

A patient with Intradialytic HYPERtension

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The case...

- Patient is a 59 yo man with a past medical history of ESKD on HD TTS (DW 90.5 kg), hypertension (HTN), diabetes (DM), peripheral arterial disease, and coronary artery disease with the following dialysis data:

Date	Predialysis Blood Pressure(BP)	Postdialysis Blood Pressure (BP)	Predialysis weight	Postdialysis weight
Tues 2/14/23	134/64	149/73	92.7	90.4
Thurs 2/16/23	139/70	151/79	94.1	90.6
Sat 2/18/23	137/68	152/77	93.8	90.2

Questions to consider.....

- Does this rise in blood pressure predialysis to postdialysis have clinical significance?
 - A. No, only out of the dialysis unit BP measurements have clinical importance
 - B. No, only very low or very high pre- and post- dialysis BPs correlate with adverse clinical outcomes
 - C. Yes, there is data demonstrating intradialytic HTN is associated with an increased risk hospitalization and mortality
 - D. No, these changes in BP are NOT large enough to be considered intradialytic HTN which has been linked to adverse clinical outcomes

More questions....

- What is the best way to manage intradialytic HTN?
 - A. Challenge DW
 - B. Given 0.1mg clonidine prior to dialysis to blunt rise in BP
 - C. Raise DW (since intradialytic HTN is represents an abnormal response to ultrafiltration) and give atenolol 50 mg predialysis
 - D. Lower the dialysate temperature to 35.5°C

Learning Objectives

- Review the definition, epidemiology, and clinical significance of intradialytic hypertension
- Discuss the pathophysiology of intradialytic hypertension
- Describe the management strategies for intradialytic hypertension

What is Intradialytic Hypertension ?

- An abnormal hemodynamic response to ultrafiltration during hemodialysis (HD) characterized by a paradoxical increase in blood pressure during or immediately after HD
- “An SBP rise of > 10mmHg from pre- to post- dialysis for 4 of 6 consecutive HD treatments..”

KDIGO executive conclusions

JE Flythe et al.: BP and volume control in dialysis: a KDIGO conference report

Table 2 | Definitions of intradialytic hypotension and intradialytic hypertension

Guideline definition	Other definitions and notes	Suggested definition
Intradialytic hypertension None	<ul style="list-style-type: none"> • BP rise of any degree during the second or third intradialytic hour • SBP rise > 15 mm Hg within or immediately post-dialysis • SBP rise > 10 mm Hg from pre- to post-dialysis • Rising intradialytic BP that is unresponsive to volume removal 	An SBP rise >10 mm Hg from pre- to post-dialysis in the hypertensive range in at least 4 of 6 consecutive dialysis treatments should prompt a more extensive evaluation of BP and volume management, including home and/or ABPM.

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative; SBP, systolic blood pressure; UF, ultrafiltration.

Flythe et al. *Kidney International* (2020) 97, 861–876
Georgianos et al. *Hypertension*. 2015;66:456-463

Epidemiology: scope of the problem

- Estimated prevalence probably between 5-15% depending upon the definition used and population examined

Table 1. Prevalence of Intradialytic Hypertension Among Hemodialysis Patients

Study ID	Patients	Definition	Prevalence Estimates
Inrig et al ⁵ <i>Kidney Int</i> 2009	438 hemodialysis patients participating in the CLIMB study	Rise in SBP \geq 10 mm Hg from pre to post dialysis	13.2% of patients met the definition of intradialytic hypertension
Inrig et al ³ <i>AJKD</i> 2009	1748 hemodialysis patients participating in the USRDS Dialysis Morbidity and Mortality Wave II study	Rise in SBP >10 mm Hg from pre to post dialysis, averaged from 3 consecutive dialysis sessions	12.2% of patients were classified as intradialytic hypertensives
Van Buren et al ¹¹ <i>Int J Artif Organs</i> 2012	362 hemodialysis patients receiving treatment in the USA	Rise in SBP >10 mm Hg from pre to post dialysis, averaged for the total number of dialysis treatments performed during 6 months of follow-up	22.3% of dialysis treatments were complicated by intradialysis hypertension. Persistent intradialytic hypertension was noted in 8% study participants

CLIMB indicates Critic-Line Intradialytic Monitoring Benefit study; SBP, systolic blood pressure; and USRDS, US Renal Data System.

Clinical Significance of Intradialytic HTN

- Inrig et al Kidney International (2007) 71, 454–461
- Secondary analysis of the CLIMB study- (Crit-Line Intradialytic Monitoring Benefit Study)- randomized controlled trial investigating whether blood volume monitoring reduced hospitalizations
- 443 patients, 6 month follow-up
- increase in SBP >10mmHg preHD to postHD was associated with increased risk for 6 month mortality and non-access related hospitalization
 - **OR 2.17 (95% CI; 1.13-4.15) p=0.012**

Table 3 | Adjusted analysis of 6-month mortality and non-access-related hospitalization among prevalent ESRD subjects^a

Variable	Odds ratio (95% CI)	P-value
SBP fell with HD (Δ SBP ≤ -10 mm Hg)	1.00 (reference)	0.012
SBP unchanged with HD (Δ SBP -10 to 10 mm Hg)	1.85 (1.15–2.98)	
SBP rose with HD (Δ SBP ≥ 10 mm Hg)	2.17 (1.13–4.15)	

Clinical Significance of Intradialytic HTN

- Inrig et al. Am J Kidney Dis. 2009 Nov;54(5):881-90
- Prospective cohort analysis of 1,748 incident HD patients followed for 2 years
- Each 10mmHg increase in BP during HD was associated with a 6% increased risk of mortality
 - HR 1.06 per 10 mm Hg (95% CI, 1.01 to 1.12; P = 0.03)

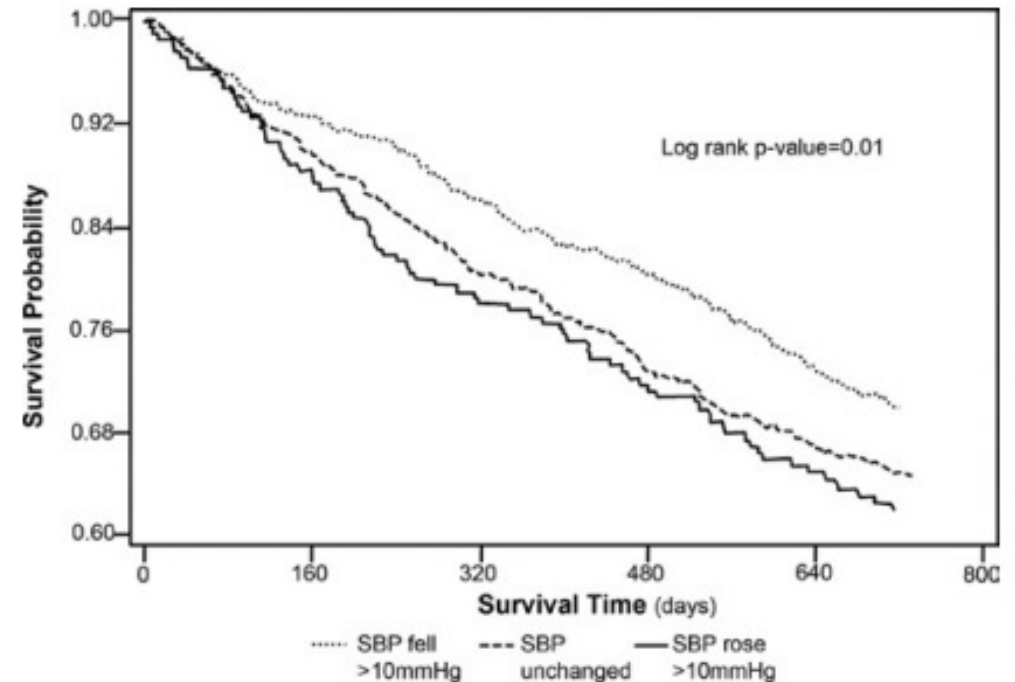
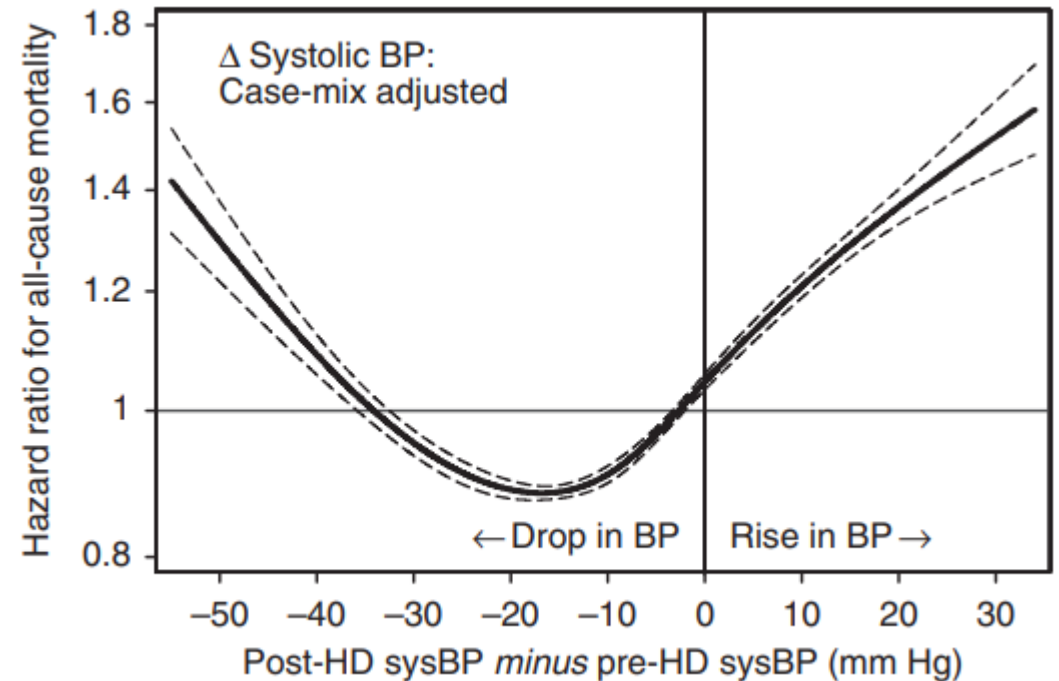


Figure 2. Kaplan-Meier survival curves of time to death over 2 years in a national cohort of incident hemodialysis (HD) patients stratified by changes in systolic blood pressure (SBP) during HD.

Clinical Significance of Intradialytic HTN

- Park et al. *Kidney International* (2013) 84, 795–802
- Retrospective cohort study examining the association of BP changes during dialysis (mean of postHD - preHD BPs) with mortality
- 113,255 HD patients analyzed over 5 years
 - 11,994/113,255 (10.6%) patients with rise in BP >10mmHg preHD to post HD
- U shaped association between BP changes and mortality during dialysis
- In fully adjusted analysis increases in BP preHD to postHD were associated with increased mortality



Pathophysiology

Most important factors hypothesized to contribute to intradialytic HTN:

- Volume overload
- Sympathetic nervous system activation
- Renin angiotensin system activation
- Endothelial dysfunction/ vasoconstriction / arterial stiffness
 - Dysregulation and imbalance between endothelial derived factors that favor vasoconstriction over vasodilation

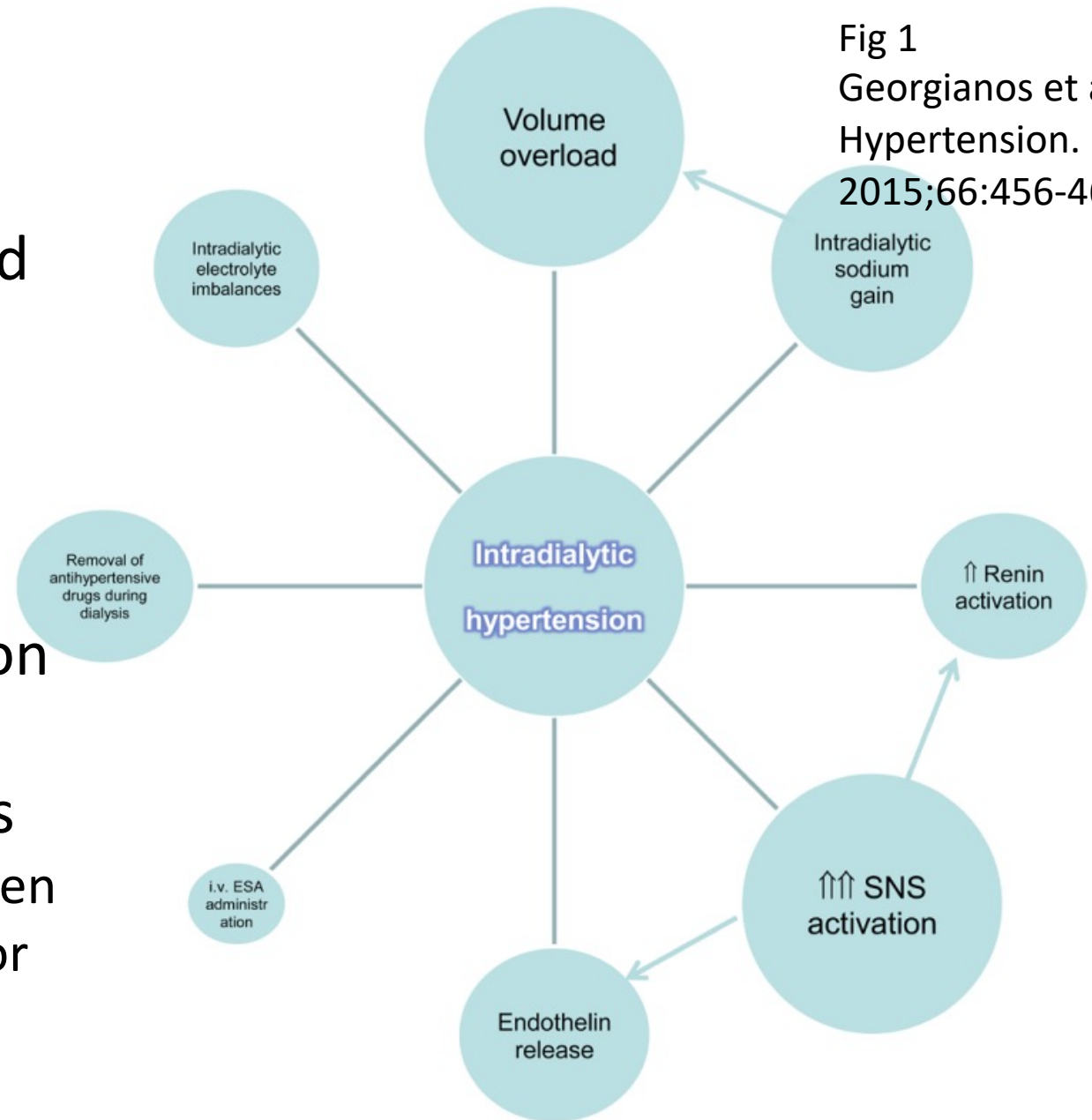


Fig 1
Georgianos et al.
Hypertension.
2015;66:456-463

Georgianos et al. Hypertension. 2015;66:456-463

Van Buren et al & Inrig. Semin Dial. 2017;30:545-552.

Intradialytic hypertension is associated with volume overload

- Nongnuch et al. *Kidney International* (2015) 87, 452–457
- Prospective observational study of 531 HD patients who had volume assessments completed by multiple frequency bioelectrical impedance (BEI)
- Comparisons of patient groups based upon change in SBP preHD to post HD were made
 - “Hypotensive”- more than a 20mmHg decrease(32.2%)
 - “stable” -20 to 10mmHg change(49.7%)
 - “hypertensive”- More than a 10mmHg increase (18.1%)
- Group with rise >10mmHg during dialysis had greater relative extracellular water volume by BEI

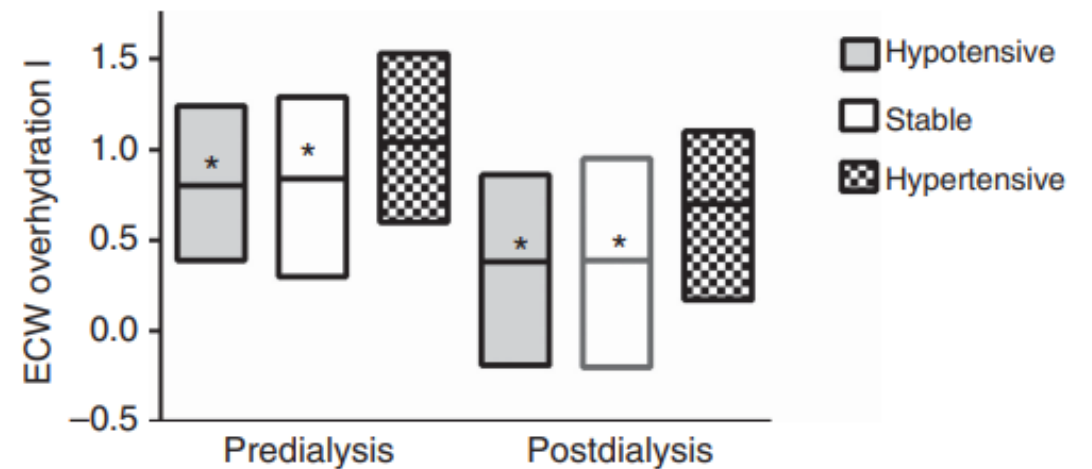


Figure 3 | Predialysis and postdialysis relative extracellular water excess according to groupings. Patients with a fall in systolic blood pressure ≥ 20 mm Hg between predialysis and postdialysis systolic blood pressure recordings (hypotensive), patients with an increase in systolic blood pressure of ≥ 10 mm Hg (hypertensive), and those patients with systolic blood pressure change < 10 mm Hg to $- 19$ mm Hg. Values expressed as median (interquartile range), * $P < 0.05$ vs. hypertensive group.

Endothelial dysfunction is associated with intradialytic hypertension

- Chou et al *Kidney International* (2006) 69, 1833–1838
- Case control study comparing HD 30 patients with intradialytic hypertension to 30 control patients without intradialytic hypertension
- Subjects with intradialytic HTN had higher endothelin-1 levels and lower high nitric oxide/ endothelin-1 ratios compared to controls

Table 4 | Plasma concentrations of nitric oxide (nitrate+nitrite) and endothelin (ET-1) before and after hemodialysis

	Hypertension prone	Control	P-value
<i>Before hemodialysis</i>			
NO (μM)	41.2 \pm 6.1	32.9 \pm 4.5	NS
ET-1 (pg/ml)	345.6 \pm 34.5	287.4 \pm 29.3	NS
NO/ET-1	0.869 \pm 0.502	0.129 \pm 0.013	NS
<i>After hemodialysis</i>			
NO (μM)	7.2 \pm 0.9**	7.9 \pm 0.9**	NS
ET-1 (pg/ml)	510.9 \pm 43.3**	276.7 \pm 30.1	< 0.05
NO/ET-1	0.018 \pm 0.003**	0.034 \pm 0.005**	< 0.05

Abbreviations: NO, nitric oxide; ET-1, endothelin; NS, not significant.

All data are presented as mean \pm s.e.m.

* $P < 0.05$ when compared with values before hemodialysis, ** $P < 0.005$ when compared with values before hemodialysis.

Abnormal sympathetic nervous system function is associated with intradialytic HTN

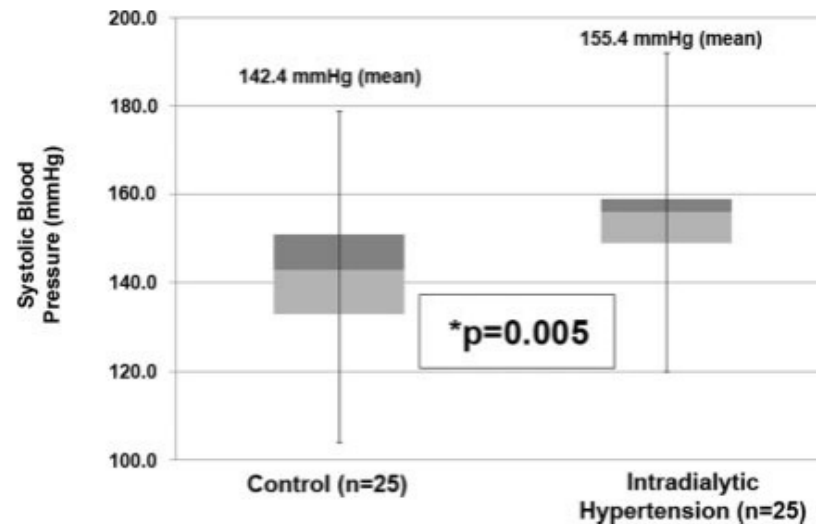
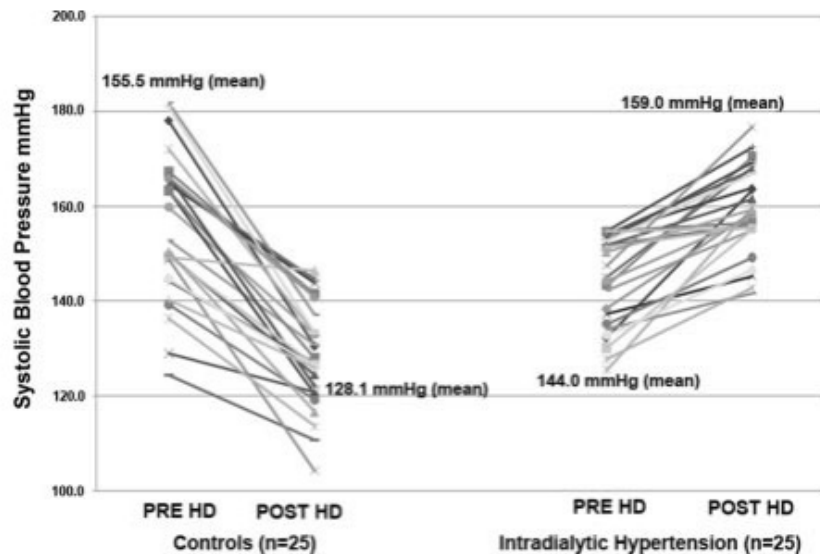
- Rubinger et al PLoS One. 2012;7(5):e36943
- Indirect measures of sympathetic nervous system activity were evaluated in HD patients with intradialytic HTN and HD patients without intradialytic HTN
 - BP variability, interbeat interval variability & baroreceptor sensitivity
- Majority of patients with intradialytic HTN had changes in parameters associated with enhanced sympathetic nervous system activity - suggesting sympathetic nervous system overactivity contributes to intradialytic HTN

Unanswered Questions

- Is the risk observed with intradialytic HTN simply a reflection of the dangers of volume overload, abnormal endothelium/ vasculature, or excessive renin angiotensin/ sympathetic nervous system activation?

Or

- Is it just a marker of overall poor HTN control?
 - Inrig et al. Clin J Am Soc Nephrol 6: 1684 –1691, 2011
 - Case control study comparing ambulatory blood pressures in patients with and without intradialytic HTN
 - Patients with intradialytic HTN had a higher BP burden



Management of intradialytic HTN

- Address underlying pathophysiology
 - Volume overload
 - Challenge the DW
 - Sodium restriction during inter/intradialytic periods
 - Endothelial dysfunction-
 - Carvedilol- improves endothelial dysfunction in vivo and blocks endothelin-1 release in vitro
 - Sympathetic nervous system (SNS) overactivation
 - Beta blockers- carvedilol or atenolol
 - Increase dialysis treatment time – reducing UF rate may reduce SNS activation
 - Renin Angiotensin system activation
 - ACE inhibitors or ARBs

Georgianos et al. Hypertension. 2015;66:456-463

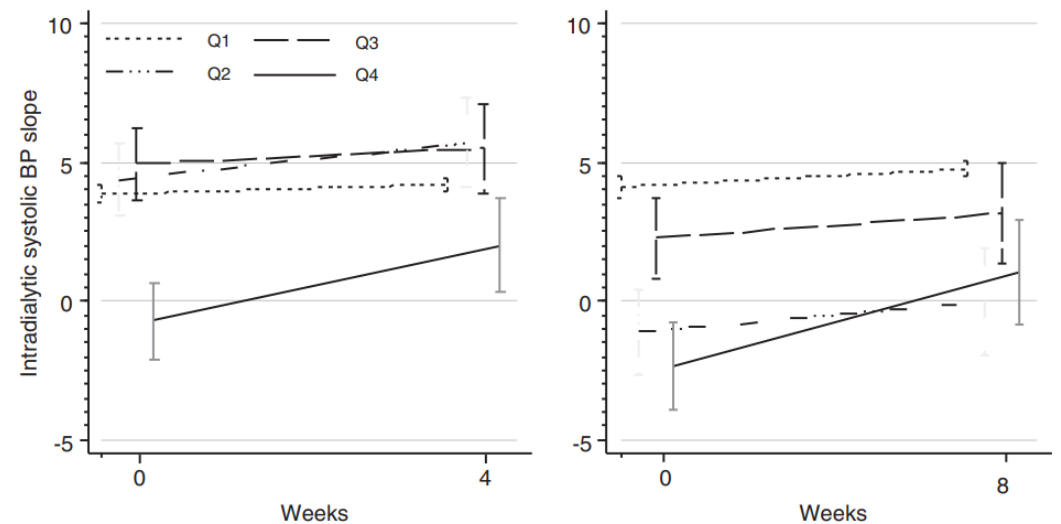
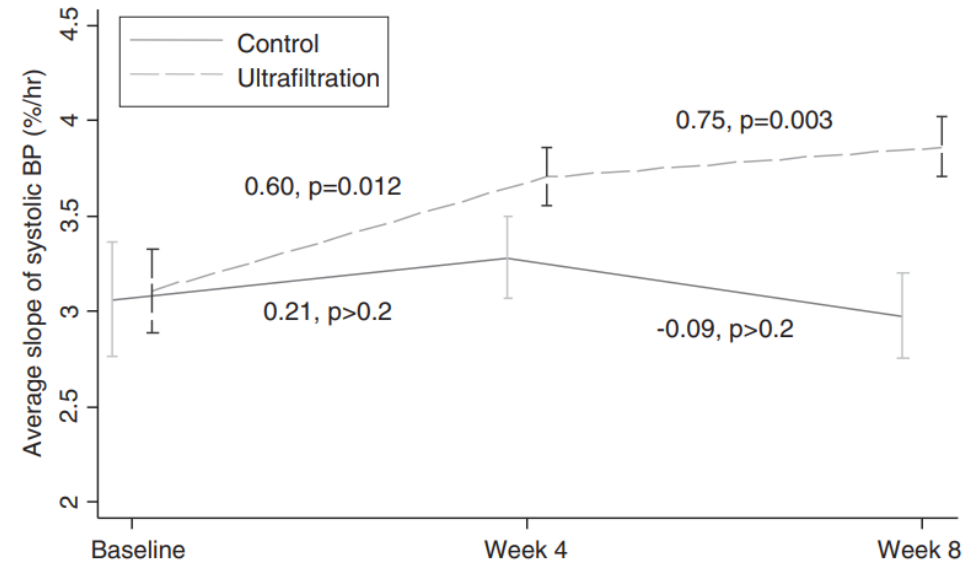
Van Buren & Inrig. Semin Dial. 2017 Nov;30(6):545-552

Intradialytic hypertension management -- address volume overload first

- Small series with intensive UF improved HTN control in patients with intradialytic HTN
 - 7 patients with intradialytic HTN unresponsive to medication had significant decreases in SBP (46 +/- 18)and DBP (22 +/- 9 mm) after mean decrease of 6.7 +/- 3.0 kg weight and became near normotensive without medications (Cirit et al. Nephrol Dial Transplant. 1995;10(8):1417-20)
 - 4 cases of patients without overt volume overload (no edema) on exam who had rises in BP >230/> 130 during HD without response to BP medications- all were treated with intensified ultrafiltration with alternate day HD and isolated ultrafiltration with decrease in DW 5-7kg over 1-2 wks with normalization in BP (Fourtounas. Am J Kidney Dis. 2010;56(2):418)

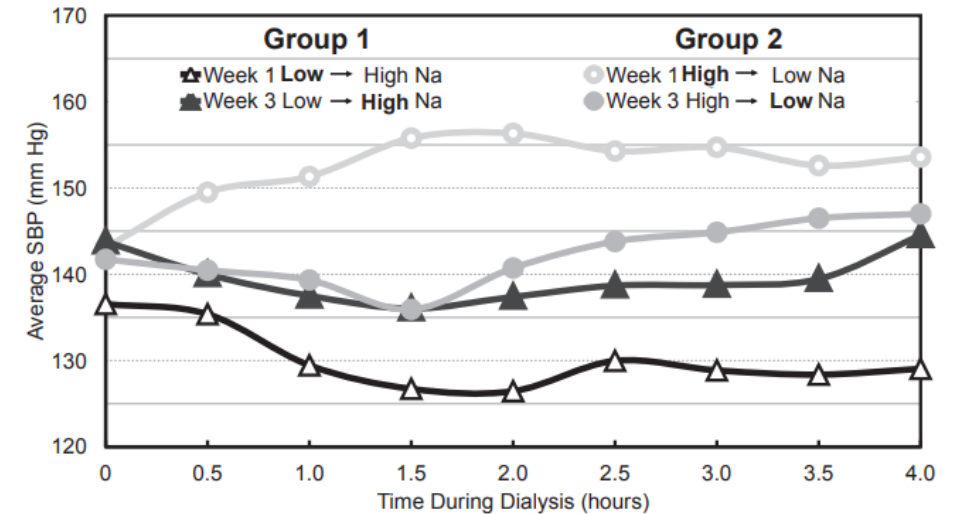
Lowering DW may impact slope of SBP during HD

- Reanalysis of the DRIP study
- Agarwal et al Nephrol Dial Transplant. 2010 Oct;25(10):3355-61
- RCT in 150 HD patients randomized to additional ultrafiltration (intervention) or not (control)
- Examined the association between weight loss and change in BP slope during HD
- Additional ultrafiltration was associated with increase in mean slope of SBP over time
- When quartiles of subjects based on weight loss were compared, highest weight loss group had the largest change in mean SBP slope
 - This group had a “negative” SBP slope at baseline implying they had a rise in BP during dialysis- with more fluid weight loss this slope became “positive” suggesting additional UF is associated with resolution of intradialytic HTN



Lower dialysate sodium may reduce rise in BP during HD in patients with intradialytic HTN

- Inrig Am J Kidney Dis. 2015 Mar;65(3):464-73
- Randomized cross over trial involving 15 HD patients with intradialytic HTN examining the effect of low sodium dialysate (serum Na -5mEq/L, no lower than 134mEq/L) compared to high serum sodium dialysate (serum Na +5mEq/L)
- Group 1 : low Na x 1 wk → washout x1 wk → high Na x 1wk
- Group 2: high Na x1 wk → washout x 1 wk → low Na x 1 wk
- Average change in systolic BP during HD was less in the low versus high sodium dialysate
 - - 6.1 mmHg [95% CI, 29.0 to 23.2] P < 0.001



- Average SBP during dialysis was lower within each Group when treated with the lower sodium dialysate compared to when treated with the higher sodium dialysate

Address endothelial dysfunction and sympathetic overactivity: carvedilol

- Inrig et, al Clin J Am Soc Nephrol 7: 1300–1309, 2012.
- Prospective 12 week pilot study in 25 HD patients with intradialytic HTN started on carvedilol
- Carvedilol blocks endothelin-1 release in vitro and improves endothelial function assessed by flow mediated vasodilation

Table 3. BP measurements before and after 8 weeks of maximally tolerated carvedilol among 25 participants with intradialytic hypertension

	Baseline (n=25)	Study End (n=25)	Mean Change from Baseline to Study end	P Value
2-wk frequency of intradialytic hypertension (%)	77% (4.6 of 6 sessions)	28% (1.7 of 6 sessions)	49% (2.9 of 6 sessions)	<0.001
2-wk average BP (mmHg) ^a				
predialysis systolic	144.0 (±9.7)	146.1 (±14.4)	2.2 (±16.9)	0.5
postdialysis systolic	159.0 (±9.3)	142.4 (±12.7)	-16.7 (±16.7)	<0.001
Δ systolic (postdialysis–predialysis)	+15.0 (±9.1)	-3.8 (±16.1)	-18.8 (±16.5)	<0.001
Ambulatory BP (mmHg) systolic (44-hr)	155.4 (±14.2)	147.7 (±16.2)	-7.5 (±16.8)	0.04

Summary

- Intradialytic HTN is a fairly common abnormal hemodynamic response during hemodialysis characterized by >10mmHg increase in SBP predialysis to postdialysis occurring in at least 4 of 6 consecutive HD treatments
- Intradialytic HTN is associated with an increased mortality risk
- Significant factors thought to contribute to intradialytic HTN include: Volume overload, endothelial dysfunction, & excess sympathetic nervous system/ renin angiotensin system stimulation
- Management should mainly focus on addressing volume overload, limited data to support use of agents that might improve endothelial function and modulate sympathetic nervous system (carvedilol)

The case...

- Patient is a 59 yo man with a past medical history of ESKD on HD TTS (DW 90.5 kg), HTN, diabetes, PAD, and CAD with the following dialysis data:

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Back to our case.

- Does this rise in blood pressure predialysis to postdialysis have clinical significance?
 - A. No, only out of the dialysis unit BP measurements have clinical importance
 - B. No, only very low or very high pre- and post- dialysis BPs correlate with adverse clinical outcomes
 - C. Yes, there is data demonstrating intradialytic HTN is associated with an increased risk for hospitalization and mortality
 - D. No, these changes in BP are NOT large enough to be considered intradialytic HTN which has been linked to adverse clinical outcomes

More questions....

- What is the best way to manage intradialytic HTN?
 - A. Challenge DW
 - B. Give 0.1 mg clonidine prior to dialysis to blunt rise in BP
 - C. Raise DW (since intradialytic HTN is represents an abnormal response to ultrafiltration) and give atenolol 50 mg pre-dialysis
 - D. Lower the dialysate temperature to 35.5°C

Thank you!

- Questions or comments?