Hemodialysis Induced Hypotension

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Association of Mortality with Various Definitions of Intradialytic Hypotension Flythe et al JASN 26:724, 2015

- Analyzed data from nearly 12,000 patients
- Emphasized the association of dialysis related hypotension and mortality
- Focuses on the definition with the highest predictive value
- For patients with pre-dialysis systolic BPs of 160 or less, an absolute nadir systolic BP of < 90 was the best predictor of mortality
- For patients with systolic BP >160, a nadir systolic BP of <100 was the best predictor

The Problem of Dialysis-Related Hypotension

Sands et al Hemodialysis International 2014 18:415-22

- Intradialytic hypotension (IH) was studied in 13 facilities, 44,801 treatments in 1137 patients using careful BP monitoring during each dialysis (iBox)
- IH was defined as >30 mmHg decrease in systolic BP to <90 mmHg.
- <u>IH was frequent (17.2% of treatments</u>) and highly variable by patient (0-100% of treatments)
- <u>75% of patients had IH and 16.2% had IH on >35% of treatments</u>
- Increased IH frequency was associated with age, diabetes, longer duration of ESRD, <u>higher ultrafiltration volume</u>, lower pre-HD systolic BP, and <u>higher dialysate temperature</u>.
- Patients with >35% IH treatments had <u>poorer survival</u> (P = 0.036), and <u>more frequent and longer hospitalization</u> (P = 0.04, P = 0.002, respectively) than patients without IH.

Intradialytic Hypotension
the problem

- Intradialytic hypotensions reflects the patient's inability to tolerate, from a BP standpoint, hemodialysis-associated ultrafiltration.
- There is an imbalance between central hypovolemia and the adequacy of reflex-mediated hemodynamic responses (impaired baroreceptor response to reductions in blood volume).
- There is an impairment in the body's defenses against hypovolemia, which include increasing vascular resistance in splanchnic and cutaneous beds, with shunting of blood to the central circulation, and increasing heart rate and contractility.
- Decreased venous return is likely the most important factor that impairs the body's ability to maintain cardiac output and BP with reduction in central volume.

Impaired Baro-Reflex Sensitivity (BRS)

Cheterton LJ et al Hemodial Int 2010: 14:18-28

- Impaired resting BRS and recognition of a suboptimal peripheral pressor response to ultrafiltration appear to predict those hemodialysis patients most likely to undergo hemodynamic instability.
- But, in those patients prone to intradialytic hypotension and with impaired resting BRS, <u>percentage reduction in cardiac output</u> at the end of HD highly correlated with <u>reduction in relative blood volume</u> (r=0.94, P=0.006).

The Problem with Dialysis-Related Hypotension

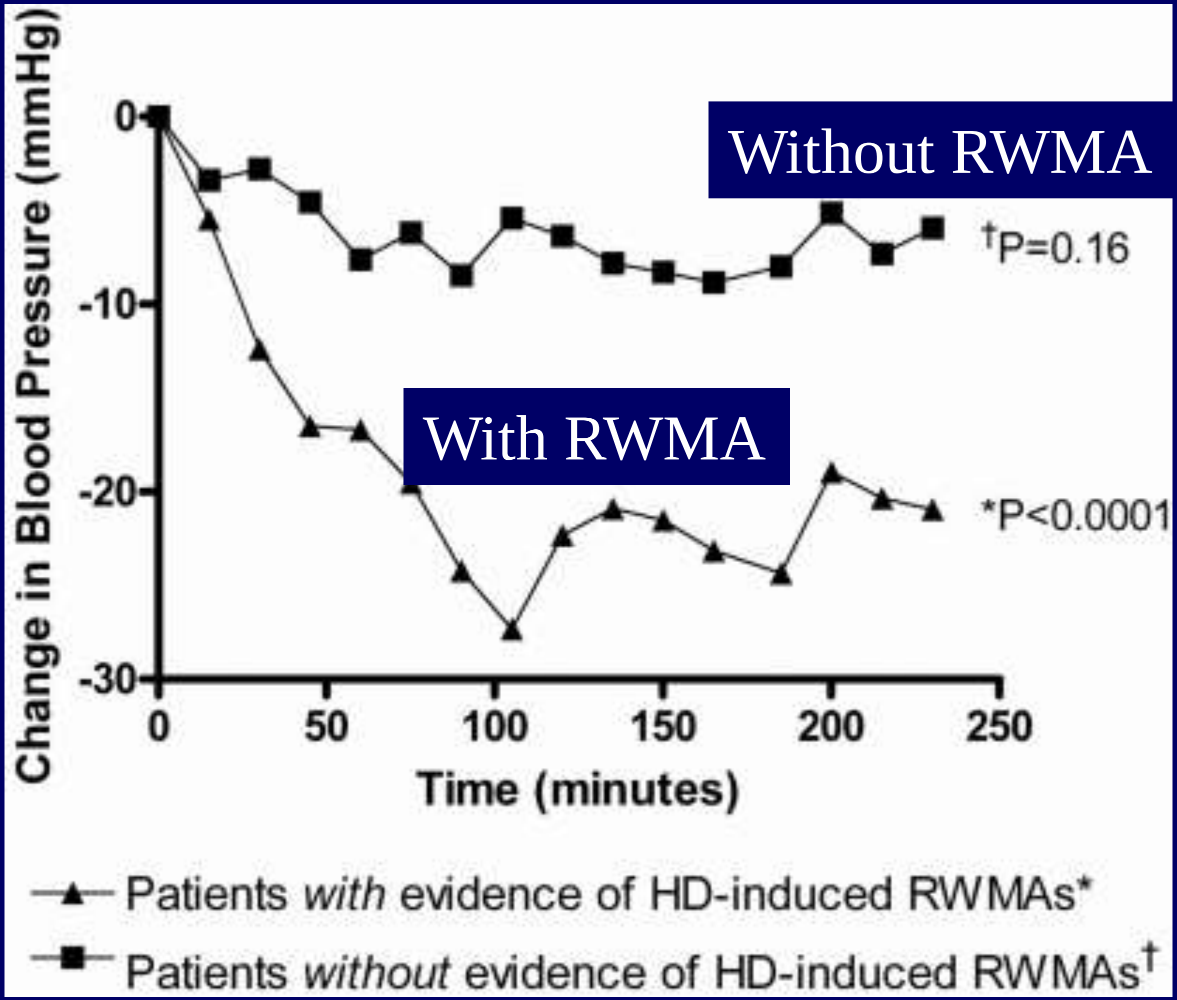
- The HD procedure itself triggers significant circulatory stress.
- This stress leads to two problems:
  a) it limits ultrafiltration capacity, because of hypotension, contributing to volume overload
  b) it leads to perfusion abnormalities in vulnerable vascular beds
- Recent attention has focused attention on the impact of dialysis related hypotension on the heart *(myocardial stunning)*, the brain *(white matter changes)*, and the GI tract *(transbowel migration of endotoxin)*

McIntyre et al: Hemodialysis-induced cardiac dysfunction is associated with an acute reduction in global and segmental myocardial blood flow. *CJASN 2008 3:19-26*

- Four prevalent hemodialysis patients <u>withou</u>t angiographically significant coronary artery disease had measurements of myocardial blood flow (MBF) using positron emission tomography during standard hemodialysis.
- Concurrent echocardiography was used to assess left ventricular function and the development of regional wall motion abnormalities (RWMAs).
- <u>Global MBF was acutely reduced during hemodialysis</u>
- <u>Multiple RWMA developed</u>
- <u>Segmental MBF was reduced to a significantly greater extent in areas that developed RWMAs compared with those that did not.</u>

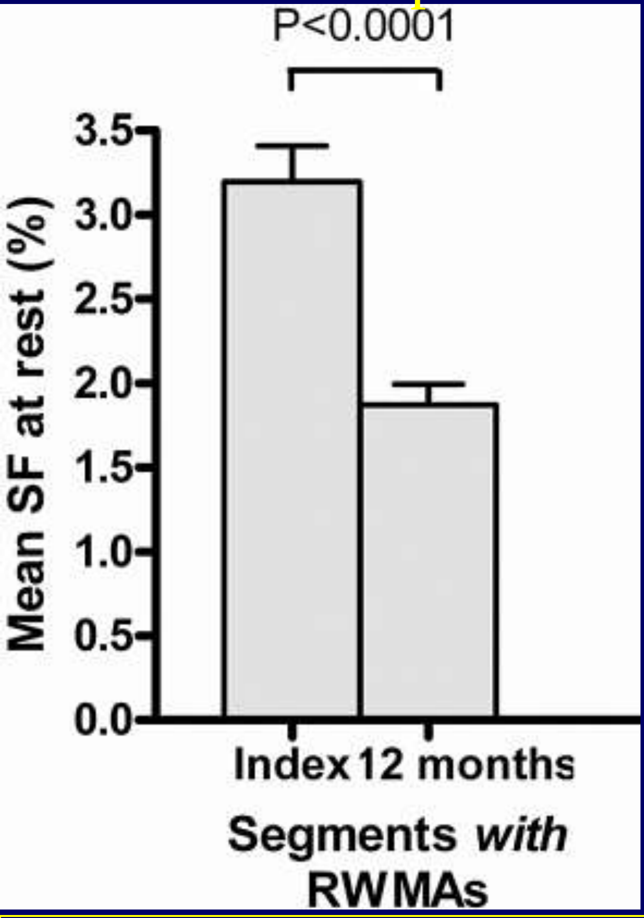
Thus, hemodialysis is associated with hemodynamic instability, acute cardiac ischemia, and the development of regional wall motion abnormalities (RWMAs) – even in patients <u>without</u> angiographically documented coronary artery disease.

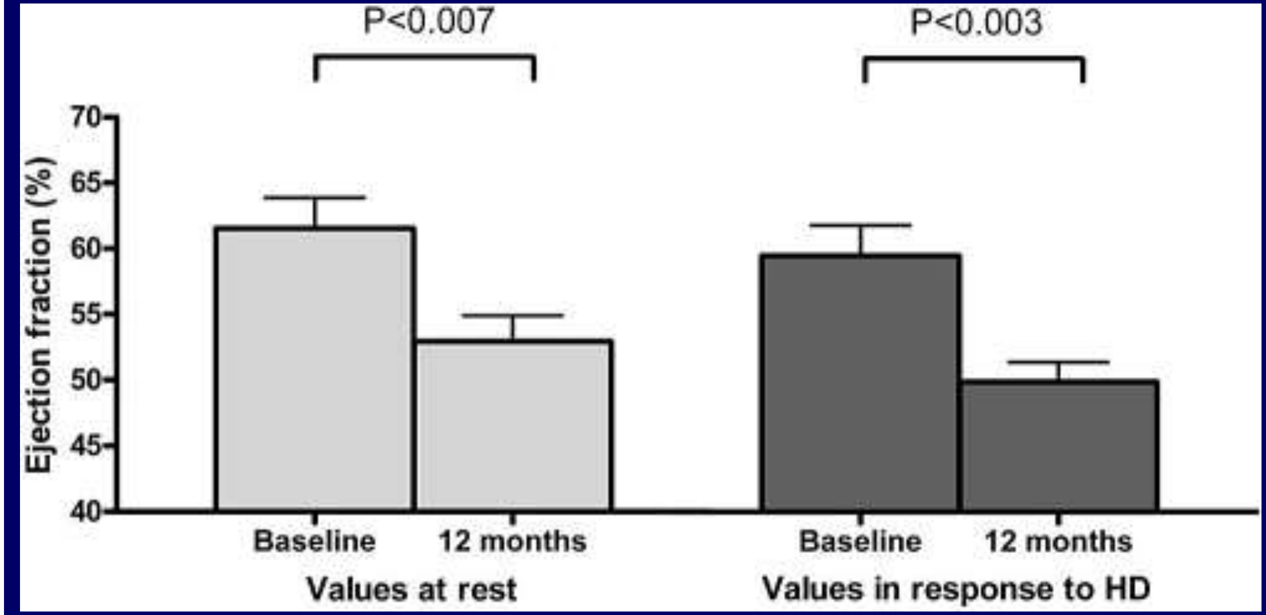
Blood pressure reduction during HD is associated with RWMA Burton et al: CJASN 2009 4:914-20



70 patients studied; 64% (45/70) had significant RWMAs during HD

RWMA and impairment in cardiac function Burton CJASN 2009 4:1925-31:





Change in regional SF (shortening fraction– measure of systolic function) over time; a significant reduction in SF over 12 mo in those segments that developed RWMAs at baseline (index)

Change in ejection fraction at rest and during HD over 12 m in patients with fixed reductions in segmental function of >60%. The development of fixed segmental reduction in previously stunned myocardial segments was associated with a significant reduction in LV EF at rest and during HD. Patients with no such change had no change in ejection fraction

What About Other Organs?

- GI tract: dialysis related hypotension results in increases in increases in endotoxin levels secondary to bowel ischemia
- CNS: dialysis hypotension results in alterations in cerebral blood flow, which may contribute to declines in cognitive functioning

Circulating Endotoxemia Is Associated With Dialysis Related Hypotension *McIntyre et al. CJASN 2011 6:133*

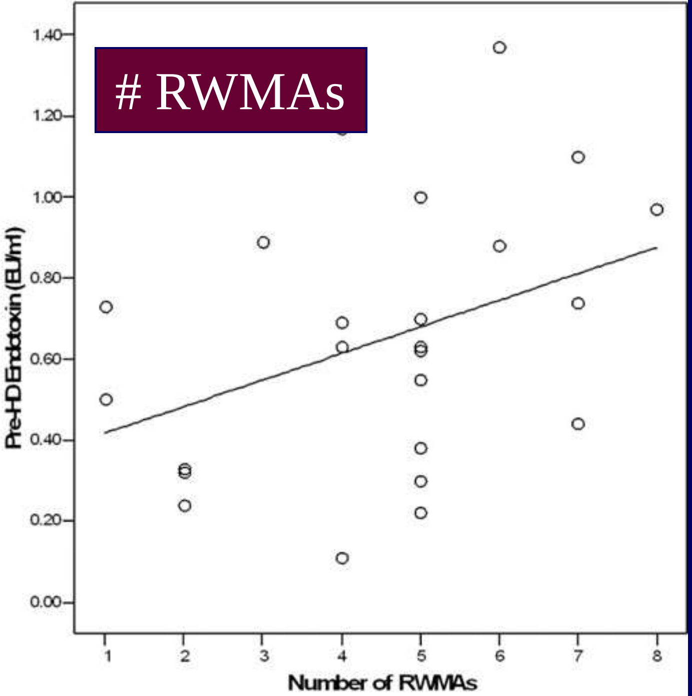
- HD initiation was associated with a significant increase in circulating endotoxin level, rising from 0.13 ± 0.3 EU/ml to 0.34 ± 0.42 EU/ml ($P = 0.002$).
- <u>Circulating endotoxin levels showed a statistically significant correlation with myocardial stunning severity ($r = 0.44$, $P = 0.035$) and maximum reduction in SBP and DBP during HD ($r = 0.45$, $P = 0.032$).</u>
- *Forty-one of 66 of established HD patients studied exhibited significant levels of dialysis-induced myocardial stunning*.

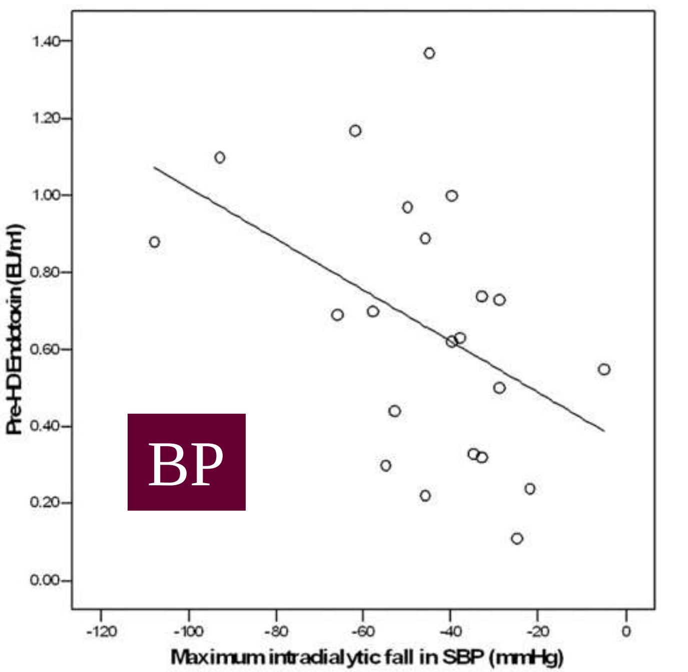
McIntyre et al. CJASN 2011 6:133

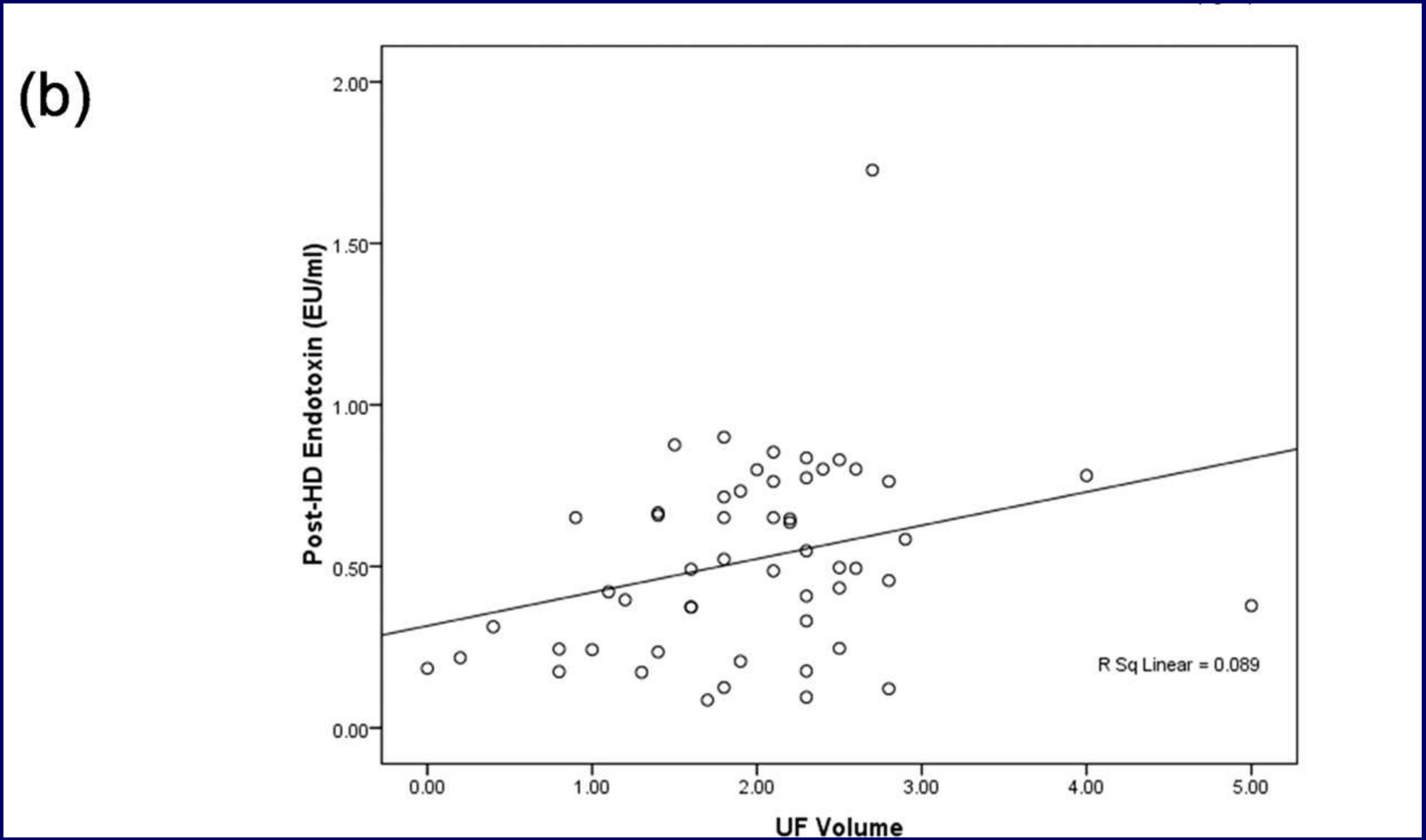
In HD patients with intradialytic hypotension, **endotoxin levels** were significantly correlated with :

(a) the number of myocardial stunned segments

(b) intradialytic hypotension



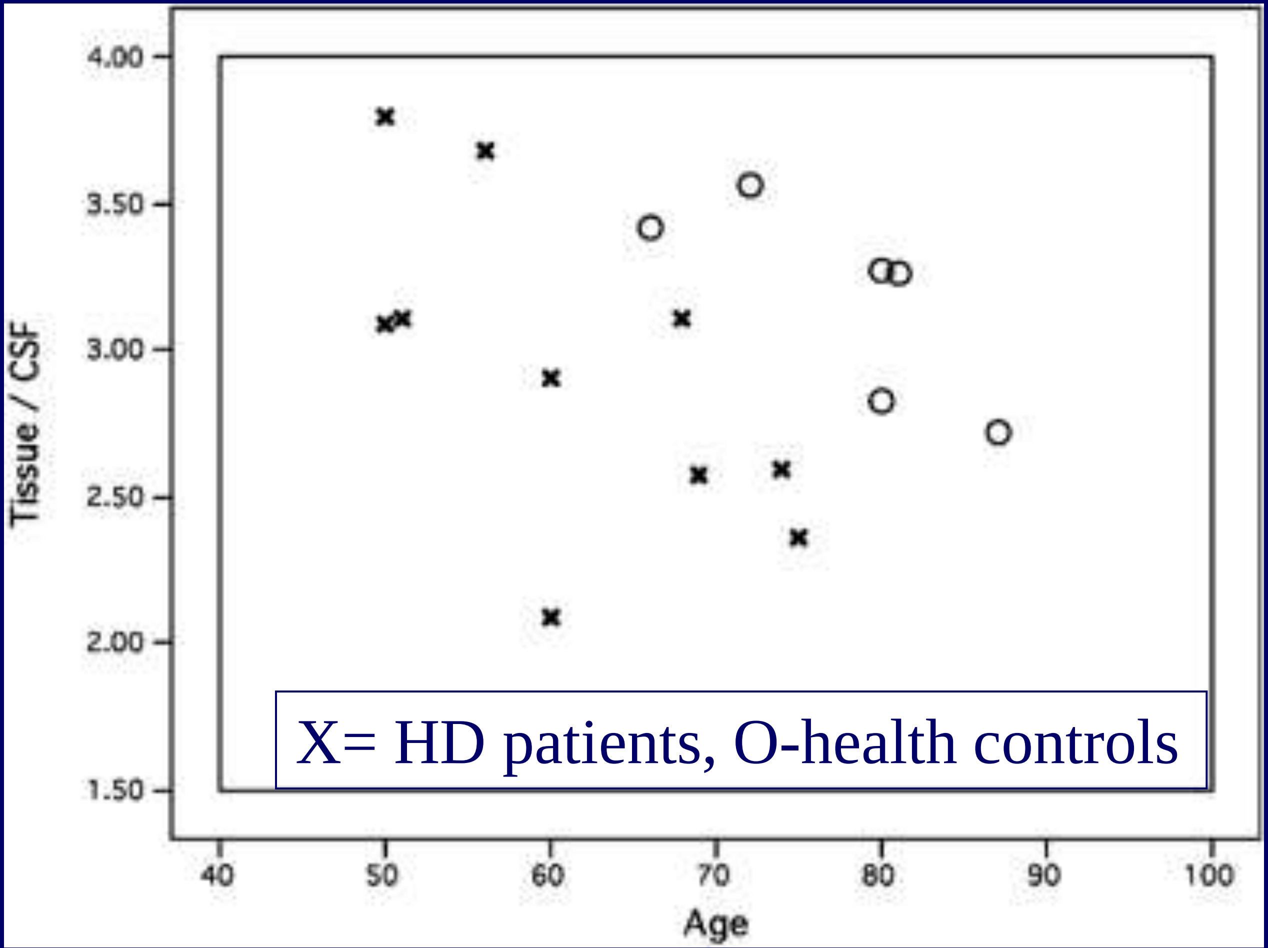




In HD patients <u>with intradialytic hypotension</u>, postdialysis endotoxin levels were significantly correlated with ultrafiltration volume, which in turn related to hypotension.

Cerebrovascular effects of hemodialysis in chronic kidney disease. Prohovnik I J Cerebral Blood Flow Metab 27:1861, 2007

End-stage renal disease patients on HD showed significant cerebral atrophy, associated with longer hemodialysis duration



Ratio of parenchymal volume (GM+WM) to CSF volume, against age, in ESRD patients, (mean age 61) (x) and healthy controls (mean age 78) (empty circles). The ESRD patients show significantly lower brain volume, suggesting atrophy equivalent to 10 to 20 years of normal aging.

The impact of hemodialysis on cognitive dysfunction in patients with end-stage renal disease: a resting-state functional MRI study (Chen HJ et al Metab Brain Dise 2015, epublished July 7)

- Conclusion: HD has an adverse effect on cerebral blood flow and cognitive function in ESRD patients.
- Used resting-state functional MR imaging (rs-fMRI) with regional homogeneity and cognitive function testing in 58 HD patients, 26 non-HD ESRD patients, and 32 healthy controls
- Compared with both controls amd non-HD ESRD patients, HD patients showed decreased regional homogneity in various brain areas (bilateral precuneus, posterior cingulate cortex, inferior parietal lobe, right postcentral gyrus, bilateral superior temporal gyri, right supramarginal gyrus and right angular gyrus).
- Reduced regional homogeneity correlated with neuropsychological tests and dialysis duration.

Brain Imaging in Hemodialysis Patients

(Eldehni, Odudu, McIntyre JASN 26:957, 2015

- Brain imaging *(increased fractional anisotropy and reduced radial diffusivity)* detected by molecular MRI) was used as measure of CNS injury
- Patients on hemodialysis exhibited a pattern of ischemic brain injury *(increased fractional anisotropy and reduced radial diffusivity).*
- Radiologic changes in brain white matter were associated with hemodynamic instability

Euvolemia in hemodialysis patients: a potentially dangerous goal?

Huang SH, et al Semin Dial. 2015 28:1-5

- Aggressive fluid removal can result in circulatory stress and multi-organ injury
- Aggressive fluid removal increases the risk of dialysis-induced hypotension
- This hypotension in turn results in significant organ injury

Can we control or minimize dialysis related hypotension??

Strategies to Reduce Hypotension

- Dietary Education
- Reduction in ultrafiltration rate (more frequent or longer dialysis sessions)
- Low dialysate temperature
- Sequential U/F and isovolemic dialysis
- Sympathetic stimulation: midodrine
- Avoiding food during dialysis
- Ultrafiltration profiling with blood volume monitors or bioimpedance monitoring
- Sodium profiling: *(abandoned)*
- Oncotic agents: albumin
- Use of bicarbonate buffers (vs acetate): *standard of care*
- Sertraline *(SSRIs)*

Dietary Education

- The easiest and simplest way to avoid dialysis induced hypotension is to limit interdialytic weight gain
- <u>An intensive dietary education program should be the cornerstone of all efforts to reduce dialysis related hypotension</u>

Dietary Counseling:
Newer Approaches: Motivational Interviewing

- Recognition that modifying or changing behavior is a challenge
- Learn techniques that enhance an individual's motivation to change with a focus on motivational interviewing (MI)
- MI uses reflective listening to seek to understand the person's frame of reference.
- MI elicits and selectively reinforces the patient's own self motivational statements and expressions of problems and explores his/her intention to and ability to change

Sympathetic Stimulation

- Midodrine: an α_1-receptor agonist and exerts its actions via activation of the alpha-adrenergic receptors of the arteriolar and venous vasculature, producing an increase in vascular tone and elevation of blood pressure.
- *But what is the impact of these drugs on the heart, brain, and GI tract?*

Lowering Dialysate Temperature

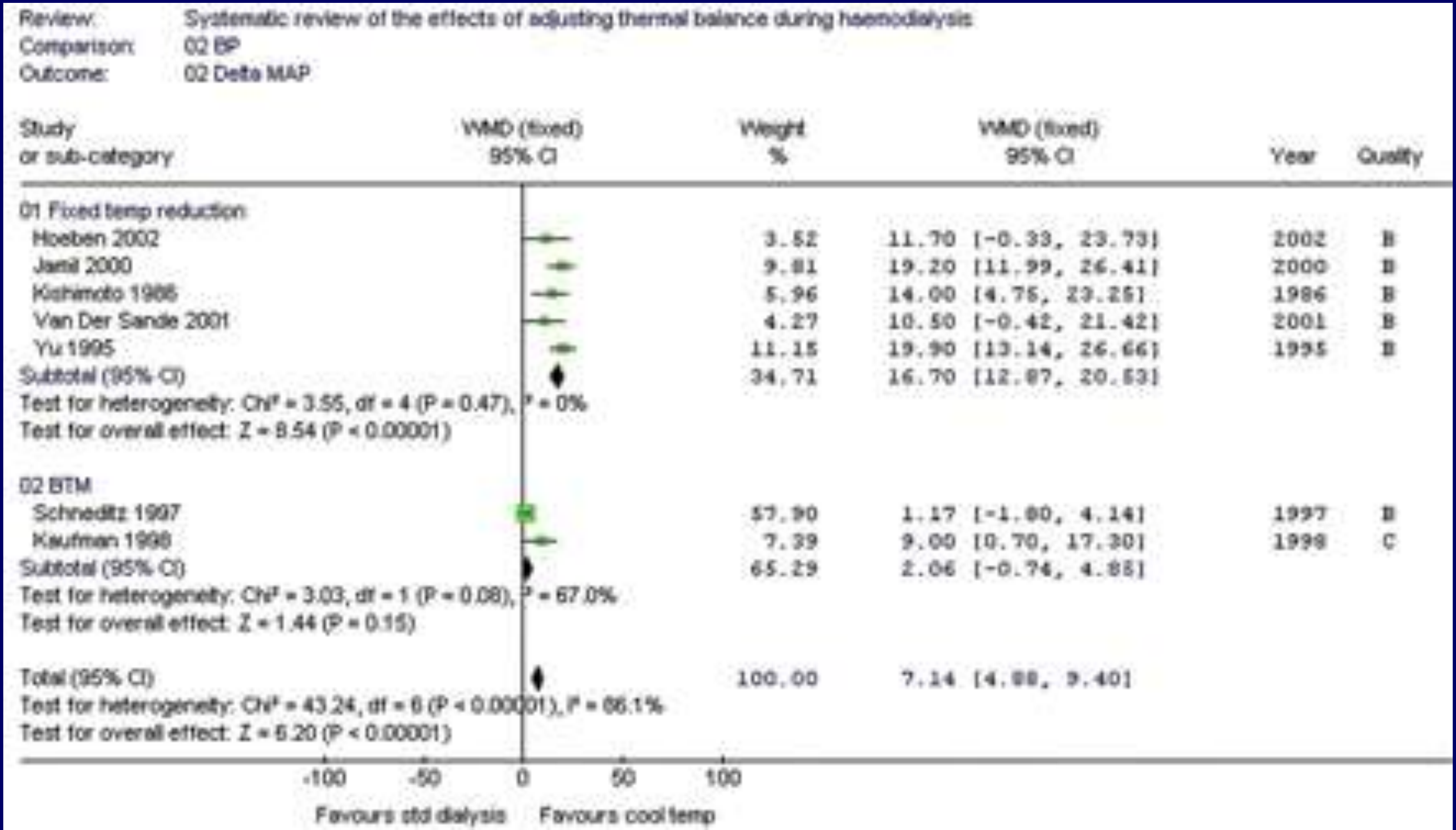
- Core body temperature increases during the course of a hemodialysis treatment because of peripheral vasoconstriction.
- After core temperature rises to a critical level, peripheral vasodilation occurs. This results in heat dissipation, but at the expense of a decrease in peripheral vascular resistance and a fall in BP.

Systematic Review Of Cool Dialysate

Selby et al NDT 21:1993, 2006

- Cooled dialysate: 34-35.7 centrigrade compared to standard dialysate temperature of 37 or higher
- A systematic review based on 22 studies in 408 pts) showed that IDH was 7.1 (95% confidence interval 5.3 to 8.9) times more frequent with standard dialysate temperatures than cool dialysis and that mean arterial pressure was 11.3 mmHg (95% CI, 7.7 to 15.0 mmHg) higher with cool dialysate .
- Side effects, primarily an unpleasant cold feeling, were 2.0 (95% CI, 0.4 to 3.6) times more frequent with cool dialysate.

Pooled results for post-dialysis MAP. Results are shown as weighted mean differences between control and intervention groups—start dialysis MAP was equal in both arms in all studies.



Cardiac Protection with Cooling of Dialysate Odudue et al CJASN 5/11/15

- Randomized trial of dialysate cooling in 73 incident HD patients
- Patients randomized to 37^0 temperature vs 0.5^0 below body temperature x 12 months
- Various cardiac parameters examined

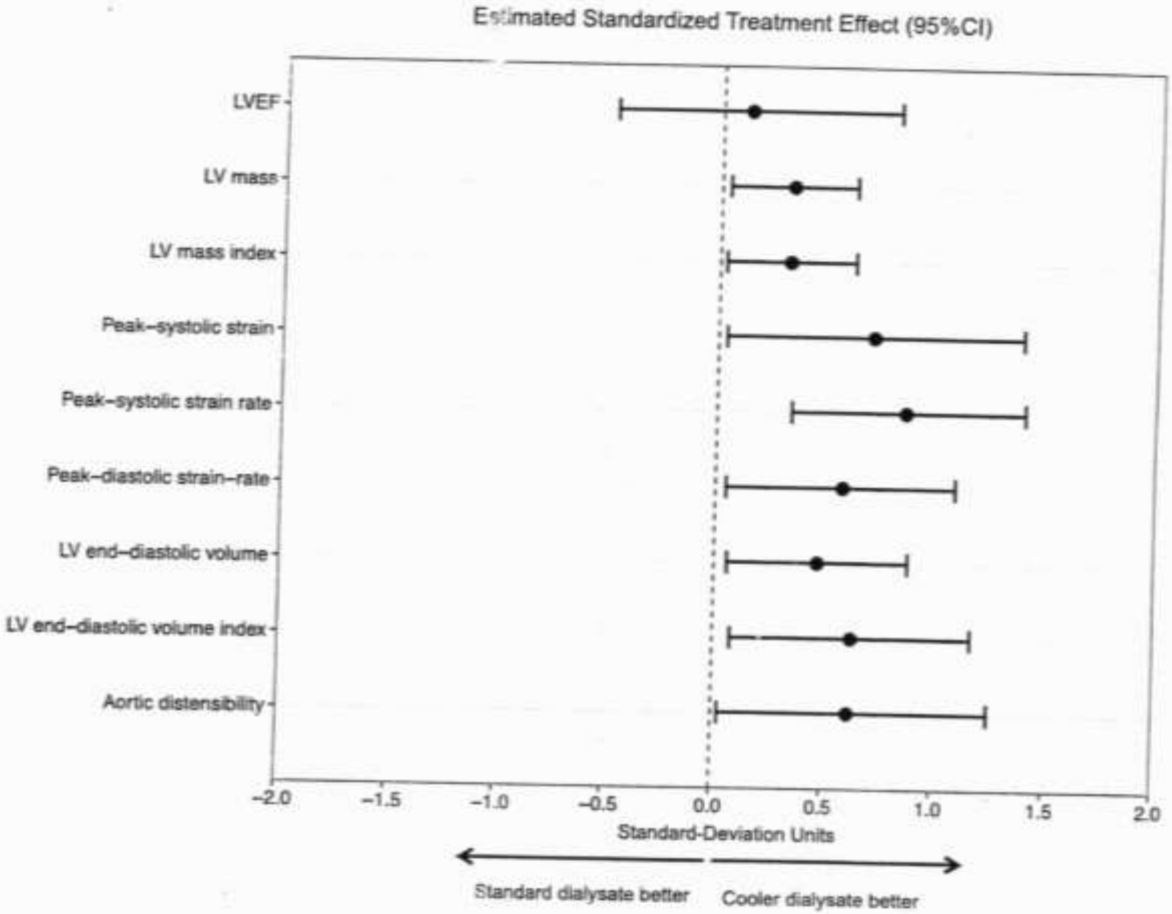


Figure 3. | Trial outcomes expressed as standardized effect sizes with 95% confidence intervals. The mean changes from Table 2 are divided by the pooled SD of the variable at baseline. LV, left ventricular; LVEF, left ventricular ejection fraction.

Randomized Trial of Dialysate Cooling and Effects on Brain White Matter Eldehni, Odudu, McIntyre JASN 26:957, 2015

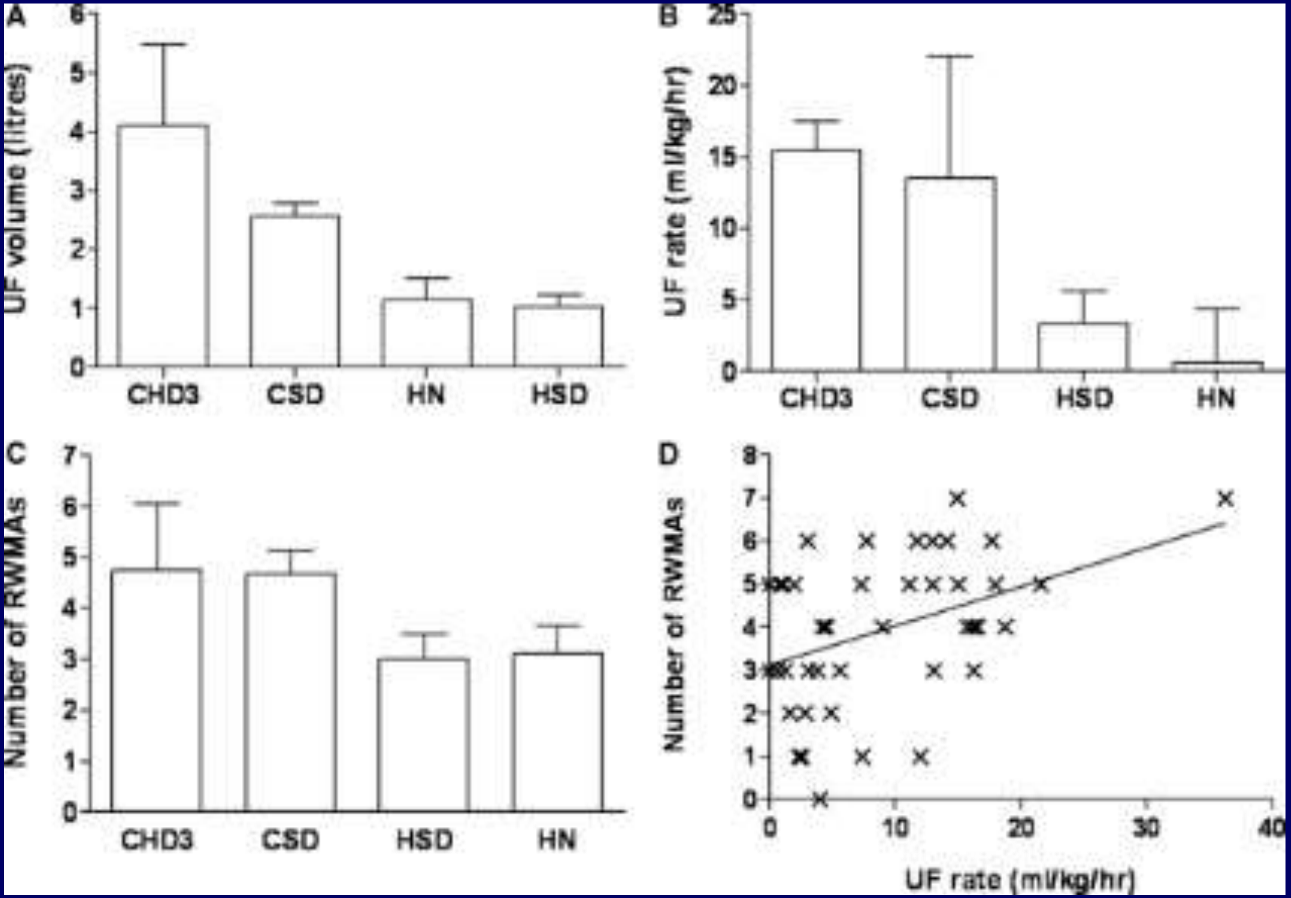
- 73 incident HD patients randomized to dialysate temperatures of 37 or 0.5 below core body temperature for 1 year
- Brain imaging (increased fractional anisotropy and reduced radial diffusivity detected by molecular MRI) was used as measure of CNS injury
- Cooled dialysate improved hemodynamic tolerability
- Changes in brain white matter were associated with hemodynamic instability
- Patients who dialyzed at 0.5°C below core body temperature exhibited complete protection against white matter changes at 1 year.
- Radiologic changes in brain correlated with hemodynamic instability which correlated with the reduced dialysate temperature

More Frequent or Longer Dialysis Time

- Lowers the ultrafiltration rate
- Decreases incidence of hypotension
- Positive effects on cardiac function
  (FHN and Alberta trials of more frequent HD showed improved cardiac size when assessed by MRI)

Jefferies et al: CJASN 2011 6:1326-32

CHD3=center 3x/wk
CSD=center 5-6x/wk
HN: home nocturnal 5-6x/wk
HSD: home day 5-6x/wk



Ultrafiltration characteristics and regional wall motion abnormalities. (A) Mean ± SD UF volume, by dialysis modality. CHD3 *versus* CSD, $P = 0.003$; CHD3 *versus* HSD, HN, $P < 0.001$; CSD *versus* HN, $P = 0.001$. (B) Mean ± SD UF rate, by dialysis modality. CHD3 *versus* HSD, HN, $P < 0.001$; CSD *versus* HN, $P < 0.001$; HSD *versus* HN, $P = 0.043$. (C) Mean ± SD number of peak stress RWMAs, by dialysis modality. CHD3 *versus* HSD, $P = 0.008$; CHD3 *versus* HN, $P = 0.019$; CSD *versus* HN, $P = 0.037$. (D) Correlation between number of peak stress RWMAs and UF rate. $r = 0.41$, $P = 0.005$.

Longer treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality (DOPPS)

Saran et al Kidney Int 2006 69:1222-8.

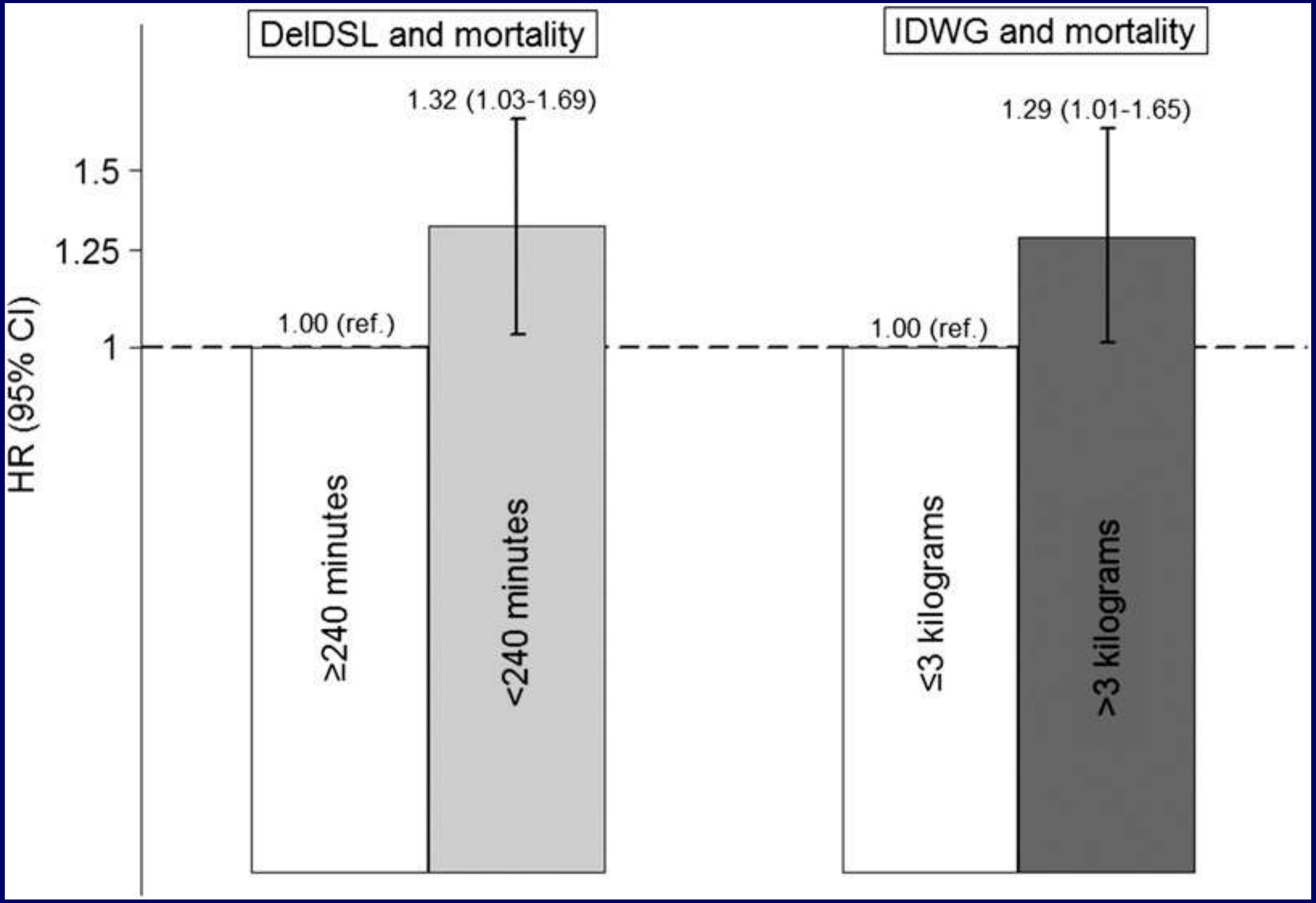
All Cause Mortality

	UFR>10 ml/hr/kg		**Treatment Time>240 min**	
	RR	***P*-value**	**RR**	***P*-value**
Adjusted	1.09	0.02	0.81	0.0005

There was no significant trend in mortality risk with lower categories of UFR.
UFR>10 ml/h/kg was significantly associated with 30% higher odds of IDH

Independent Impact of Treatment Time and Ultrafiltration Rate (Flythe et al CJASN 2013 8:1151-61)

National Cohort of 14,643 patients



DelDSL=treatment time

Blood volume monitoring

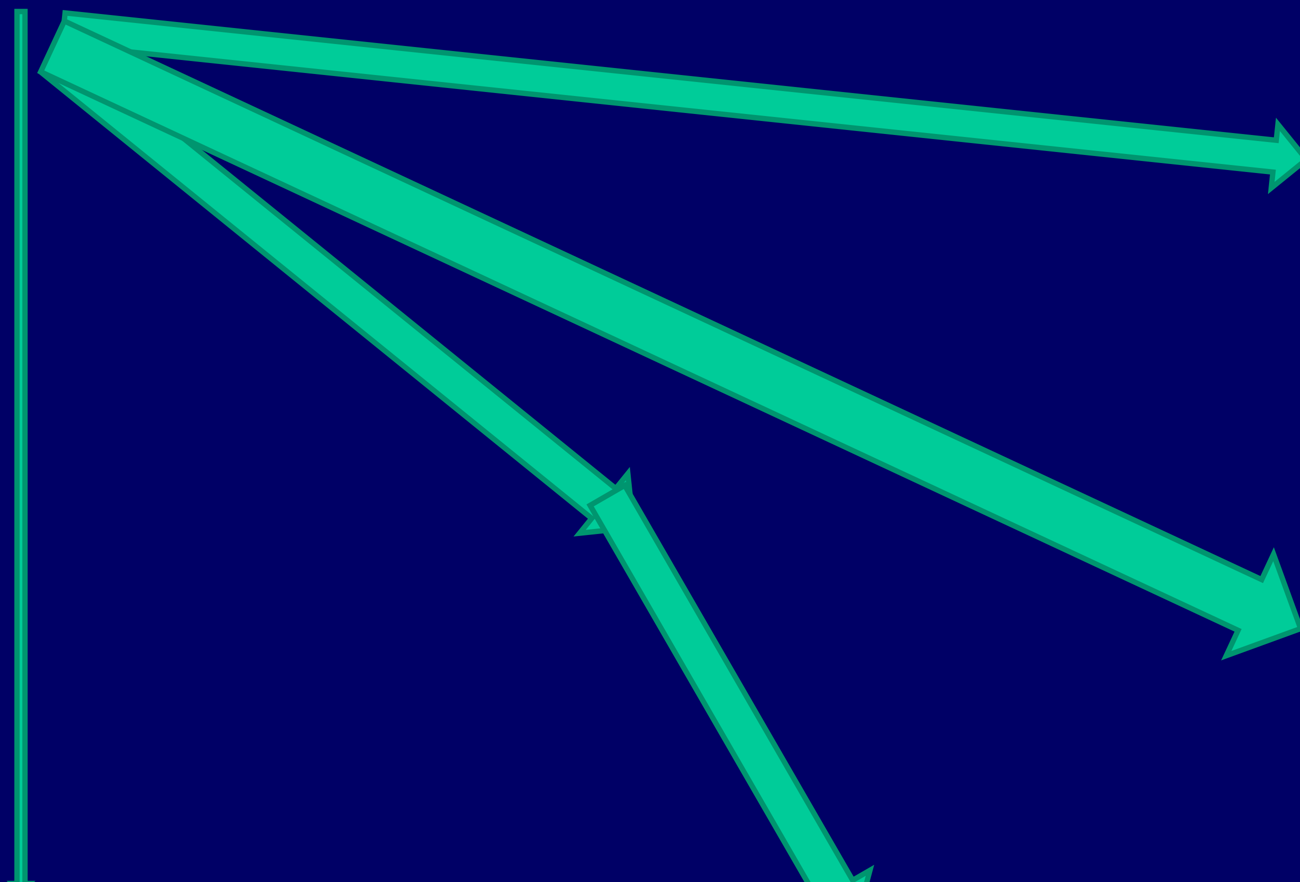
- Crit Line
- Bioimpedance: whole body and/or calf

Crit Line

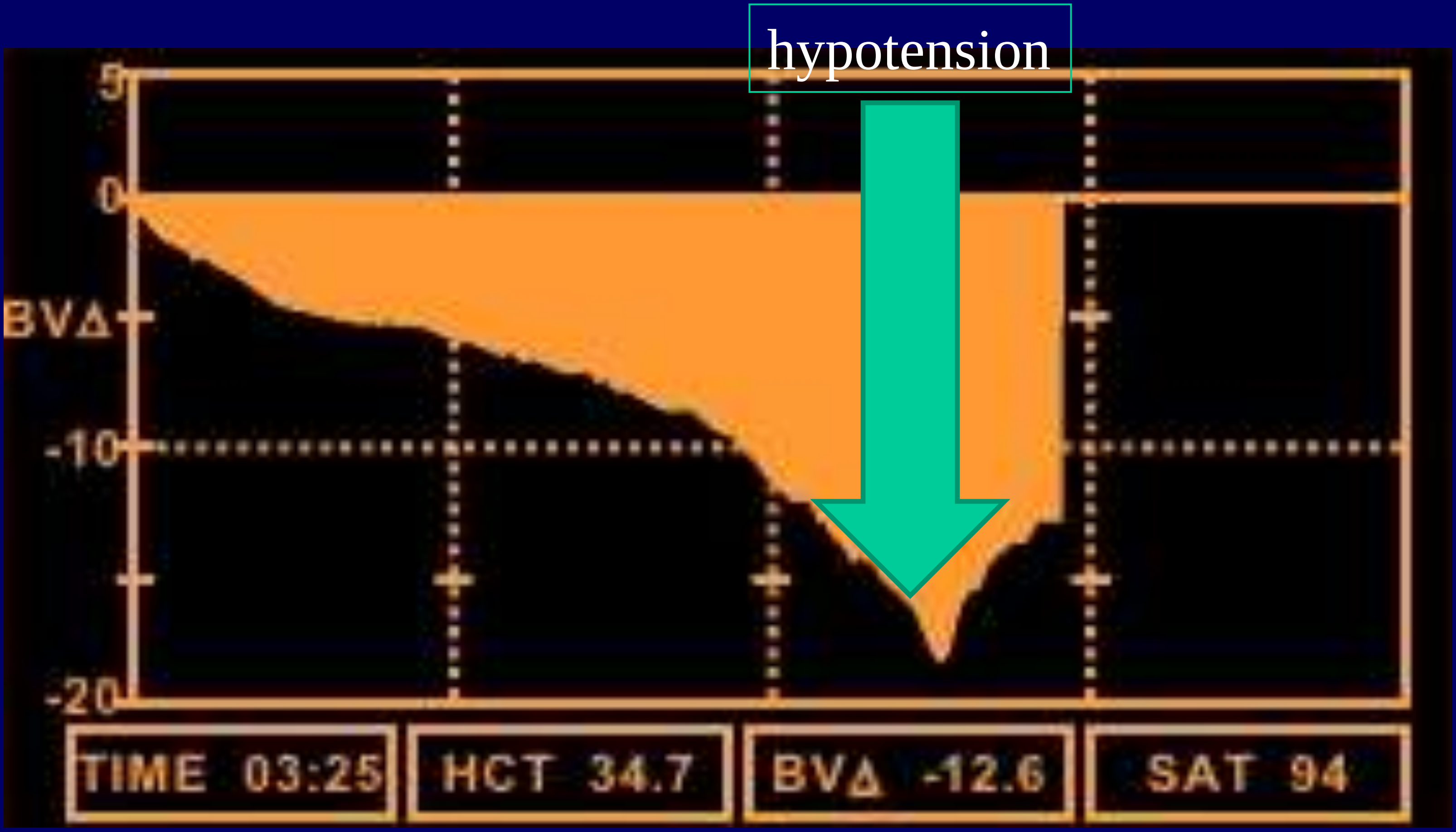
Balter et al: Blood Purification 2015 39:21-4

- The Crit-Line graphically displays and records the hematocrit and the percent blood volume change (which is derived from the hematocrit)
- The hematocrit is measured by an optical sensor
- The rate of change in the Hct– a marker of change in blood volume -- theoretically could predict hypotensive episodes

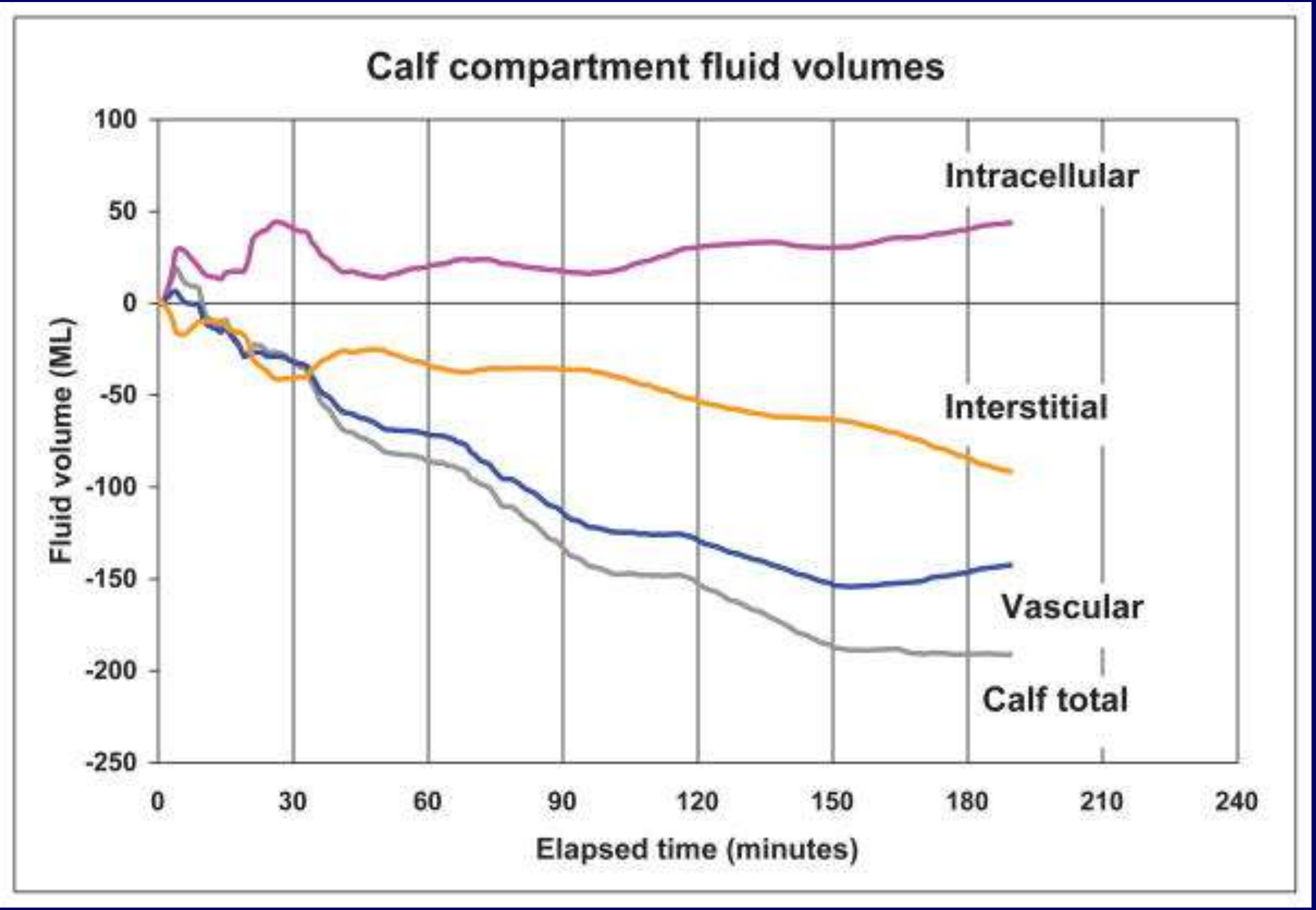
Crit Line



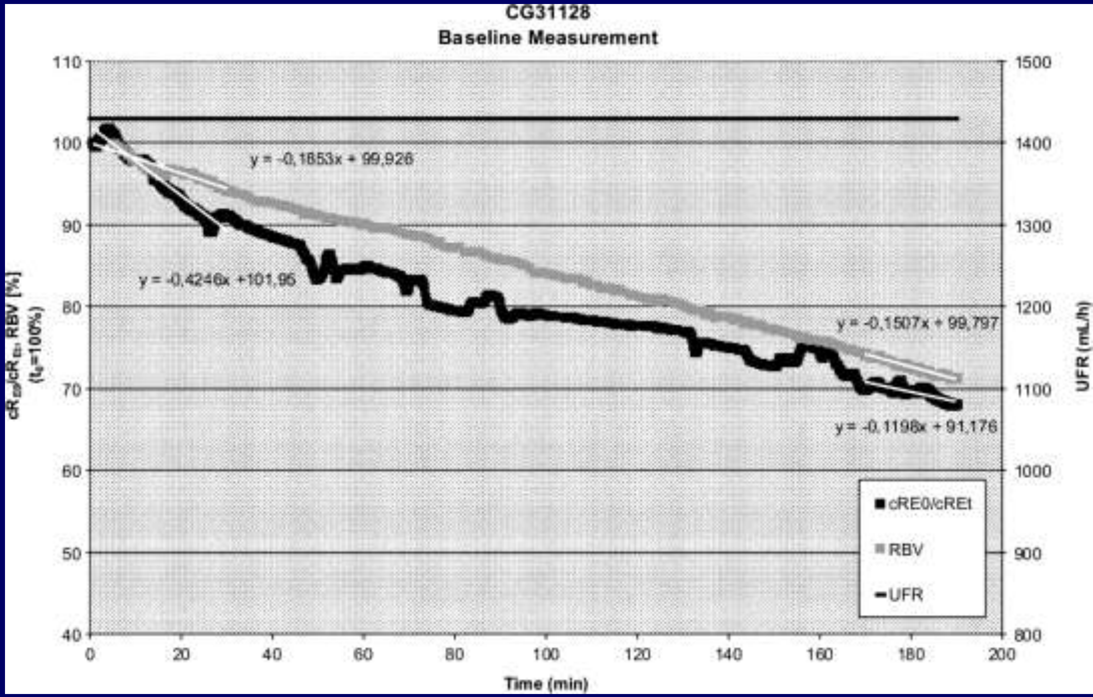
Crit Line Anticipating Hypotension

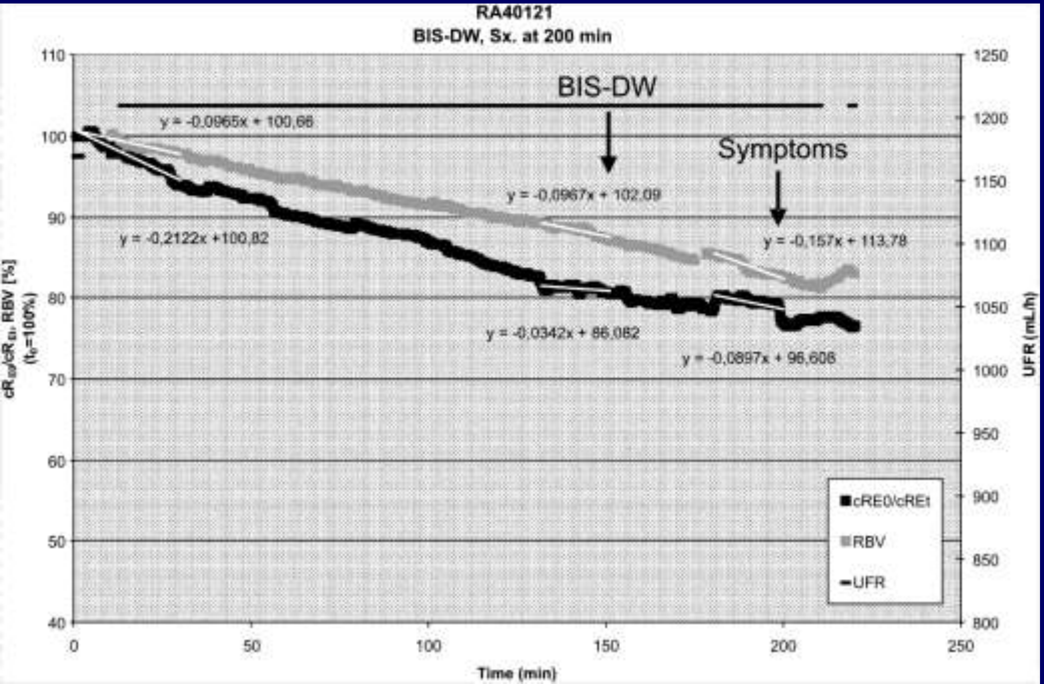


Montgomery et al Bioimpedance assessments of calf fluid compartments during HD Med Biol Eng Comput. 2013 51:1167-75



Zhu F et al Physiol Meas
2008 29:S503-16





Black line: *calf resistivity measured by Xitron bioimpedance*
Gray line: *blood volume based on ultrasound-velocity measurements.*

Attainment of DW is defined by flattening of the change in the resistance curve during dialysis so that at DW little further change is observed

Conclusion

- Dialysis related hypotension is a common problem
- It is related to mortality and hospitalization rates
- It contributes to end organ damage (heart, brain, GI tract, inflammation)
- There are various strategies that can be employed to decrease the risk of hypotension during dialysis

Conclusion:

the best strategies to reducing its incidence include

- Reduce interdialytic weight gains: dietary instructions and patient counseling
- Reduce dialysate temperature
- Reduce ultrafiltration rate by prolonging dialysis time or more frequent dialysis
- Blood volume monitoring?
- Sympathetic stimulation?