U.O. di Nefrologia, Dialisi ed Ipertensione

Policlinico S.Orsola-Malpighi

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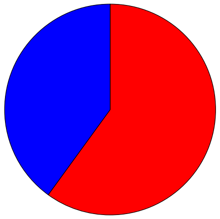
Bologna - ITALY

Do advances in hemodialysis technology (e.g.the use of biofeedback, blood volume and clearance monitoring) offer better outcomes ?

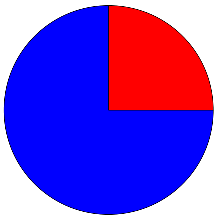
Pro : Antonio Santoro M.D.

Dialysis related complications in Conventional HD



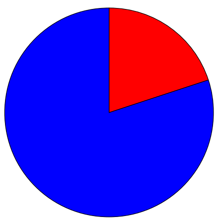
Hypertension

- Mittal SK, Clin Nephrol,1999, 51 (2), 77-82
- Chazot C et al, ND &T, 1995, 10, 831-837



Hypotension

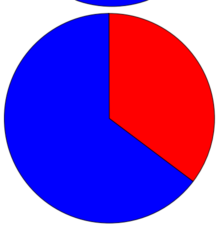
- De Santo G et al, AJKD, 2001, 38 (4) S1, S38-S46.
- Agarwal et al, AJKD, 2008, 51, (2), 242-254



Vascular access failure

(Probability of vascular access failure within one year)

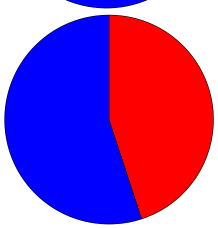
- Reyner HC et al, Kidney Int, 2003, 63 , 323–330



Cardiac arrhythmias

Narula AS, Ren Fail. 2000

Abe S Am Heart J. 1996



Micro.macro inflammation

- Stenvinkel P, Kidney Int., Vol. 62 (2002), 1791–1798

1.1

Hospitalization

(Rate per patient-year)

- Rayner HC et al, ND & T (2004) 19: 108–120.
- O'Brien T, AJKD, 2008, 51 (1), S1, S137-154

Intra-dialytic Hypotension may….

- **Interfere with the delivery of adequate dialysis**
- **Induce or aggravate hypoperfusion in different districts**:
  - cerebral
  - mesenteric
  - cardiovascular
- **Influence the patient outcome**

Hemodynamic instability and outcome

The effect of frequent or occasional dialysis-associated hypotension on survival of patients on maintenance hemodialysis

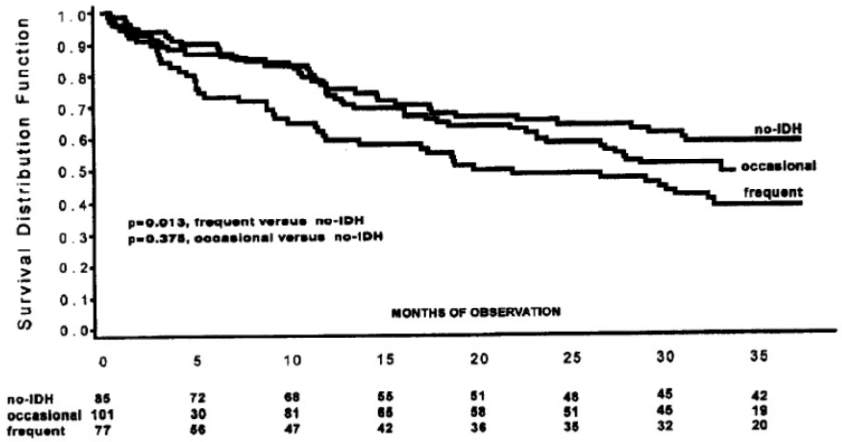
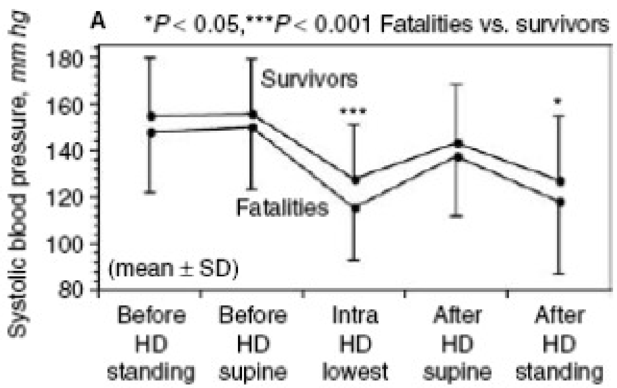
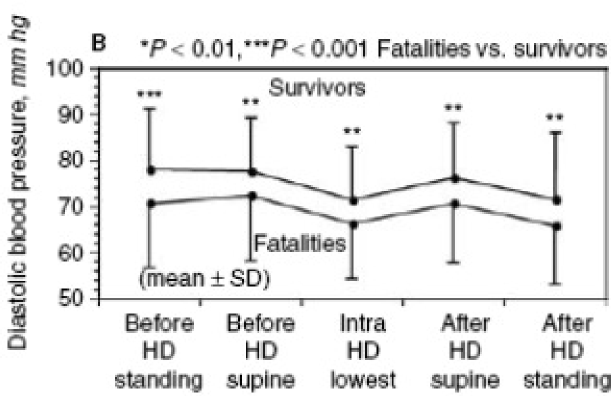


Fig. 1. Kaplan–Meier survival curves of patients with frequent, occasional and no IDH.

Tisler A, NDT 2003





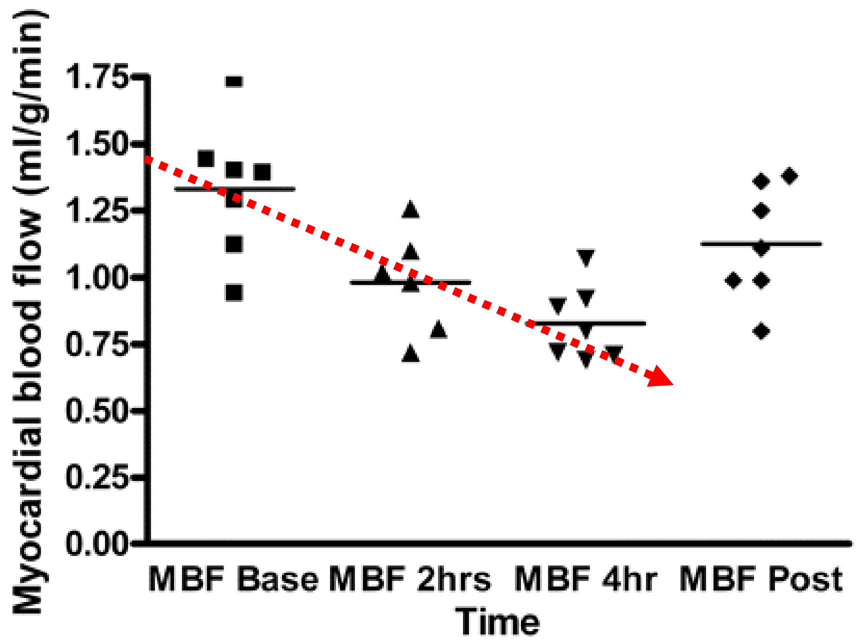
Hemodialysis-associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients

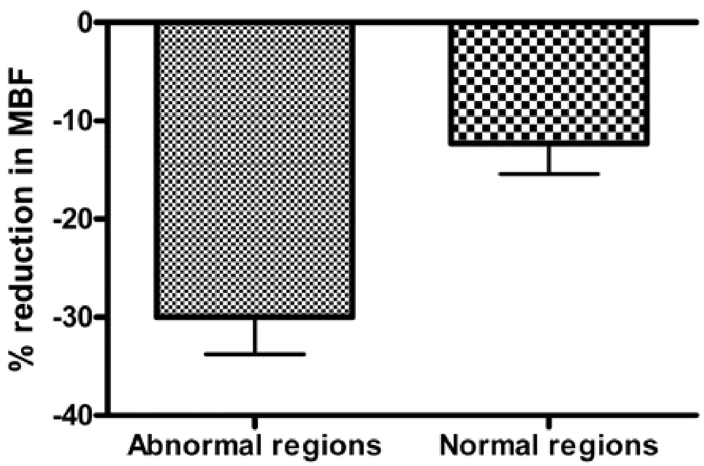
Shoji T, Kidney Int 2004

Hemodynamic stability during HD has to be considered a dialysis ADEQUACY PARAMETER

Hemodialysis-induced myocardial stunning

PET, for myocardial
perfusion assessment





Mc Intyre, CJASN 2008

Hemodialysis-induced myocardial stunning

HEMODIALYSIS

↓

↓ Myocardial blood flow

↓

Myocardial ischemia

↓

Regional wall motion abnormalities

↓

Myocardial dysfunction

Towards a more physiological dialysis

Daily frequency

Long duration

REVIEW

www.nature.com/clinicalpractice/neph

The advantages and challenges of increasing the duration and frequency of maintenance dialysis sessions

Charles Chazot* and Guillaume Jean

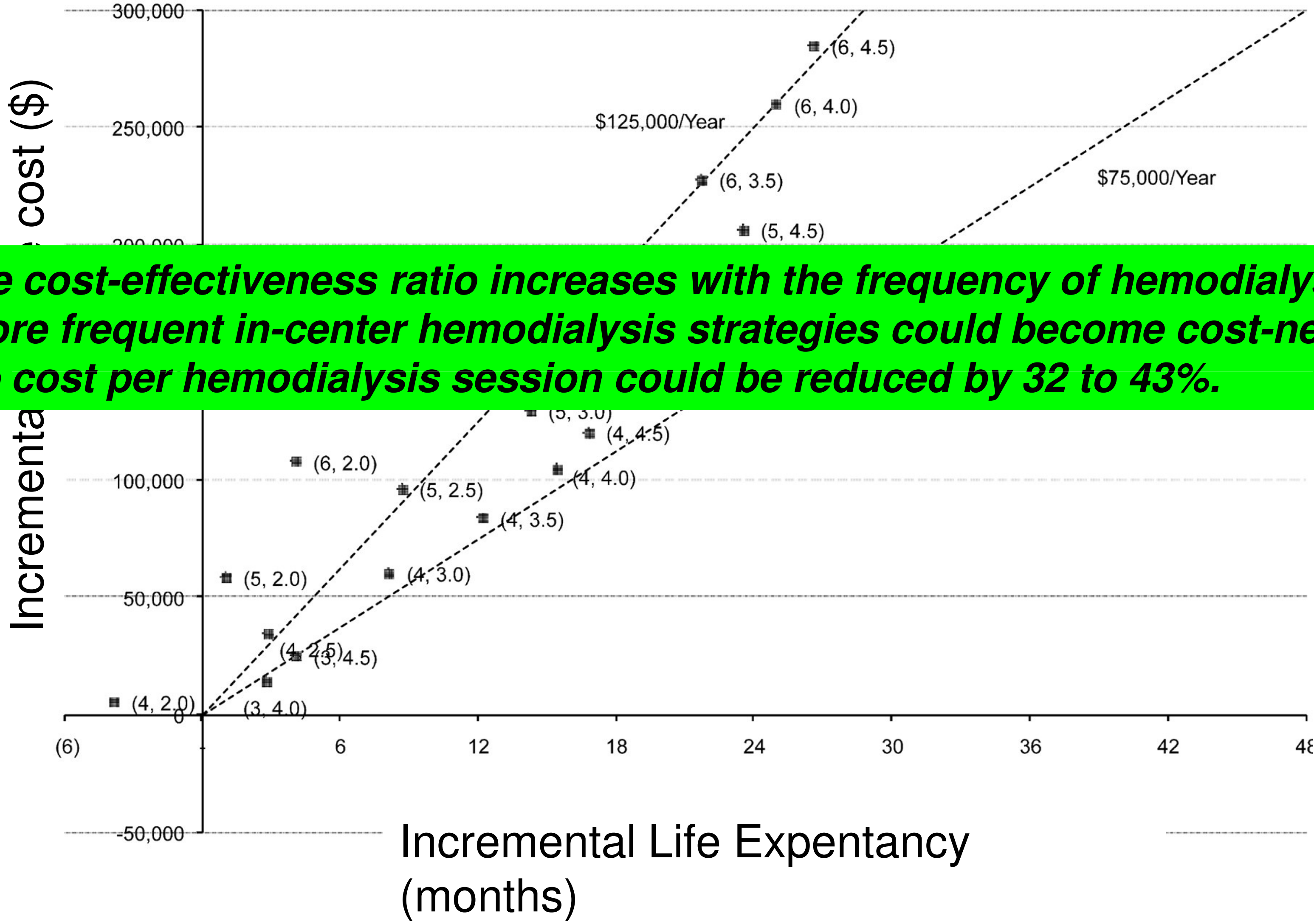
Nephrol Dial Transplant (2009) 24: 1077–1078
doi: 10.1093/ndt/gfn680
Advance Access publication 4 December 2008

Intensifying dialysis: how far should we go and at what cost?

Lieven Annemans

Department of Public Health, Ghent University, Belgium

Incremental cost and incremental life expectancy relative to current practice under baseline assumptions.



The cost-effectiveness ratio increases with the frequency of hemodialysis. More frequent in-center hemodialysis strategies could become cost-neutral if the cost per hemodialysis session could be reduced by 32 to 43%.

Lee CP. et al. JASN 2008;19:1972

Towards a more physiological dialysis

Daily frequency

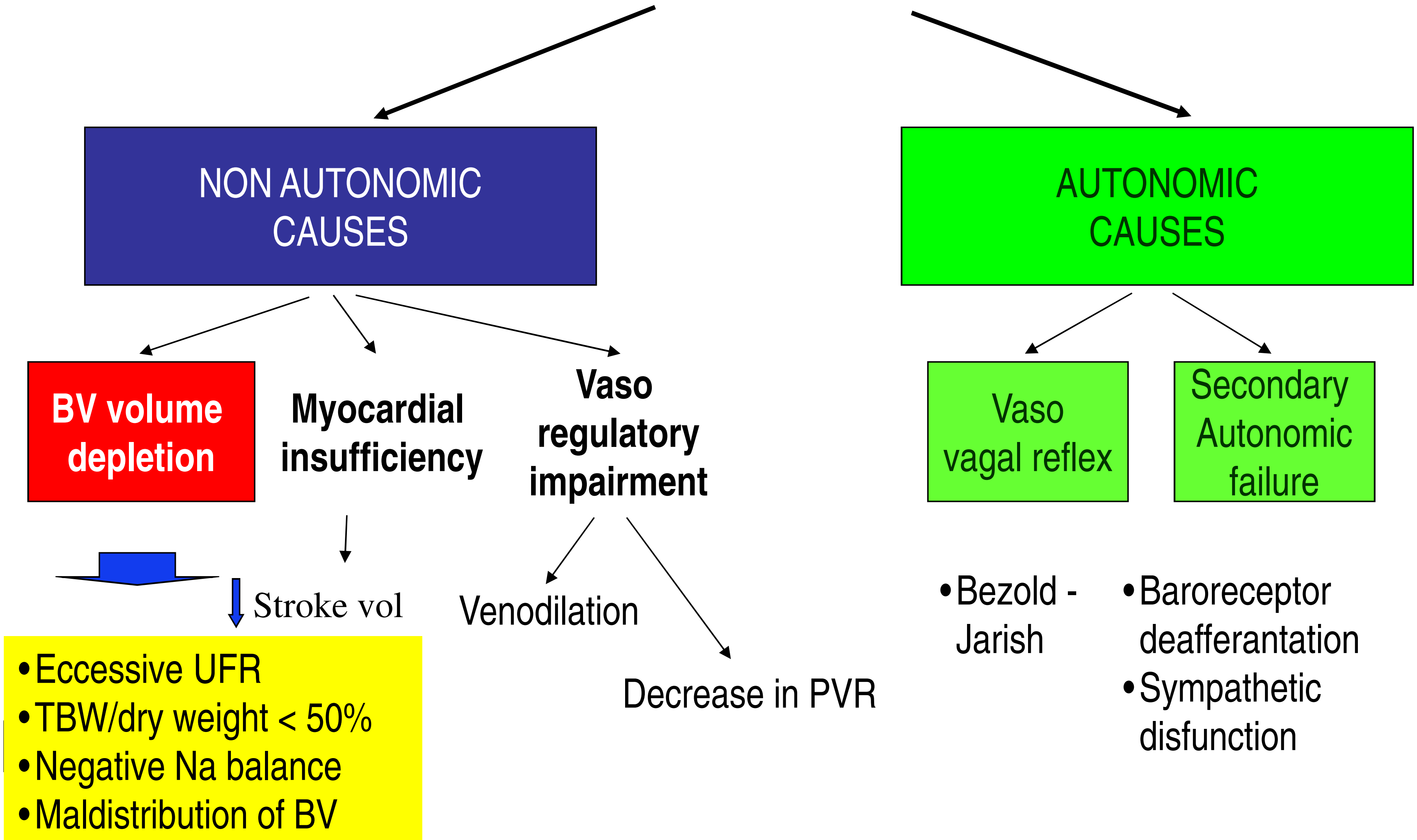
Long duration

Alternatively or combined with :

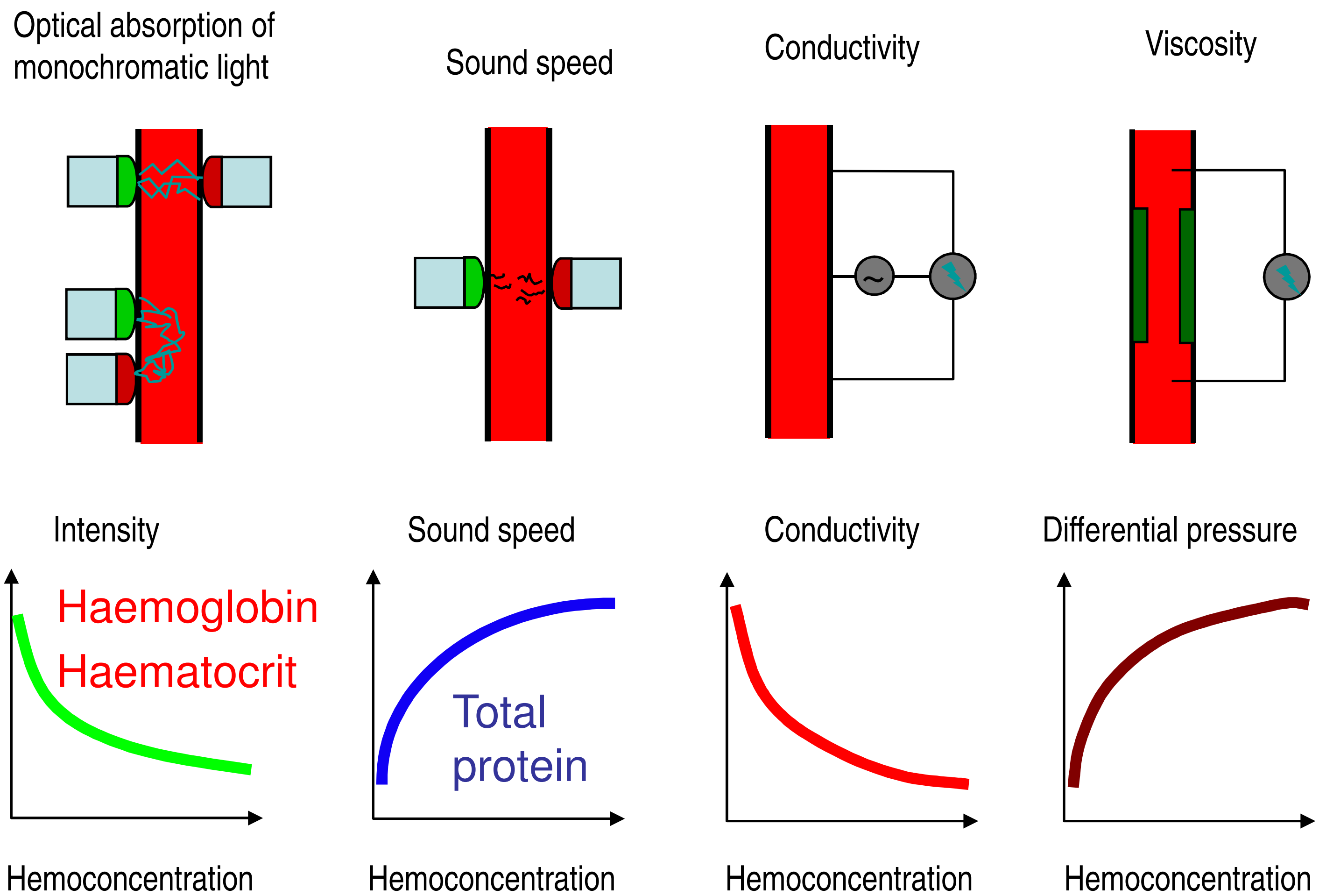
high technology

- ✓ *Control of dialysate chemical and physical properties (temperature)*
- ✓ *Control of dialysis efficiency*
- ✓ *Monitoring and control (in open or closed loop) of the hemodynamic patient variables: SAP, TPVR, BV, HR, CO*
- ✓ *Tailoring of ultrafiltration and conductivity by means of feedback control systems*

DIALYSIS-RELATED CARDIOVASCULAR INSTABILITY

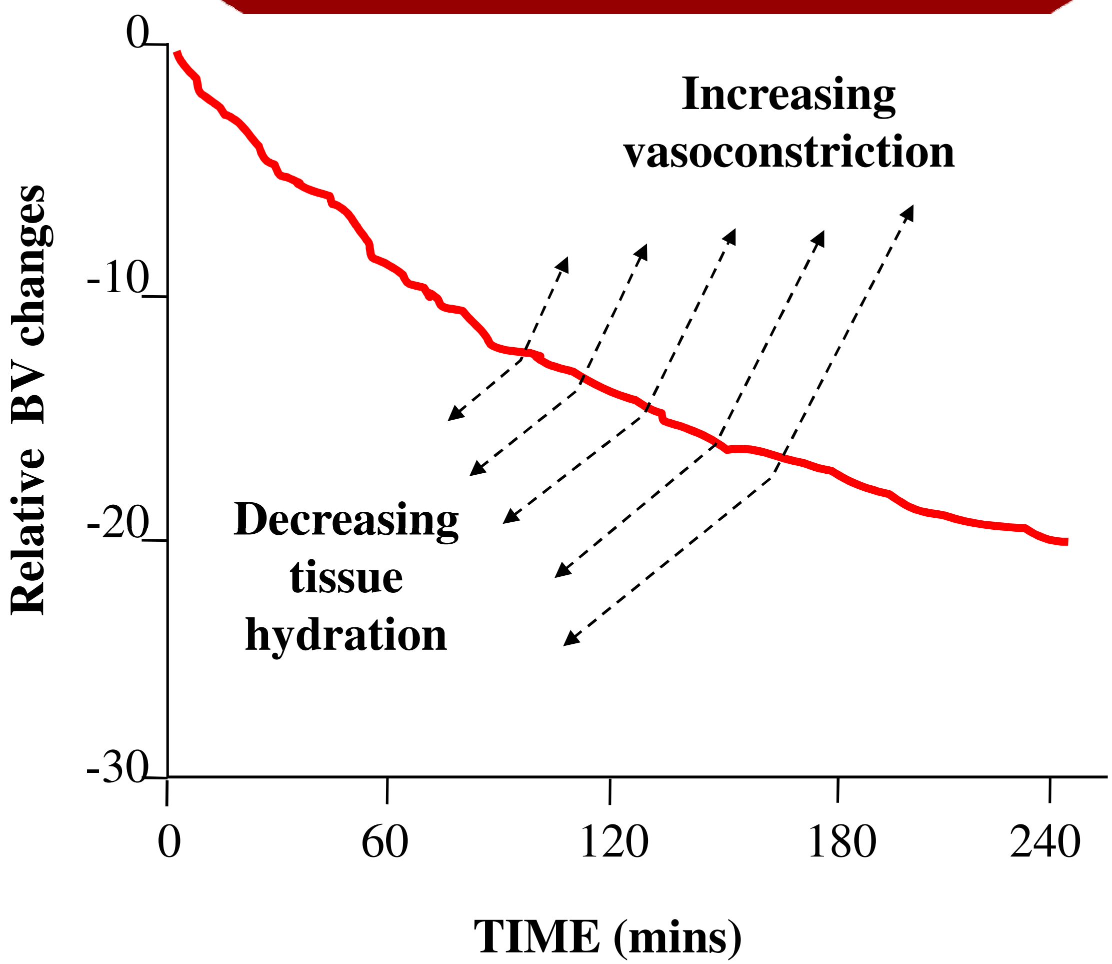


CONTINUOUS METHODS FOR MEASURING RELATIVE BLOOD VOLUME



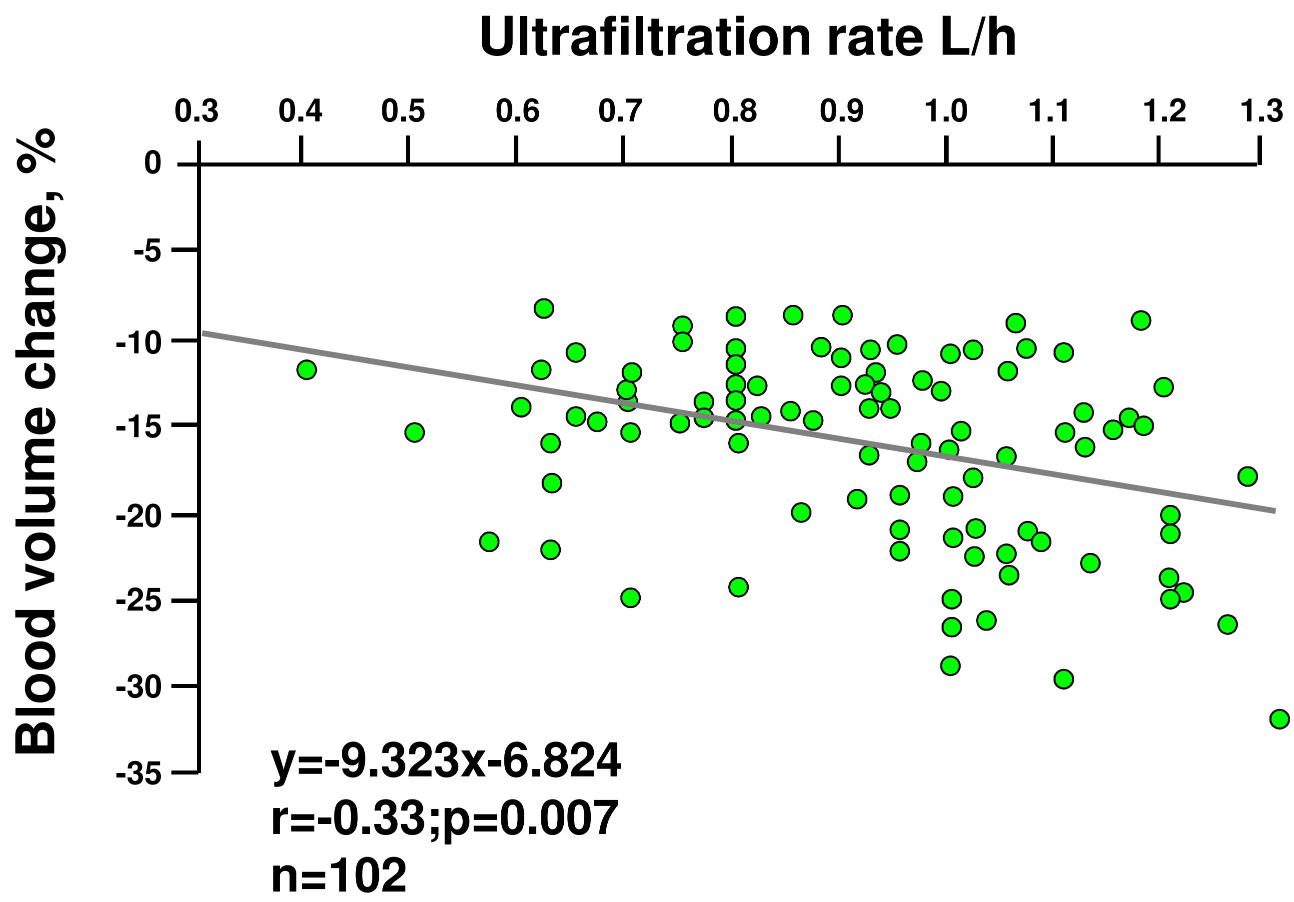
Mass conservation principle ; blood substances confined to the vascular space change proportionally as a result of changes of the plasma volume

$$\frac{d\,BV}{dt} = -\left[F_{A(t)} + UF\right] + R_{V(t)}$$



Plasma Volume Change rate = Vascular refilling rate - Ultrafiltration rate

Relationship BV - UFR



Mancini et al. IJAO, 1996

Hematocrit threshold determined by the Crit-Line Instrument When Intradialytic Morbid Events Occurred

Patient No.	No. Of IME*	Hematocrit Threshold (mean ±SD)	Mean H change before IME from start of treatment
1	9	40 ± 1.6	8
2	6	38 ± 1.3	4
3	7	31 ± 2.7	4
4	4	46 ± 1.9	12
5	2	44 ± 0.5	10
6	3	38 ± 2.2	8
7	9	44 ± 0.5	6
8	3	40 ± 1.2	4
9	6	38 ± 0.4	5
10	3	49 ± 0.9	11
11	2	36 ± 0.5	6
12	7	49 ± 2.2	9

* Total number of IME occurring during the six study sessions for each patient

Steuer R. et al, ASAIO J, 1994

Nephrol Dial Transplant (2003) 18: 1353–1360
DOI: 10.1093/ndt/gfg171

Nephrology
Dialysis
Transplantation

Original Article

Characteristics of hypotension-prone haemodialysis patients: is there a critical relative blood volume?

Claudia Barth[1], Walter Boer[2], Daniela Garzoni[3], Thomas Kuenzi[4], Wolfgang Ries[5], Ralf Schaefer[6], Daniel Schneditz[7], Theoharis Tsobanelis[8], Frank van der Sande[9], Ralf Wojke[10], Holger Schilling[10] and Jutta Passlick-Deetjen[10]

[1]KfH Dialysis Centre Koeln-Lindenthal, [5]Diakonissenkrankenhaus Flensburg, [6]KfH Dialysis Centre Marl, [8]KfH Dialysis Centre Frankfurt-Roedelheim and [10]Fresenius Medical Care, Bad Homburg, Germany, [2]University Hospital Utrecht and [9]University Hospital Maastricht, The Netherlands, [3]Kantonsspital St Gallen and [4]Stadtspital Waid Zürich, Switzerland and [7]Renal Research Institute, New York, USA

An individual RBV limit exists for nearly all patients and this treshold may mark the individual window of haemodynamic instabilities

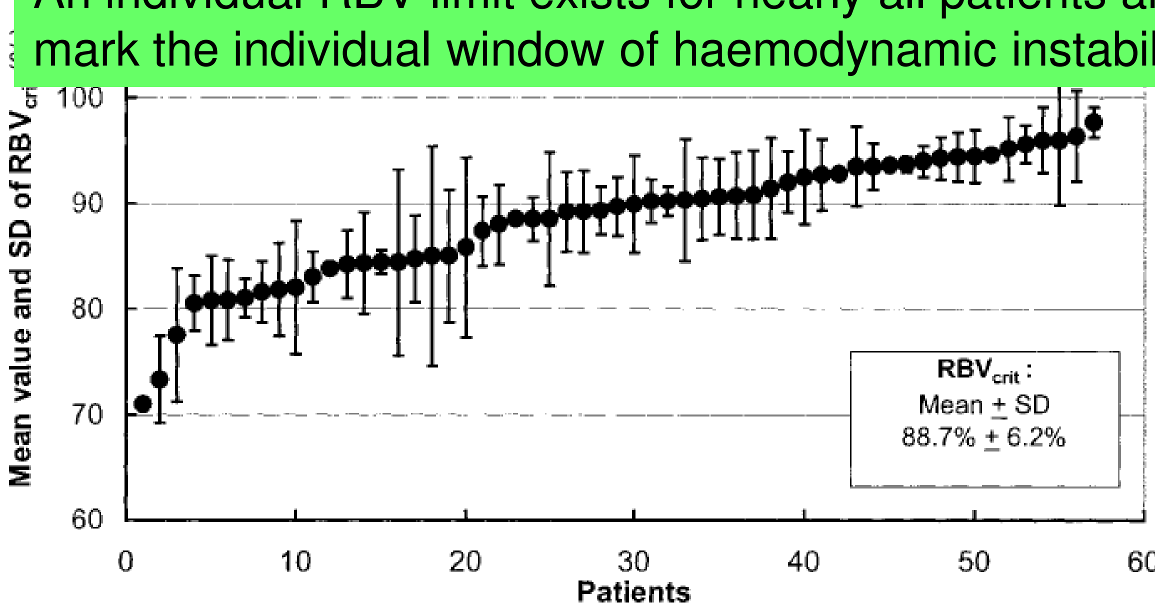
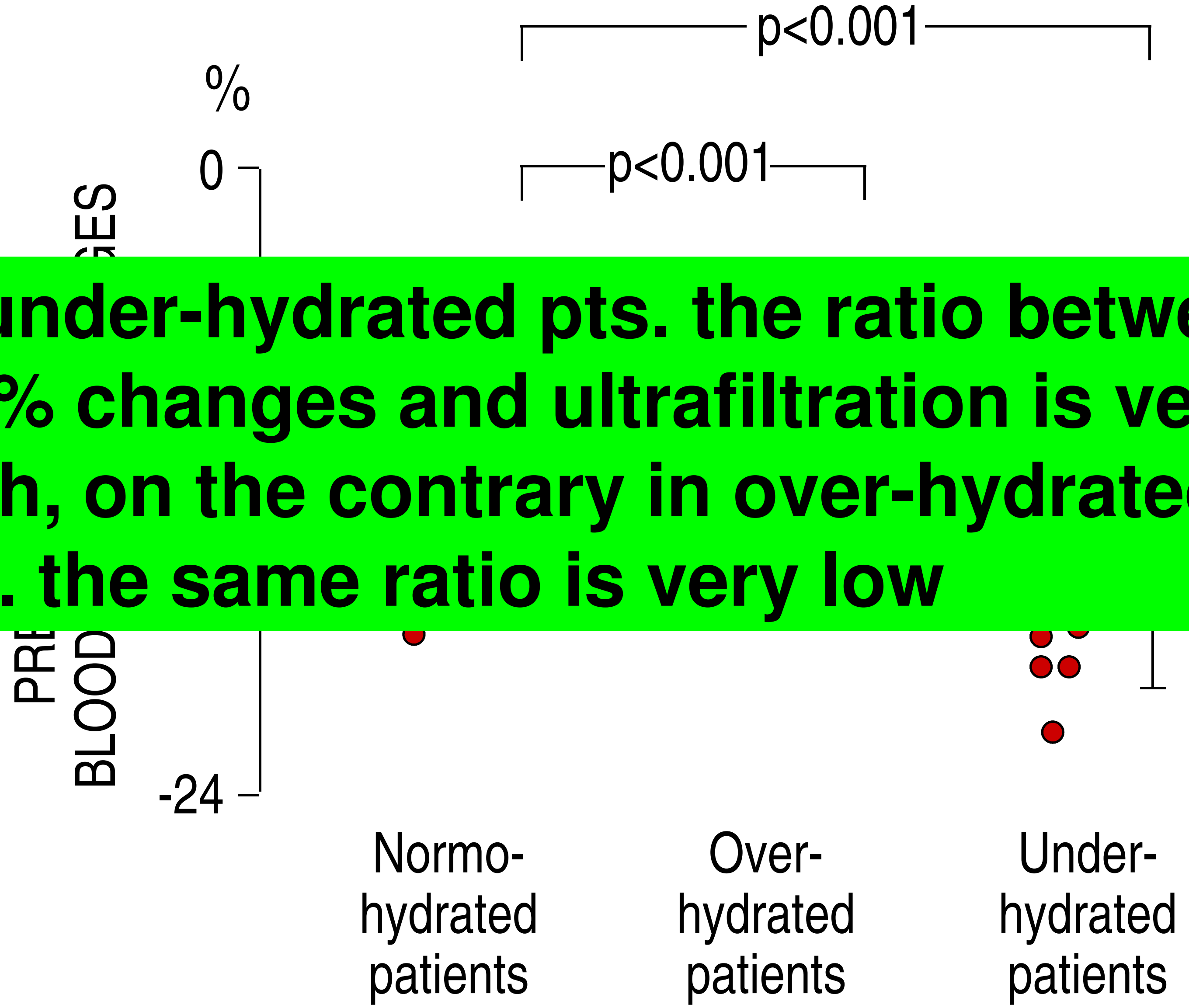


Fig. 2. Individual RBV$_{crit}$ of all patients with intradialytic morbid events (IME). RBV$_{crit}$ was calculated as the average of all RBV measurements during IME of the individual patient ($n = 58$).

MECHANISMS WHICH CAN AFFECT PLASMA REFILLING DURING DIALYSIS

1. **Impairment of peripheral vasoconstriction during volume removal**
   - Acetate
   - Release of cytokines (IL1-TNF-IL6)
   - Autonomic neuropathy
   - Thermal stress
2. **Increase in hydrostatic capillary pressure**
   - Compromised cardiac function
   - Peripheral pooling of blood volume
3. **Depletion of interstitial volume**
   - Low dialysate sodium concentration
   - High transcellular urea gradient
   - Dry body weight error or high UF
4. **Oncotic pressure changes**
   - Hypoalbuminemia
   - Alteration in interstitial fluid drainage and lymph flow

Blood volume changes
in normo- over- and under-hydrated patients



In under-hydrated pts. the ratio between BV% changes and ultrafiltration is very high, on the contrary in over-hydrated pts. the same ratio is very low

The monitoring of RBV trends *alone* may be misleading and confusing

Intradialytic Blood Volume Monitoring in Ambulatory Hemodialysis Patients: A Randomized Trial

Donal N. Reddan,[*†‡] Lynda Anne Szczech,[*‡] Vic Hasselblad,[*] Edmund G. Lowrie,[§]
Robert M. Lindsay,[||] Jonathan Himmelfarb,[¶] Robert D. Toto,[#] John Stivelman,[**]
James F. Winchester,[††‡‡] Linda A. Zillman,[*] Robert M. Califf,[*‡] and William F. Owen, Jr[‡§§]

J Am Soc Nephrol 2005; 16: 2162–2169

443 HD patients randomized to 6 months to Crit-line conventional monitoring (227) or conventional monitoring (216)

Results

- More non-access-related hospitalizations were seen in the BVM compared with conventional groups (120 vs 81 episodes)

- The unadjusted and adjusted risk ratios for non-access-related hospitalization were 1.49 and 1.61 respectively

- The adjusted risk ratios for cardiovascular admissions was 1.85

- The mortality at 6 months was greater in the BVM than the conventional monitoring (8.7% vs 3.3%)

Limitations to the study

- The study population was not limited to those with clinical issues of volume management and hemodynamic instability

Changes in the profiles without any correlations with UF and body weight of the patients were intended to support modifications in the target post-dialysis weight and/or antihypertensive medications

and hospitalization rate , which may exacerbate the differences between the two groups

- Cause of hospitalization was not centrally adjudicated

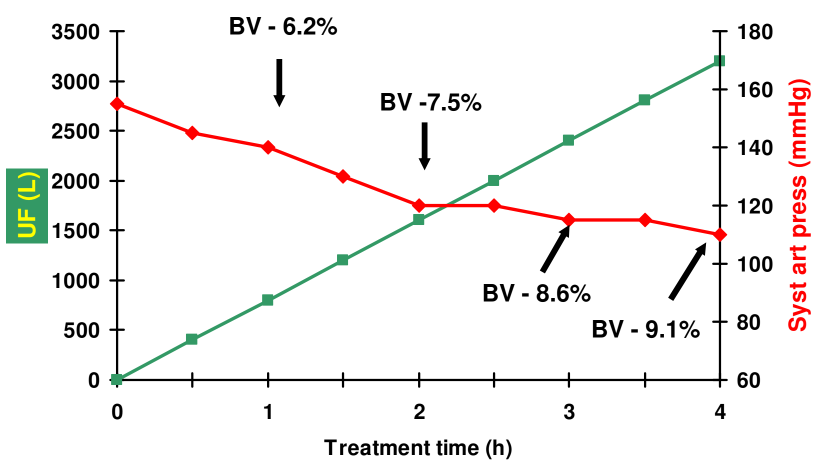
- The study period only 6 months, a longer horizont might have different findings

Summary of randomized BVM and BVT trials, characterized by study population

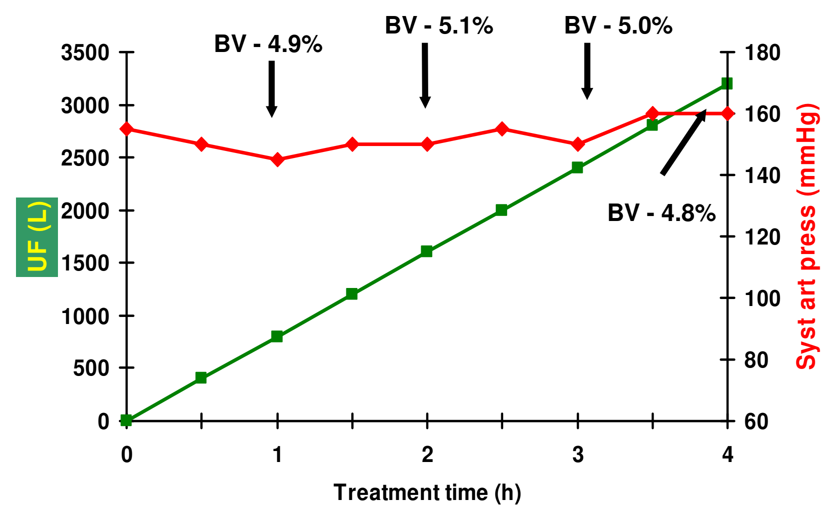
Study	Study design	Intervention	Primary end point	Outcome
Conventional BV monitoring				
Non-IDH-prone Population Reddan (JASN 2005)	RCT	Crit-line (conventional monitoring)	Morbidity	Increased hospitalization in BVM group, Adjusted RR 1.61 (95% CI 1.15–2.25)
Gabrielli (JN 2009)	Cross-over RCT	Fresenius 4008HD (conventional monitoring)	Intra-dialytic morbidity	Reduction in IDH in BVM group (24% *vs* 32%, *P* = 0.04)

READING BLOOD VOLUME & BLOOD PRESSURE DURING HD

RBV behaviour in normohydrated pt.

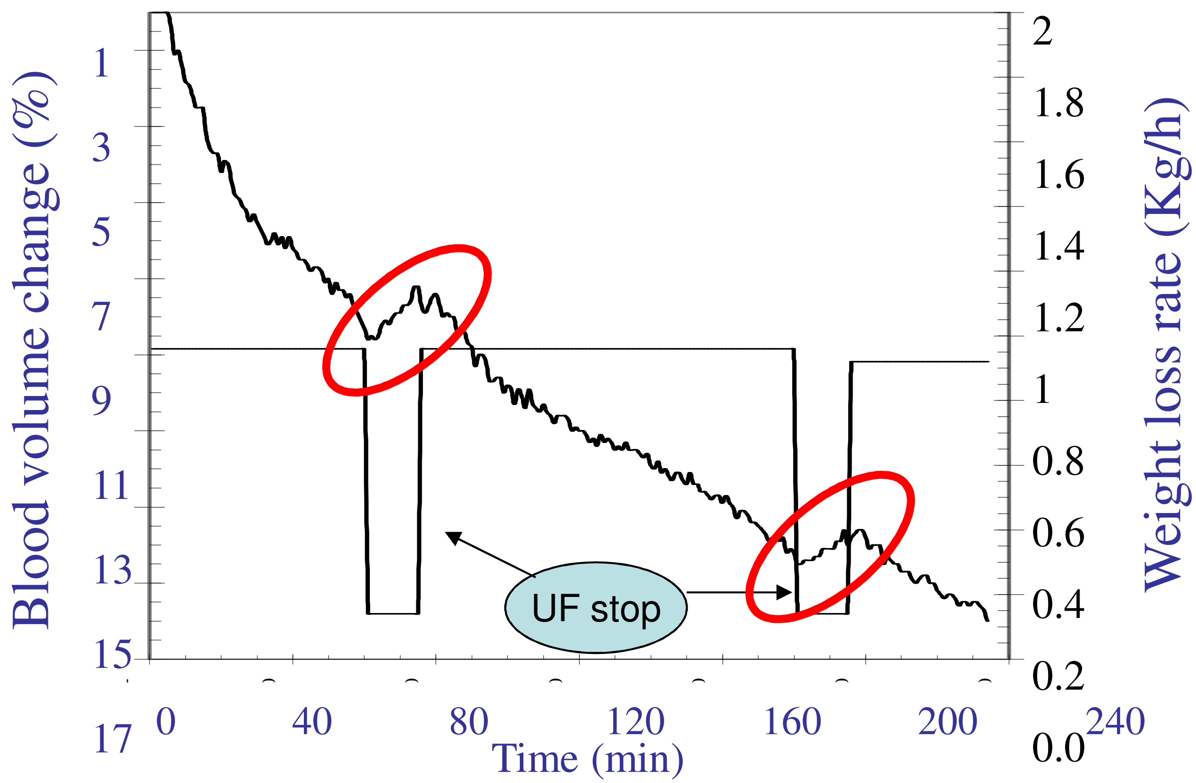


RBV behaviour in overhydrated pt.



Clinical significance of Monitoring the Blood Volume variations

Assesement of plasma refilling rate



"The use of dynamic test, based on ultrafiltration stops, may be useful for optimising the patient's dry-weight and to evaluate the individual capillary filtration coefficient."

Santoro A et al, Int. J Art. Org, 1997.

Linear Decay of Relative Blood Volume During Ultrafiltration Predicts Hemodynamic Instability

Sandip Mitra, MD, Paul Chamney, PhD, Roger Greenwood, MD, and Ken Farrington, MD

American Journal of Kidney Diseases, Vol 40, No 3 (September), 2002: pp 556-565

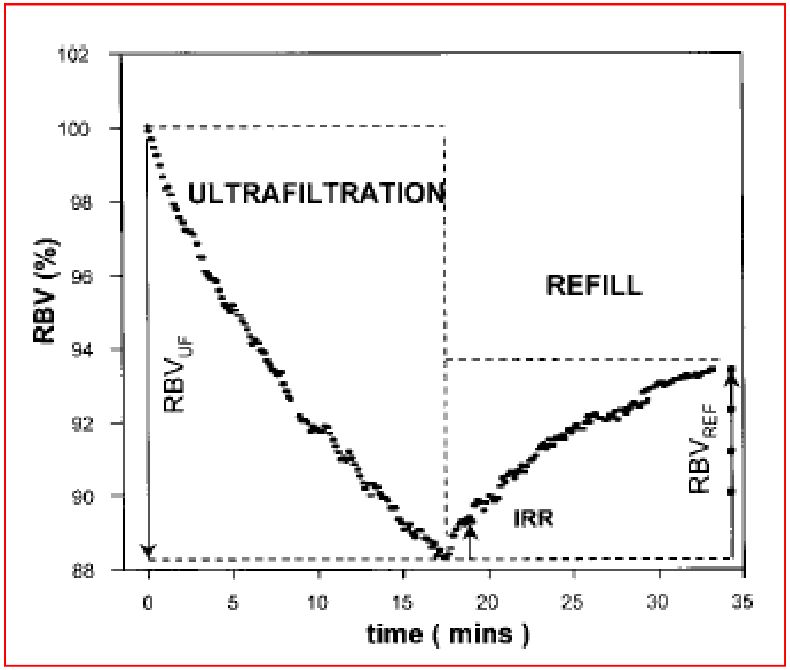


Fig 1. A typical RBV profile obtained in response to a UF pulse showing decay, subsequent refill phase, and measured parameters. Values for ΔRBV in percentage, and for IRR, in percentage per minute. Abbreviation: ΔRBV_{ref}, the magnitude of RBV change during the refill phase, in percentage.

Chi-Square Analysis Comparing UF and Refill Characteristics Between Hypotensive and Normotensive UF Pulses

Parameter	Hypotensive UF Pulses (n=30)	Normotensive UF Pulses (n=60)	*P*
RBV at UF pulse initiation (%)	90.5±4.2	94.6±3.5	<0.001
ΔRBV_{UF}(%)	7.4±1.8	6.9±1.5	NS
UFV_S(mL)	457±123	457±123	NS
$\Delta RBV_{UF}/UFV_S$(%/mL)	0.017±0.005	0.016±0.004	NS
UF decay amplitude (b)	71.2±12.9	79.4±13.9	0.007
τ_{UF}	21.6±8.5	12.8±2.8	<0.001
Linear divergence (%.s)	155±285	662±405	<0.001
IRR (%/min)	0.86±0.45	0.76±0.35	NS
Refill phase amplitude	3.4±1.1	4.8±2.4	0.001
τ_{ref}	0.25±0.69	0.14±0.10	NS

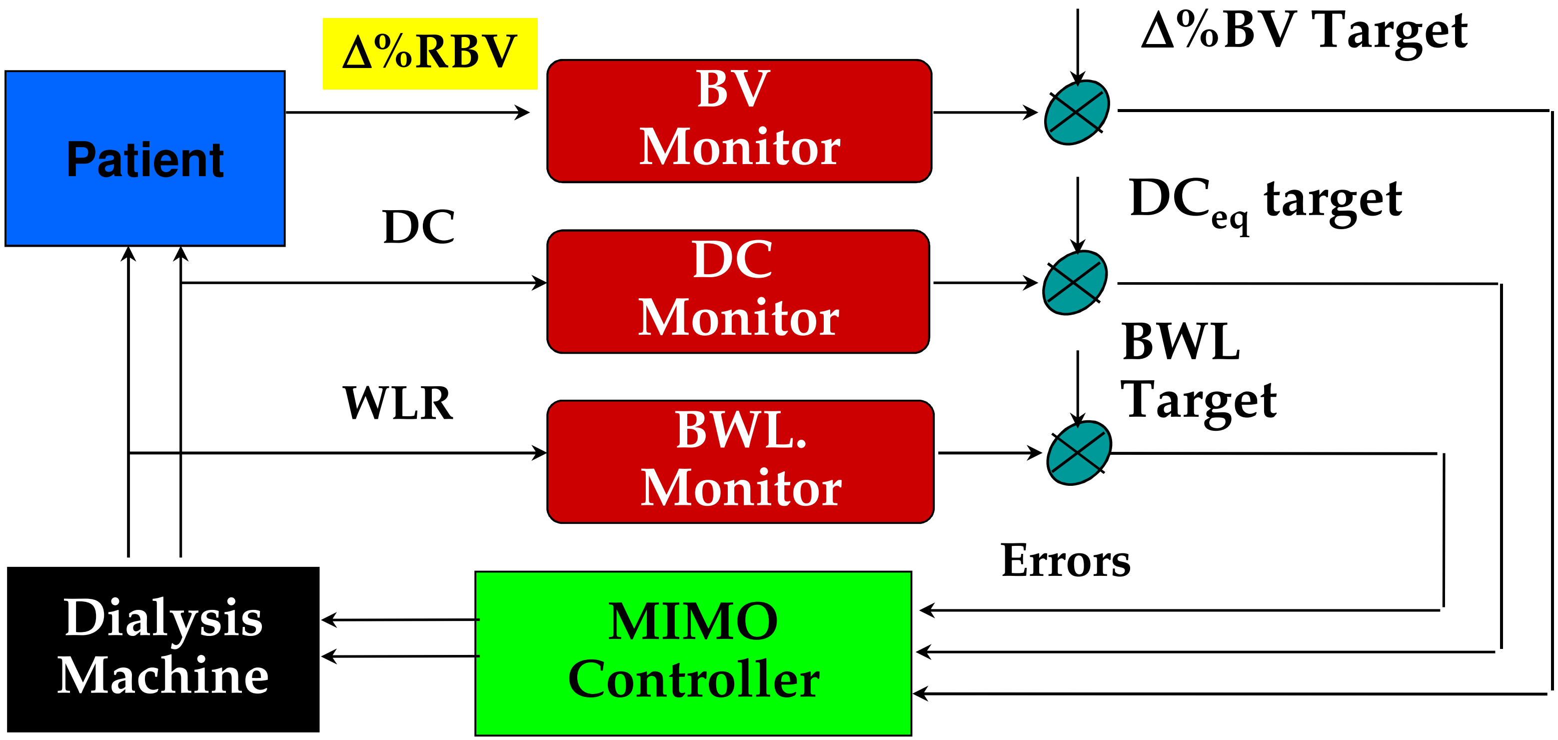
Mitra S; Am J Kidney Dis 2002;40:556-565

Covariates related to symptomatic hypotension

multivariate logistic regression	p	Relative Risk	95% CI
Group	<0.001		
C *vs* A	NS	1.25	0.54-2.89
B *vs* A	<0.001	7.26	3.07-17.13
Baseline plasma-dialysate Na^+ gradient (for each 1 mEq/L increase)	<0.001	1.13	1.06-1.22
Δ BV from 20 to 40 min of dialysis (for each 1% decrease)	0.030	1.23	1.02-1.48
Irregularity of BV over time (yes/no)	0.001	3.13	1.65-5.96
HR decrease from the start to the 20^{th} min of dialysis (for each 1 beat/min decrese)	0.017	0.95	0.91-0.99

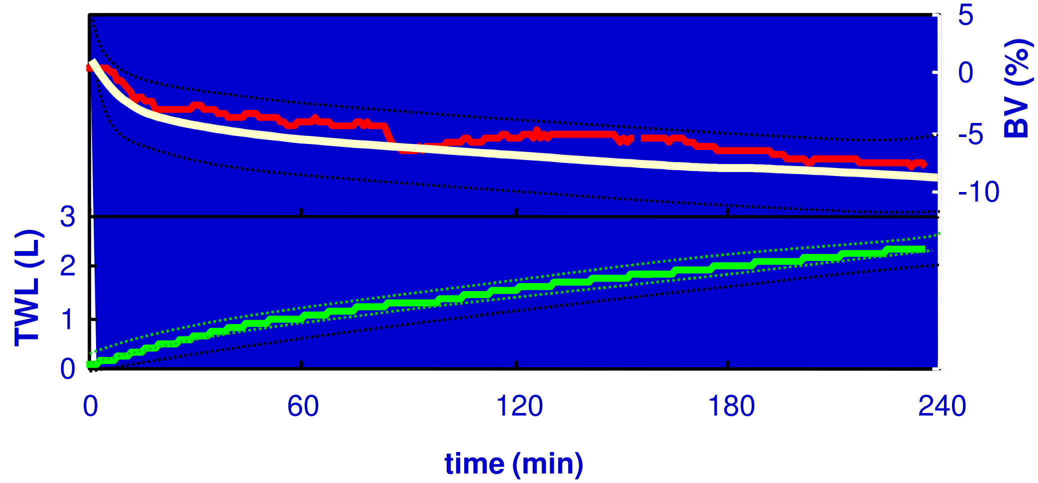
Andrulli S, Am J Kidney Dis 2002

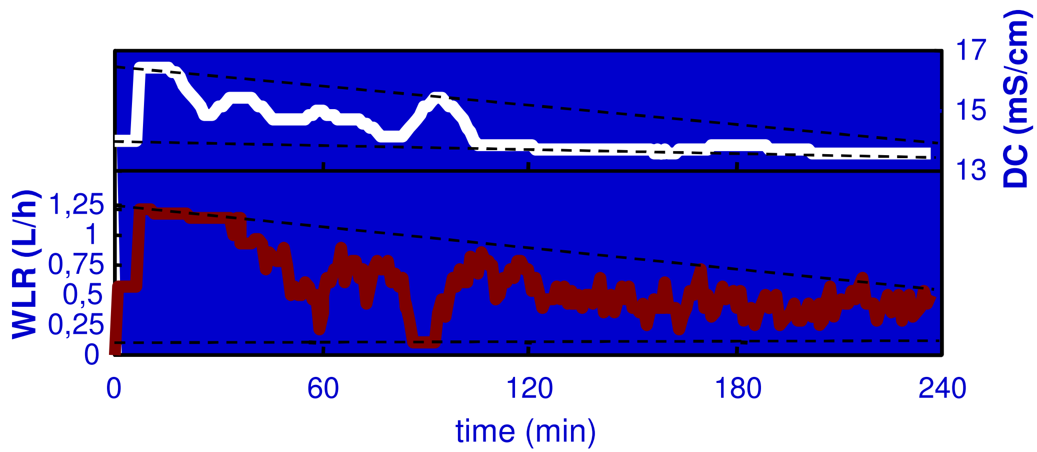
Blood volume tracking SYSTEM



Santoro A et al. Blood Volume Regulation During Hemodialysis, Am J Kidney Dis, 1998

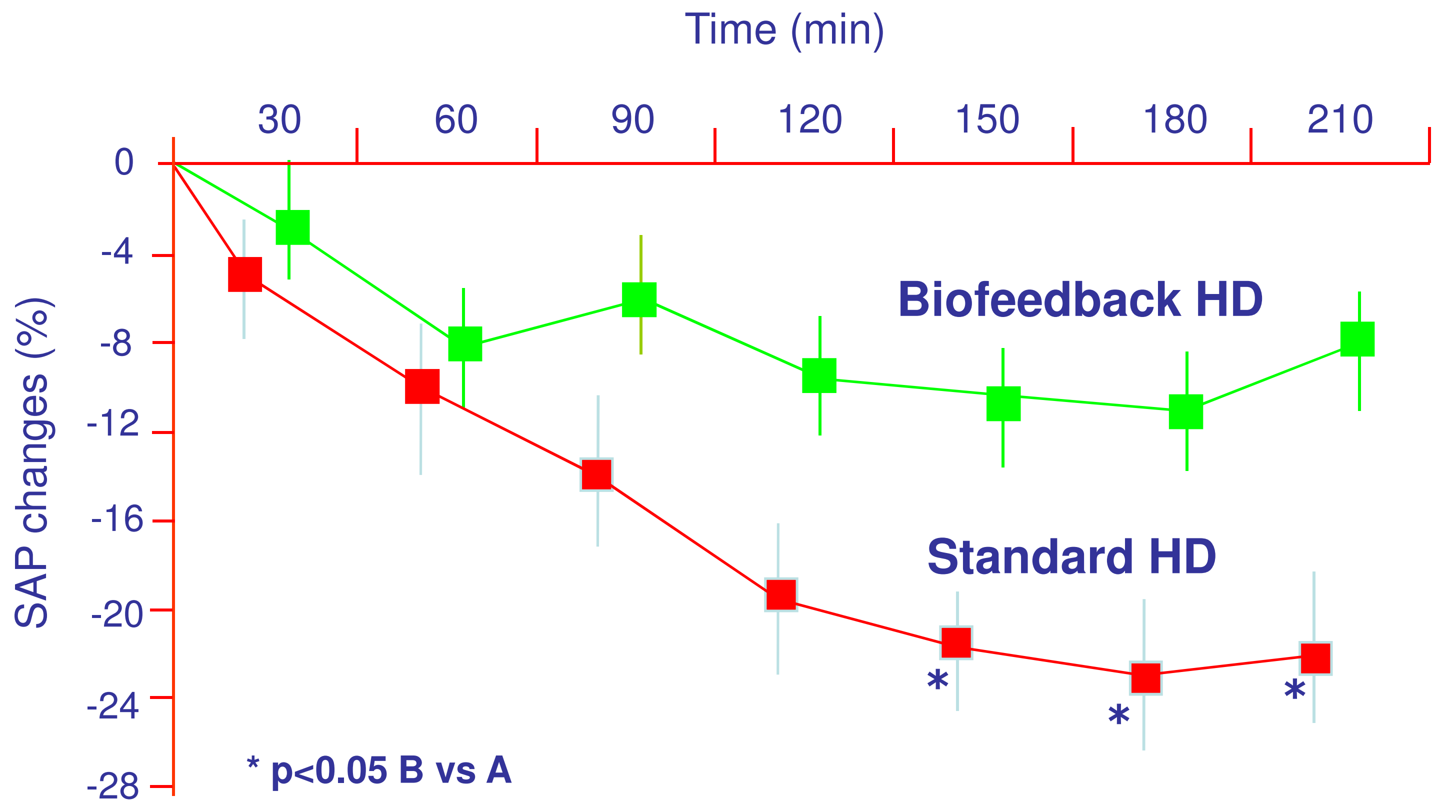
Blood Volume Tracking





Santoro A. AJKD1998

The first experiences with the biofeedback control of Blood Volume



Effects of automatic blood volume control over intradialytic hemodynamic stability, *E. Mancini et al, Int, J. Art. Org., 1995, 18, 9: 495-498*

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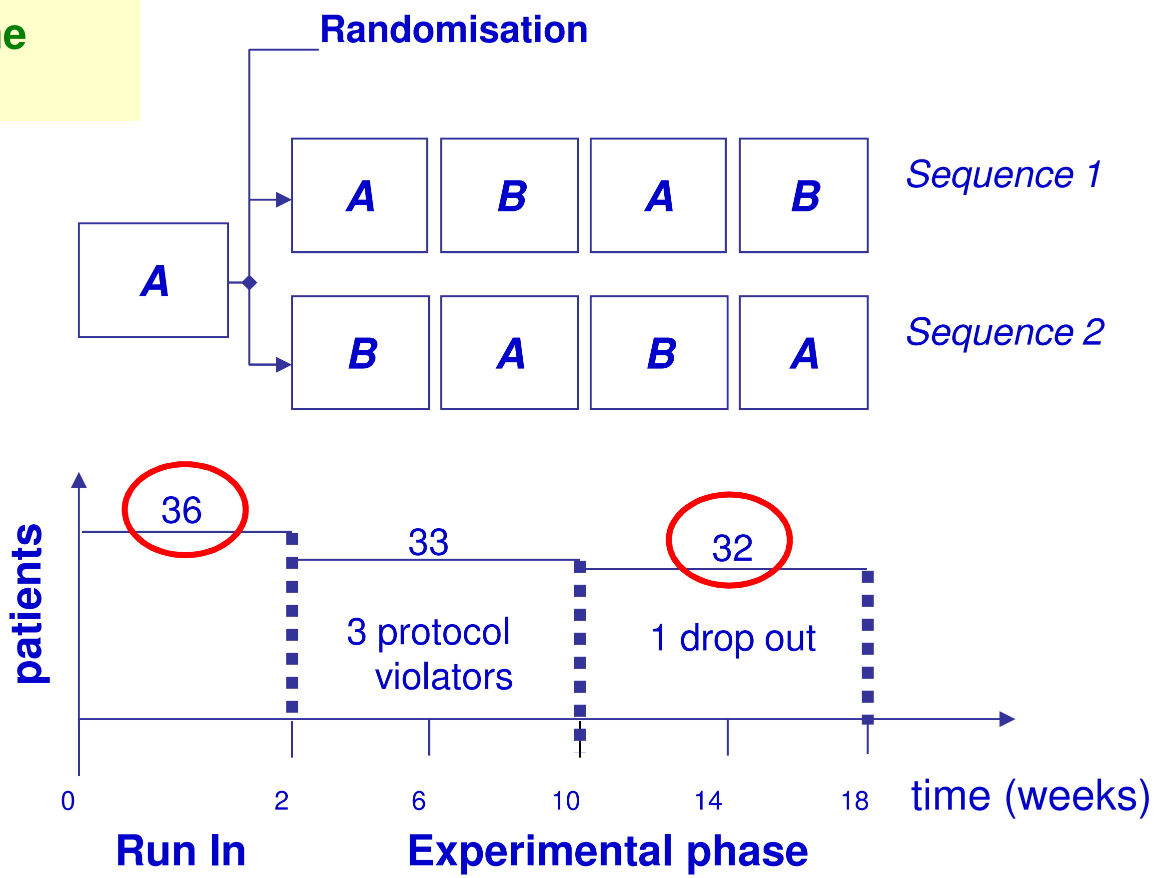
Blood volume tracking (closed loop) haemodialysis (Hemo-Biofeedback)				
IDH-prone population Santoro (KI 2002)	Cross-over RCT	BVT (conventional HD)	IDH reduction	30% reduction in IDH, (*P* =0.004) sessions in BVT Group
Ronco (KI 2000)	Cross-over RCT	BVT (conventional HD)	IDH reduction	Less IDH in BVT group (24 *vs* 59 HDx sessions, $P \leq 0.001$)
Nersallah (ASAIO J 2008)	RCT	Hemo-biofeedback systems (conventional monitoring)	Change in ECV at 6 months	Lower IDH in HBS group (0.13 *vs* 0.31) *P* = 0.04)

A multicenter cross-over RCT

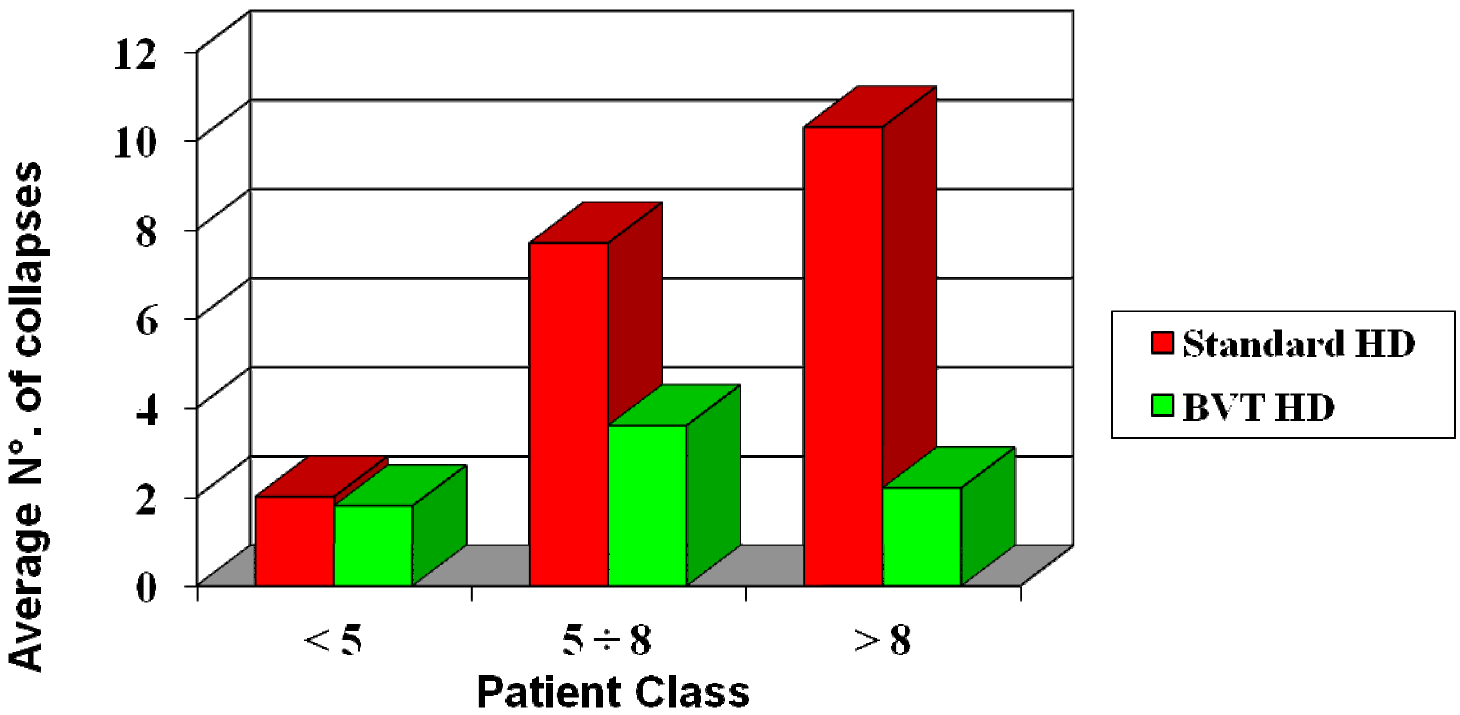
A = conventional HD

B = Blood Volume tracking HD



Santoro A. et al., Kidney Int 2002

30% reduction in IDH during BV tracking HD



Santoro A. et al, Blood volume controlled hemodialysis in hypotension-prone patients: A randomized, multicenter controlled trial, Kidney Int. 2002, 62, 1034-1045

Dialysis efficiency

Less IDH in Biofeedback HD (p< 0.001)

	Standard	**Biofeedback**	
Single Pool Kt/V	1.34 ± 0.08	1.26 ± 0.06	$p < 0.005$
Equilibrated Kt/V	1.03 ± 0.08	1.12 ± 0.05	$p < 0.001$
Urea Rebound %	14.2 ± 2.7	6.4 ± 2.3	$p < 0.001$
Urea removal (grams)	30.4 ± 4.1	35.4 ± 3.7	$p < 0.005$
Solute Removal Index	1.77 ± 0.15	2.01 ± 0.23	$p < 0.005$

Bland-Altman test (N=144 dialysis sessions)

Impact of biofeedback-induced cardiovascular stability on hemodialysis tolerance and efficiency
C. Ronco et al, Kidney Int., 2000, 58: 800-808

Intradialytic hypotension

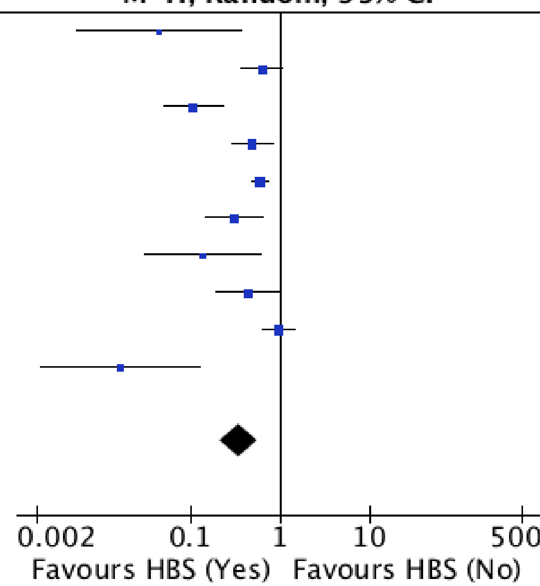
The number of dialysis complicated by hypotensions over the total number of assessed dialysis

	HBS (Yes)		HBS (No)			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
1994 Santoro (1)	1	30	13	30	3.8%	0.05 [0.01, 0.38]
1998 Santoro (2)	25	96	68	192	12.8%	0.64 [0.37, 1.11]
2000 Ronco	24	72	59	72	10.9%	0.11 [0.05, 0.24]
2001 Basile (3)	26	171	45	171	12.8%	0.50 [0.29, 0.86]
2002 Santoro	180	766	256	766	14.8%	0.61 [0.49, 0.77]
2002 Wolkotte	10	158	28	157	11.0%	0.31 [0.15, 0.67]
2003 McIntyre	2	133	13	133	6.0%	0.14 [0.03, 0.64]
2006 Moret (4)	9	110	18	110	10.3%	0.46 [0.19, 1.06]
2007 Deziel (5)	56	204	63	228	13.7%	0.99 [0.65, 1.51]
2008 Winkler (6)	1	648	9	108	3.9%	0.02 [0.00, 0.14]
Total (95% CI)		**2388**		**1967**	**100.0%**	**0.35 [0.21, 0.56]**
Total events	334		572			

Heterogeneity: $Tau^2 = 0.38$; $Chi^2 = 47.17$, df = 9 ($P < 0.00001$); $I^2 = 81\%$

Test for overall effect: Z = 4.38 ($P < 0.0001$)

Odds Ratio
M-H, Random, 95% CI



(1) Data pooled over A1, A2 study phases
(2) Data pooled over A1, A2 study phases
(3) Data referred to the short-term study phase
(4) Data referred to the conventional vs HBS phases
(5) Data referred to 4 weeks recording (2 weeks at the beginning and 2 weeks at the end)
(6) Data referred to the short-term study phase

Santoro A. submitted

EBPG guideline on hemodynamic instability

Guideline 3.1.2a Individualized, automatic BV control should be considered as a second-line option in patients with refractory IDH (Evidence level II).

Rationale

With blood volume controlled treatments, ultrafiltration rate and/or dialysate conductivity are adjusted according changes in relative blood volume.

[…] Nevertheless, several randomized cross-over studies have shown a reduction in IDH and intra-dialysis symptomatology with the use of automatic blood volume feedback [1,2,4-6]. Moreover, one study showed an increase in dialysis efficacy with the use of this approach, due to a reduction in intra-dialytic interventions [1].

[…] No adverse effects on sodium balance have yet been reported [2,7].

[…] Summarizing, various studies have shown a beneficial effect of automatic blood volume controlled feedback in the prevention of IDH episodes.

NDT (2007) 22 [Suppl. 2]: ii22-ii44

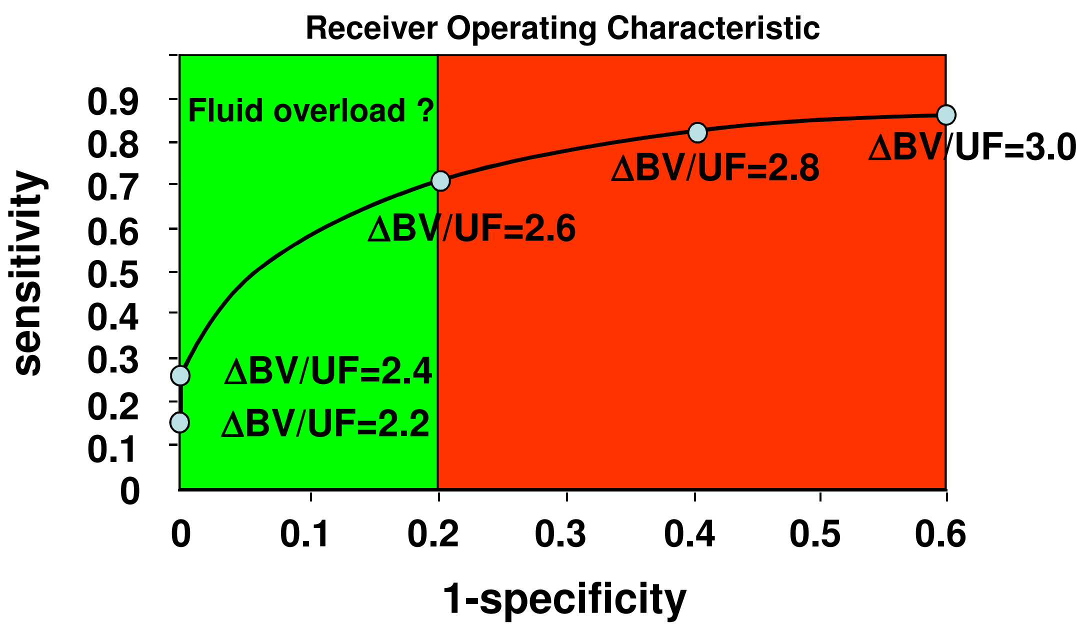
Measurement of blood volume during hemodialysis is a useful tool to achieve safety adequate dry weight by enhanced ultrafiltration

Method: N=12

- Single dry weight reduction the mid-week dialysis = -0.5 Kg
- BV reduction recording

Results:

- 58 % of patients were successful (no symptoms)
- 42 % of patients failed (symptoms)



Zellweger M et al, ASAIO J, 2004, 50, 242 - 245

ASAIO Journal 2007

Effects of Relative Blood Volume–Controlled Hemodialysis on Blood Pressure and Volume Status in Hypertensive Patients

JUDITH J. DASSELAAR,*† ROEL M. HUISMAN,*† PAUL E. DE JONG,* JOHANNES G. M. BURGERHOF,‡ AND CASPER F. M. FRANSSEN*†

- Prospective, randomized, parallel group study with two arms (standard HD vs BVT)
- Study duration: 4 wk Run-in + 12 weeks
- Enrolled patients = 28 (14 per arm)
- Hypertensive pts (pre-HD and/or post-HD BP >150/90 mmHg) in antihypertensive treatment or with cardiotoracic ratio >0,5
- No intervention were designed in each arm to reduce the dry body weight but the judgment of the nephrologists according to the overhydration status

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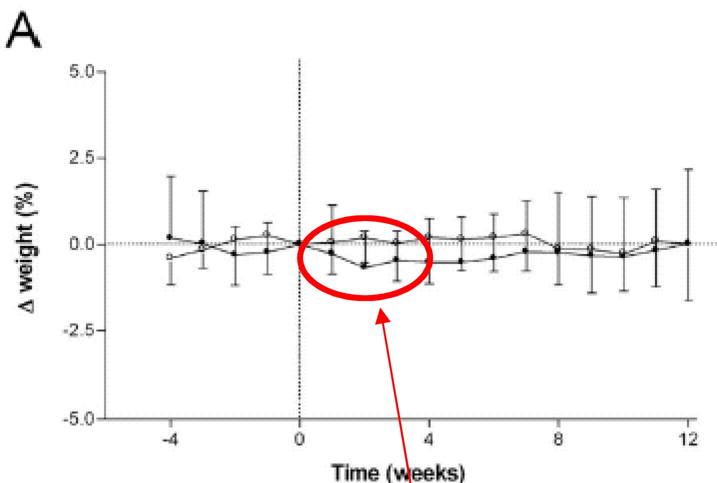
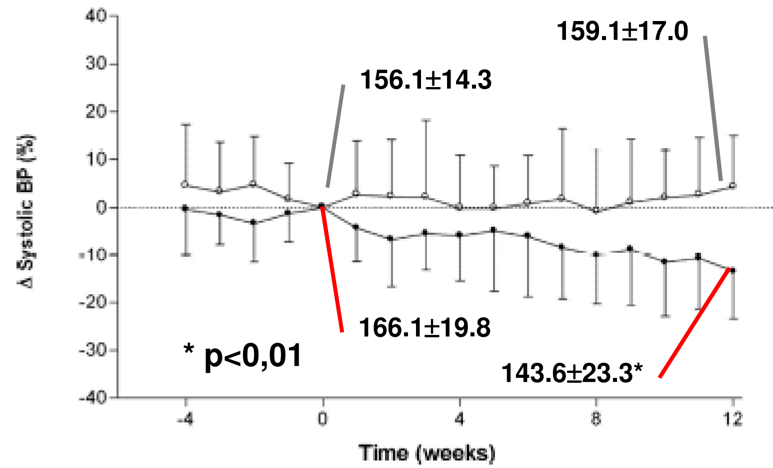
○ Standard-HD
● BVT

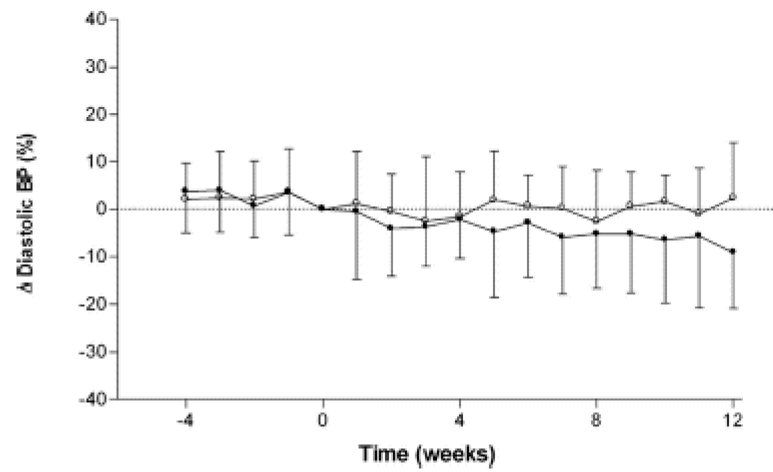
Pre-Hemodialysis



On average a reduction of <u>0.7Kg</u> in the dry weight was observed in the first 3 weeks

Pre-Hemodialysis





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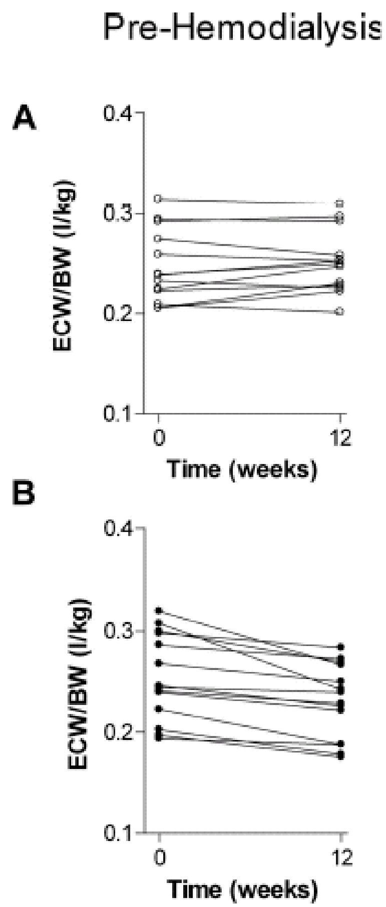
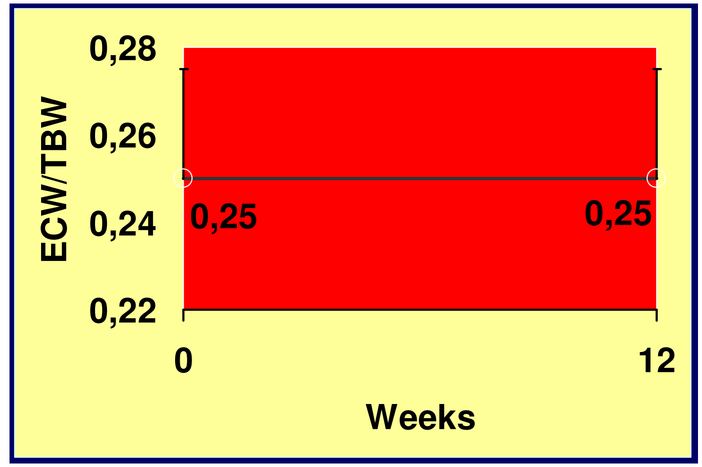
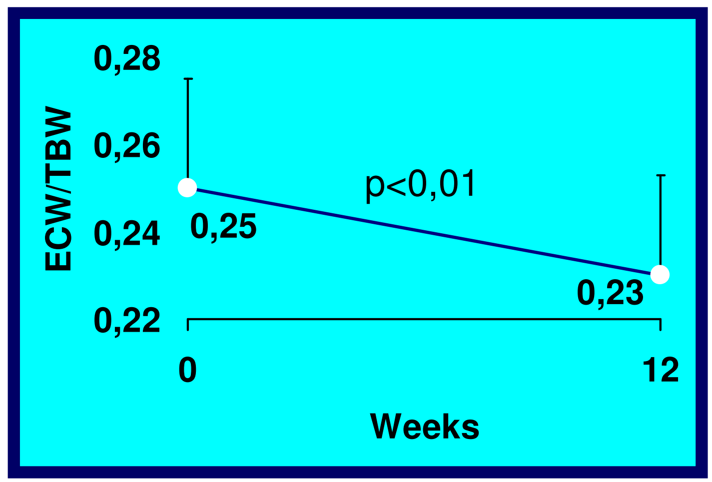
Standard HD





BVT



Conclusions

- RBV monitoring has to be adjusted for UF rate and weight in determing BV and hydration status
- BV controlled HD (Hemo-biofeedback systems) proved useful to improve the hemodynamic stability and the overall tolerance to the HD treatment in DH-prone population.
- Frail, critical, co-morbid patients are the target patient population for BV controlled HD.
- EBPG consider automatic BV control in the strategies to prevent hemodynamic instability.
- Furthermore BV controlled HD has been shown to be useful in the assessment of IBW in hypertensive pts. with latent over-hydration.

Factors influencing KT/V

K **filter type, priming, Qb, clotting,….**
T **by-passes, blood pump stops**
V **dry weight, hydration status**

Problems with conventional adequacy assessment

- V- based dose measure may result in underdialysis of women/ children/smaller patients
- May fail to detect marked underdialysis if postBUN drawn incorrectly
- Expense of monthly postBUN blood drawn
- Once-a-month measurement may not reflect montly treatment (shortened, missed treatments)
- Large month-to-month variability

Current on-line adequacy methods

- Estimation of on-line dialyzer clearance using sodium conductivity
- Measuring or estimating the change in spent dialysate urea during the treatment

Advantages of automated monitoring of K or urea removal

- Elimination of pre- and post-dialysis blood urea nitrogen measurement
- Ensuring that the patient receives the prescribed dose of dialysis each time
- More accurate delivery of a dialysis prescription to new patients
- Detection of access recirculation
- Performing quality assurance of reprocessed dialyzers

The aims of on-line monitoring

- Keeping under continuous control physiological, biochemical and haemodynamic parameters.
- Preventing critical clinical situations
- Modifying, in open-loop or with automatic feedback (closed loop) the dialysis actuators

Limiting factors in intradialytic on.line monitoring

- Extra costs
- Plentifully signals and poor knowledge
- Polyedral interpretation
- Larger validation studies in different groups of patients may be needed so as to evauated actual outcome effect