
- EPC function (VEGF migration assay)
- CVS surrogate: LVMI, SBP

Chan et al: Am JPhysiol Renal Physiol 289: F679–F684, 2005.

Results

Table 1. *Demographic characteristics*

Variable	Normal (n = 10)	CHD (n = 12)	NHD (n = 10)
Age, yr	41±4	41±3	42±4
Gender (M:F)	7:3	8:4	7:3
Etiology of ESRD	Not applicable	HTN: 4 Congenital: 3 GN: 2 DM: 3	HTN: 3 Congenital: 2 GN: 3 DM:2
Cardiovascular	None	2.3±0.4	0.3±0.2*
Medications, per patient			
α-Blocker		1	0
ACE inhibitor		4	1
ARB		5	0
β-Blocker		8	1
Calcium channel blocker		7	1
Diuretics		4	0
Vasodilators		2	0

Chan et al: Am JPhysiol Renal Physiol 289: F679–F684, 2005.

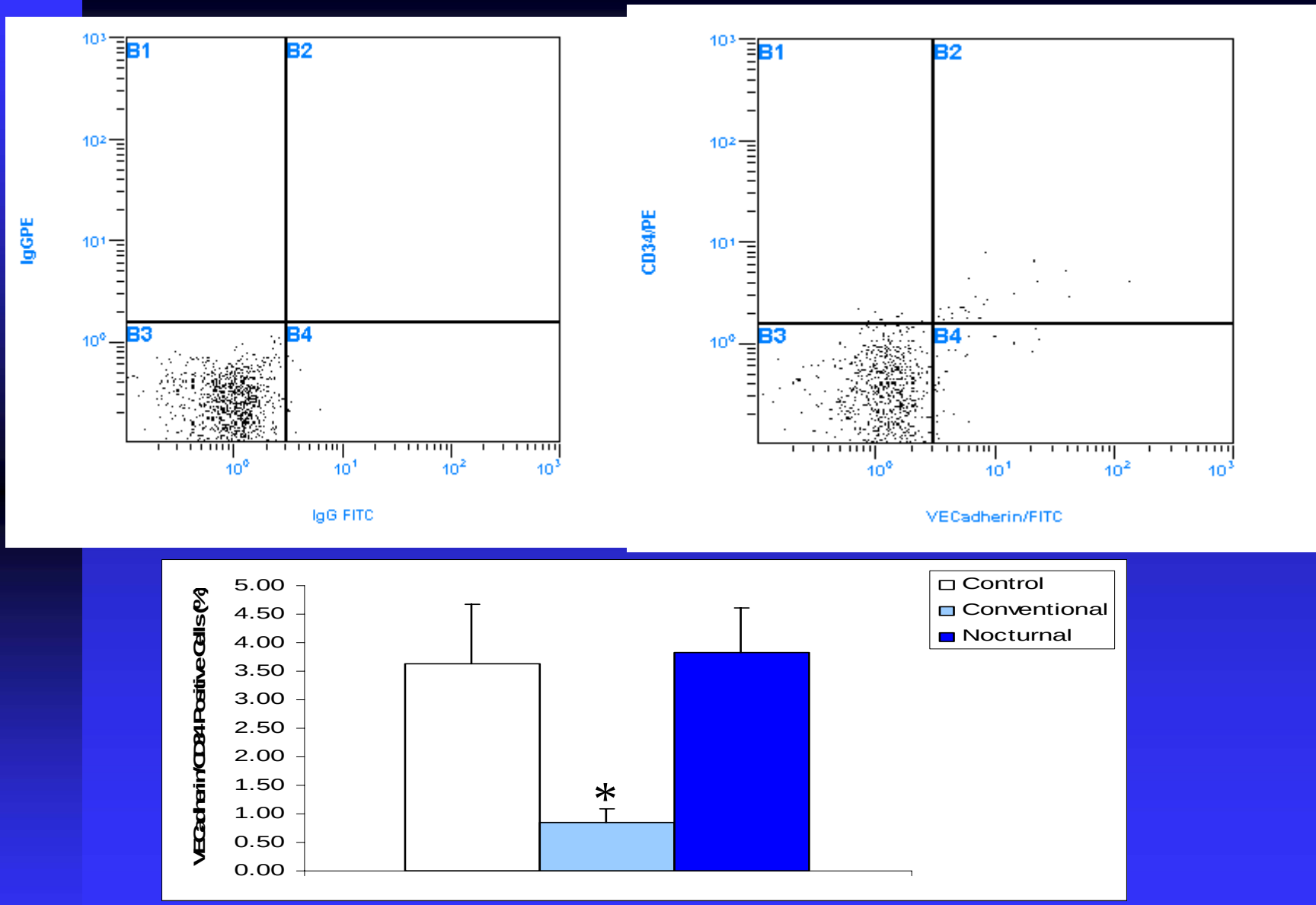
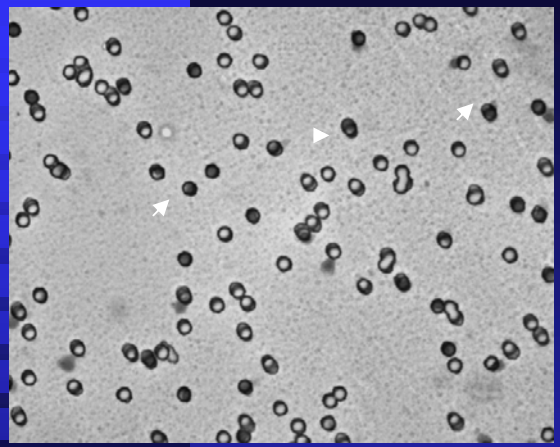


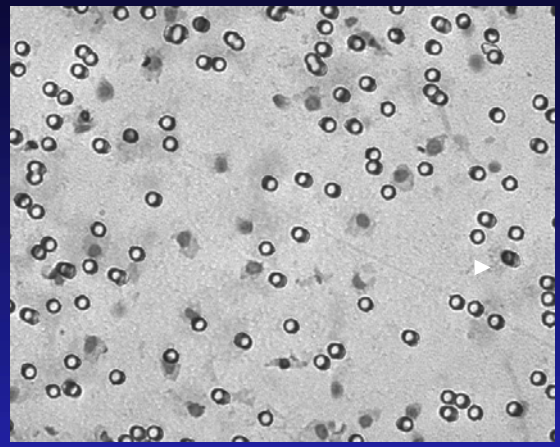
Figure. Effect of dialysis on CD34/VECadherin-positive cells.

Chan et al: Am JPhysiol Renal Physiol 289: F679–F684, 2005.

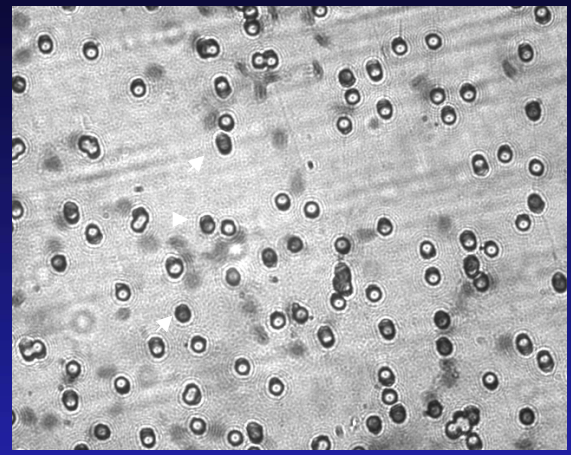
Control



Conventional



Nocturnal



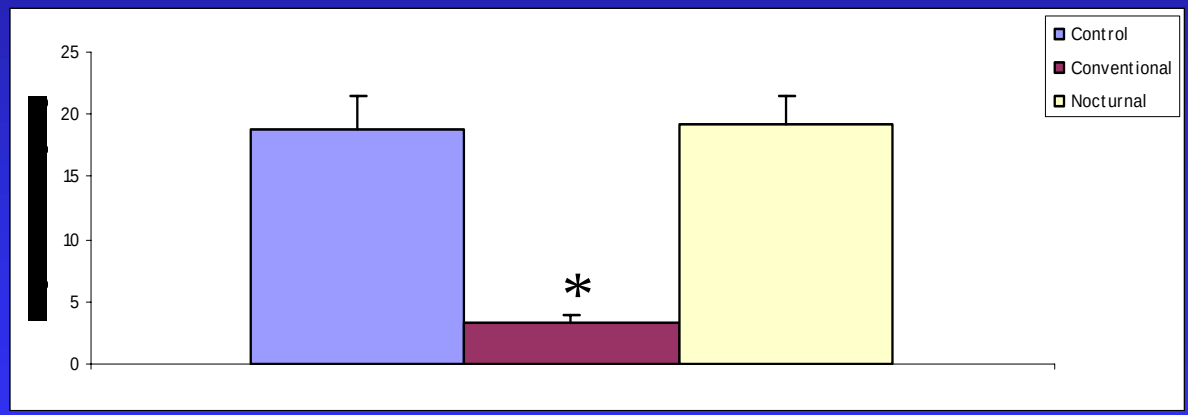
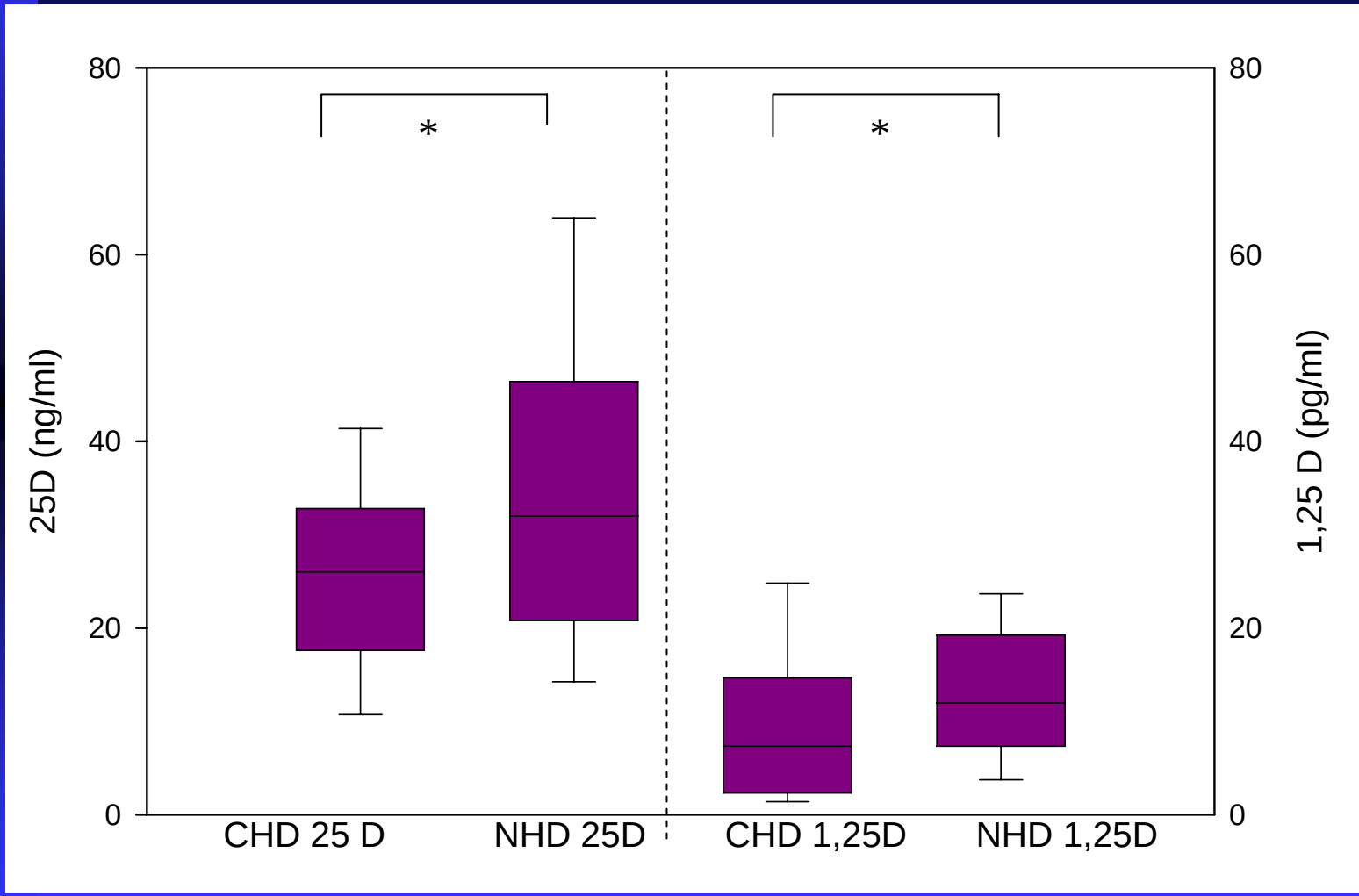


Figure. Functional activity of EPCs was assessed by their migratory capacity. (Control vs. CHD vs. NHD)

Chan et al: Am JPhysiol Renal Physiol 289: F679–F684, 2005.

Improvement in Vitamin D Levels after Conversion to Home Nocturnal Hemodialysis

Vitamin D levels before and after conversion to NHD



Nessim et al - KI

n = 35

*p < 0.05

The quality of life and cost utility of home nocturnal and conventional in-center hemodialysis

PHILIP A. MCFARLANE, AHMED M. BAYOUMI, ANDREAS PIERRATOS, and DONALD A. REDELMEIER

Table 3. Summary of costs[a]

	Mean annual cost				
	Quality of Life study subgroup			Full-study group	
	IHD	HNHD	*P* value[b]	IHD	HNHD
Number	19	24		23	33
Staff	$22,005	$10,938	<0.01	$22,056	$10,932
Direct hemodialysis materials	$ 6,413	$16,669	<0.01	$ 6,575	$16,587
Medications	$11,546	$ 8,150	0.11	$12,029	$ 8,989
Overhead and support	$12,365	$ 4,181	<0.01	$12,393	$ 4,178
Physician fees	$ 6,650	$ 6,650	1.00	$ 6,650	$ 6,650
Admissions and procedures	$ 5,271	$ 818	0.09	$ 6,997	$ 1,173
Depreciation	$ 871	$ 6,139	<0.01	$ 871	$ 6,139
Lab tests and imaging	$ 1,246	$ 1,594	0.04	$ 1,364	$ 1,744
Total	$66,367	$55,139	0.03	$68,935	$56,394

Abbreviations are: IHD, in-center hemodialysis; HNHD, home nocturnal home dialysis.
[a]All costs expressed in year 2000 Canadian dollars
[b]*P* value for comparison of IHD quality of life subgroup to HNHD quality-of-life subgroup

Mcfarlane et al: KI 1004 – 1011, 2003

Longer treatment time and slower ultrafiltration in hemodialysis: Associations with reduced mortality in the DOPPS

R Saran[1], JL Bragg-Gresham[2], NW Levin[3], ZJ Twardowski[4], V Wizemann[5], A Saito[6], N Kimata[7], BW Gillespie[8], C Combe[9], J Bommer[10], T Akiba[7], DL Mapes[2], EW Young[11] and FK Port[2]

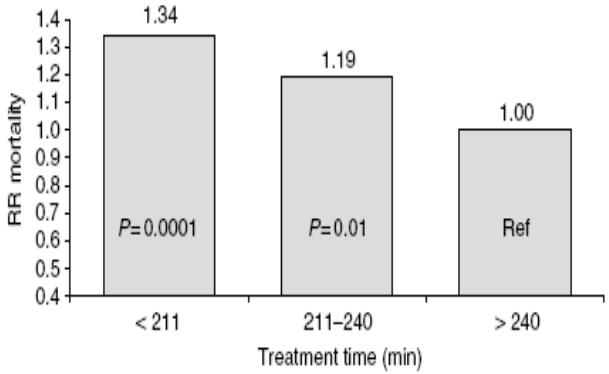


Figure 2 | RR of all-cause mortality, by TT category.
The incremental RR of mortality with decreasing TT categories in all DOPPS regions combined. The referent category is TT > 4 h (240 min).

Table 3 | Associations between ultrafiltration rate (UFR) and treatment time (TT) and mortality

	UFR > 10 ml/h/kg		TT > 240 min	
Outcome	RR	*P*-value	RR	*P*-value
All-cause mortality				
Unadjusted	1.01	0.75	0.68	< 0.0001
Adjusted[a]	1.09	0.02	0.81	0.0005
Cardiopulmonary mortality				
Unadjusted	1.00	0.97	0.73	< 0.0001
Adjusted[a]	1.04	0.41	0.84	0.03

[a]Based on Cox regression, adjusted for: age, sex, race, ethnicity, time on dialysis, 14 summary comorbid conditions, living status, height, weight, *Kt/V*, blood flow, residual renal function, and catheter use as vascular access, TT (in UFR model), and UFR (in TT model). Stratified by geographical region and phase of study. Accounts for facility clustering.

Saran et al: KI 1222-1228, 2006

Associations of hemodialysis dose and session length with mortality risk in Australian and New Zealand patients

MR Marshall[1], BG Byrne[2,3], PG Kerr[4] and SP McDonald[2]

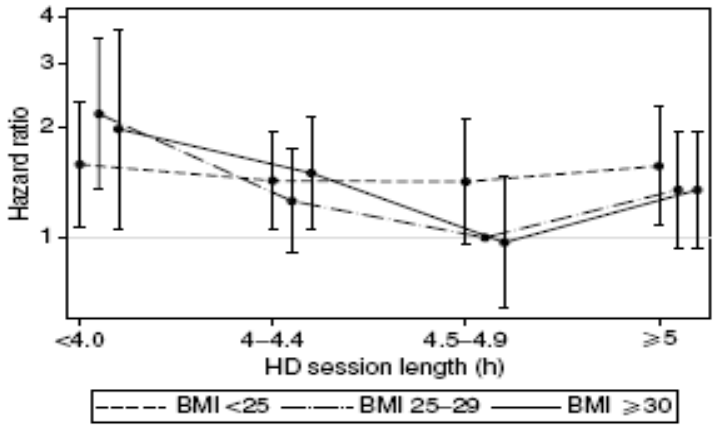


Figure 5 | Hazard ratios (HR) for mortality by HD session length and body mass index (BMI). The multivariate analyses are fully adjusted using the final regression model. All HR are relative to the group with BMI 25–29 and session length 4.5–4.9 h. Mortality risk is the same for different session lengths in group with BMI <25 ($P = 0.85$), although differences are more likely in the groups with BMI 25–29 ($P = 0.01$) and $\geqslant 30$ ($P = 0.06$). Error bars indicate 95% confidence intervals.

Marshall et al: KI1229 – 1236, 2006

Clinical Benefits of NHD

Clinical Observations

- Normalization of BP
- LVH regression
  - Chan et al, KI 2002
- LV EF improvement
  - Chan et al, NDT 2002
- PVD improvement
  - Chan et al, AJKD 2003
- BP changes with Tx
  - McCormick et al (NDT,2004)
- Sleep apnea correction
  - Hanly et al, NEJM 2001
- Normalization of Phosphate
  - Musci et al KI 1999

Mechanistic analysis

- Restoration of TPR
- Selective decrease in PNE
- Improvement in FMD (endothelial function) and EIV (VSMC)
  - Chan et al (Hypertension, 2003)
- Restoration of nocturnal cardiac sympathetic outflow
  - Chan et al (KI 2004)
- Restoration of EPC biology
  - Chan et al (AJP)

Cross-Sectional Comparison of Quality of Life and Illness Intrusiveness in Patients Who Are Treated with Nocturnal Home Hemodialysis *versus* Peritoneal Dialysis

Edwin Fong, Joanne M. Bargman, and Christopher T. Chan
Toronto General Hospital–University Health Network, Toronto, Ontario, Canada

Table 1. Baseline patient characteristics[a]

Variable	NHD	PD	*P*
Age (yr; mean ± SD)	49 ± 12	61 ± 13	<0.01
Male (%)	67	55	0.28
Race (%)			0.16
white	73	52	
black	6	16	
Asian	9	28	
other	12	4	
Highest education level (%)			0.051
elementary school	0	14	
high school	28	30	
college/undergraduate	53	43	
postgraduate	19	13	
Previous kidney transplant (%)	31	14	0.08
Living alone (%)	25	18	0.41
Charlson Index (mean ± SD)	1.14 ± 0.25	1.82 ± 0.33	0.14
Years of renal replacement (yr; mean ± SD)	10.8 ± 1.7	7.6 ± 1.0	0.10

[a]NHD, nocturnal home hemodialysis; PD, peritoneal dialysis.

Table 2. Comparisons of biochemical indices between NHD and PD patients

Variable	NHD	PD	*P*
Plasma creatinine (μ mol/L)	503 ± 34	800 ± 43	<0.001
Hemoglobin concentration (g/L)	124 ± 2	117 ± 2	0.026
Plasma urea (mmol/L)	11.7 ± 1.0	18.4 ± 0.8	<0.001
Plasma calcium (mmol/L)	2.41 ± 0.03	2.27 ± 0.30	0.002
Plasma phosphate (mmol/L)	1.11 ± 0.06	1.63 ± 0.07	<0.001
Plasma albumin (g/L)	39 ± 2	37 ± 2	<0.001

Table 3. Comparisons of KDQOL values between NHD and PD patients

Variable	NHD	PD	*P*
Symptom problem list	76.3 ± 2.5	71.9 ± 2.6	0.22
Effect of kidney disease	61.5 ± 3.7	60.7 ± 2.7	0.85
Burden of kidney disease	37.0 ± 4.4	47.0 ± 3.8	0.092
Work status	48.6 ± 7.6	36.0 ± 5.4	0.17
Cognitive function	75.6 ± 4.8	81.4 ± 2.2	0.27
Quality of social interaction	73.5 ± 3.0	75.8 ± 2.3	0.55
Sexual function	81.7 ± 5.4	61.8 ± 9.0	0.07
Sleep	52.8 ± 3.9	54.1 ± 2.7	0.79
Social support	65.7 ± 5.3	79.2 ± 2.8	0.027
Dialysis staff encouragement	89.2 ± 2.6	85.7 ± 2.8	0.37
Patient satisfaction	75.5 ± 4.3	79.2 ± 2.7	0.46

Table 4. Comparisons of illness intrusiveness score between NHD and PD patients

Variable	NHD	PD	*P*
Physical well-being and diet	3.81 ± 0.3	3.98 ± 0.20	0.65
Work and finance	3.77 ± 0.35	3.30 ± 1.64	0.27
Marital, sexual, and family relations	3.32 ± 0.31	2.78 ± 0.22	0.16
Recreation and social relations	3.23 ± 0.28	3.11 ± 0.18	0.72
Other aspects of life	2.46 ± 0.25	2.47 ± 0.20	0.96

Pregnancy Outcomes - NHD

	Weeks at delivery	Mode of delivery	Birth weight (g)	APGAR
Patient 1	36	C/S	2020	9/9
Patient 2	38	SVD	3000	5/8
Patient 2	37^{4}	SVD	2785	9/9
Patient 3	36^{5}	Induced labor	2690	6/9
Patient 4	38^{5}	C/S	2750	8/9
Patient 5	30	SVD	1260	5/7
Mean	36^{2}		2418	

Barua et al – CJASN (in press)

clinical nephrology

Original

Reduction in cardiovascular related hospitalization with nocturnal home hemodialysis

A. Bergman, S.S.A. Fenton, R.M.A. Richardson and C.T. Chan

	Dialysis or cardiovascular related admissions (per patient year)	Duration of Dialysis or Cardiovascular related admissions (days per patient year)	All cause hospitalization (per patient year)	Duration of all cause hospitalization (per patient year)	ER visits (per patient year)
NHD					
Pre-conversion to NHD	0.50 ± 0.15	6.72 ± 4.17	0.53 ± 0.15	7.03 ± 4.16	1.03 ± 0.26
Post-conversion to NHD	0.17 ± 0.06[a,b]	1.39 ± 0.65	0.21 ± 0.07	1.49 ± 0.66	0.93 ± 0.27
CHD					
Baseline	0.48 ± 0.14	7.4 ± 4.2	0.64 ± 0.17	9.22 ± 4.45	0.88 ± 0.15
End of study	0.40 ± 0.12	2.9 ± 1.0	0.49 ± 0.12	3.37 ± 1.03	0.77 ± 0.15

[a] denotes $p < 0.05$ compared with baseline; [b] denotes $p < 0.05$ compared with CHD; NHD = nocturnal hemodialysis; CHD = conventional hemodialysis; ER = emergency room.

Bergman et al (in press)

Table 4. Distribution of causes of admission.

	NHD		CHD	
Causes	Hospitalization rate pre-NHD (per patient year)	Hospitalization rate post-NHD (per patient year)[a]	Hospitalization rate during CHD_1 (per patient year)	Hospitalization rate during CHD_2 (per patient year)[b]
CVS related	0.1 (9%)	0.05 (9%)	0.2 (22%)	0.2 (37%)
Access related	0.3 (27%)	0.3 (56%)	0.3 (39%)	0.2 (37%)
Transplant related	0.2 (18%)	0.03 (6%)	0.2 (17%)	0.02 (3%)
Other	0.5 (45%)	0.16 (31%)	0.2 (22%)	0.2 (23%)

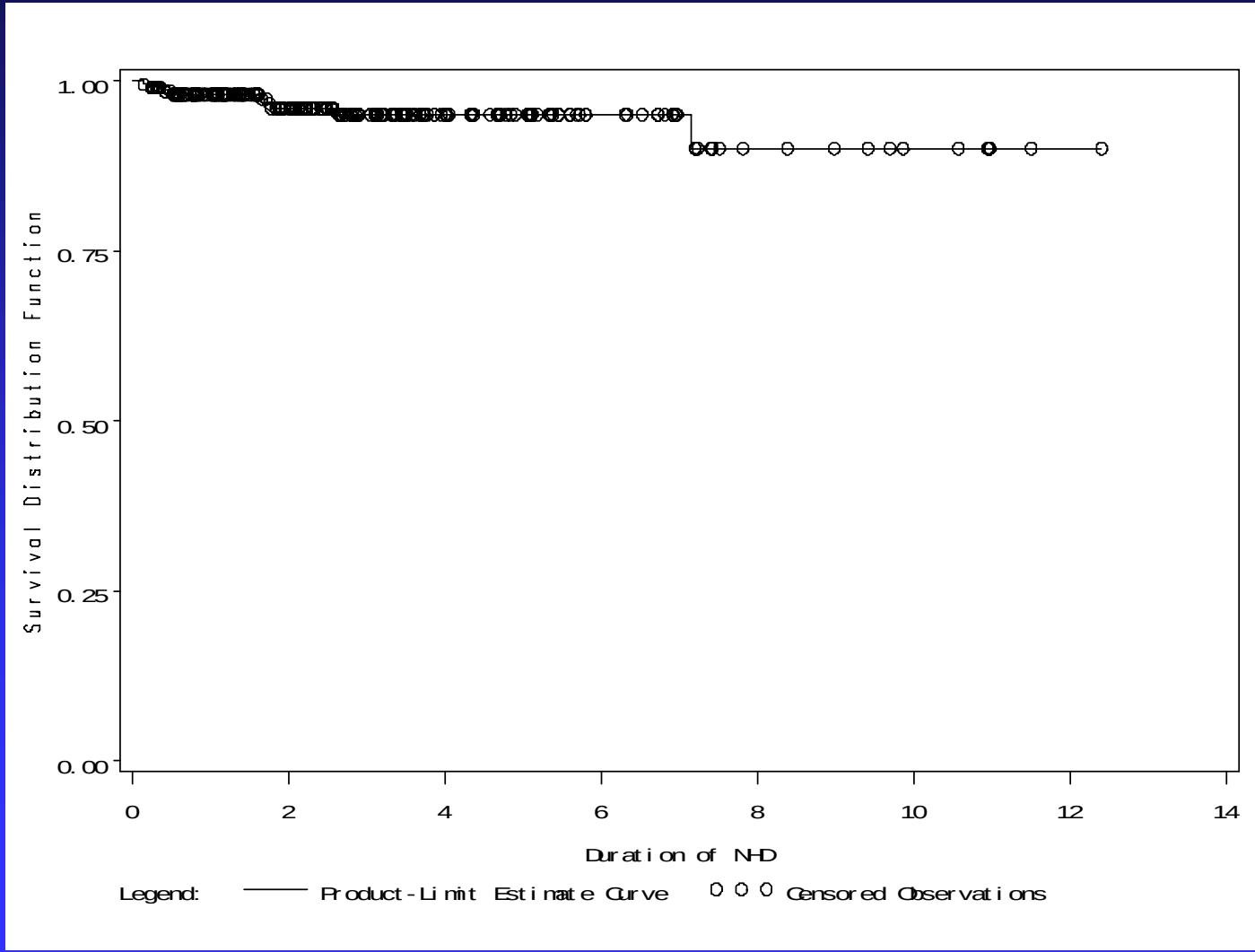
NHD = nocturnal hemodialysis; CHD = conventional hemodialysis; CHD_1 = conventional hemodialysis (baseline); CHD_2 = conventional hemodialysis (end of study); CVS = cardiovascular system; [a] denotes $p < 0.05$ comparing the distribution of causes of hospitalization before and after conversion to NHD; [b] denotes $p < 0.05$ compared with NHD.

Bergman et al (in press)

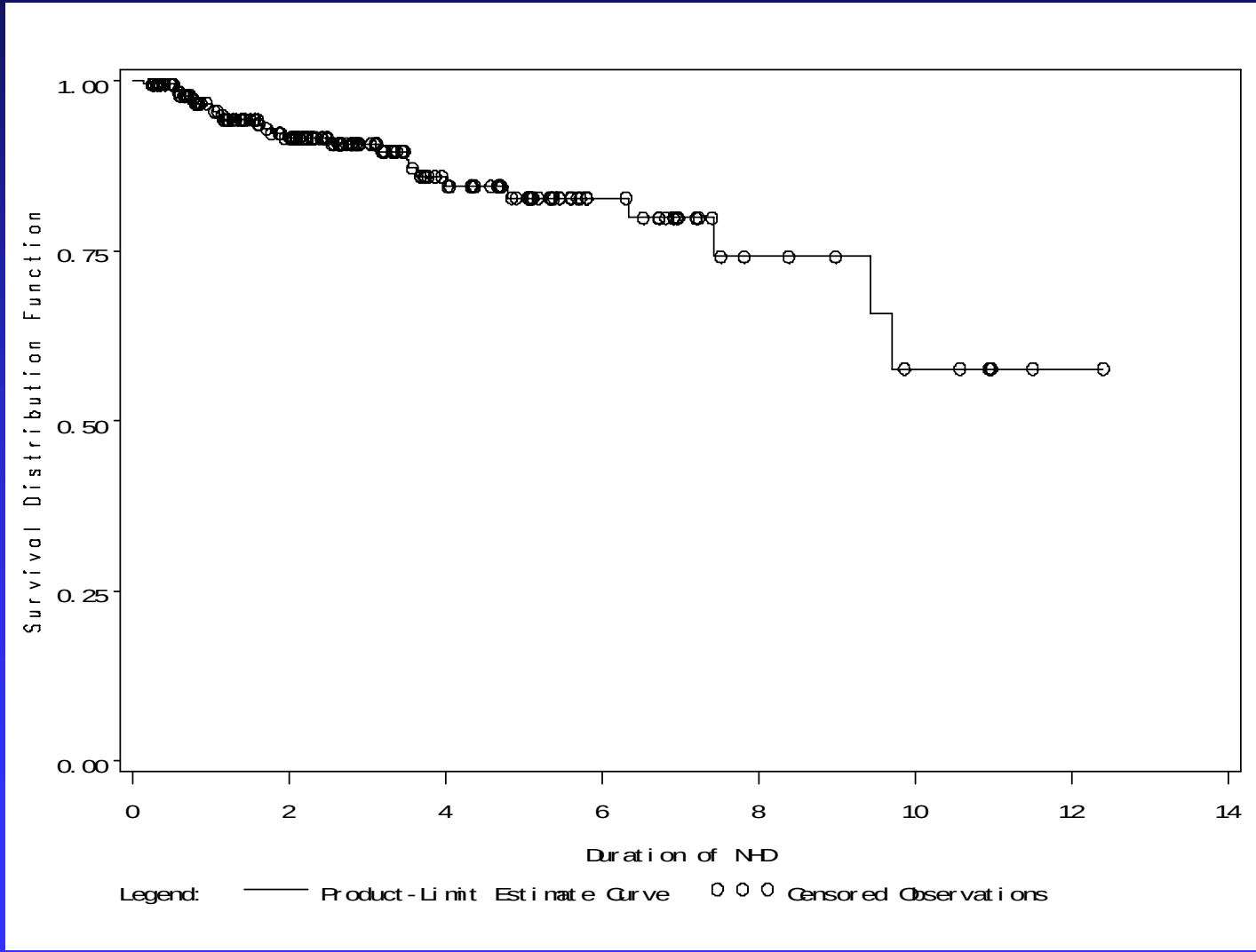
Other Data…

- Bone – DEXA
- Baroreflex
- AV access outcomes
- Genomics

Technique Survival of Toronto NHD patients N = 215, Median F/U = 3.2 yrs



Survival of Toronto NHD patients (n = 215) [F/U = median 3.2 yrs]



Future

- Need for RCT to validate NHD prospectively
  - NIH sponsored FHN study
    - Results (2010)
- Need to better understand patient selection / criteria
- Improvement in technology
  - Era of Information Technology

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