

Ultrafiltration, Intradialytic Hypotension & Mortality

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2^{ème} Symposium Infirmier
romand en Néphrologie



Disclosure

Speaker name: Prof. Bernard Canaud

- I have the following potential conflicts of interest to report:
- Consulting
- Employment in industry (FMC)**
- Shareholder in a healthcare company
- Owner of a healthcare company
- Other(s)
- I do not have any potential conflict of interest



Outlook of the Presentation

1. Sodium & fluid volume homeostasis in CKD5 HD patient
 - Basics of physiology – Challenges for nephrologist & care giver
2. Intradialytic hypotension:
 - Definition – Frequency – Causes – Consequences
3. Sodium & fluid management in HD
 - Diffusive/Convective Na
 - Ultrafiltration
4. Preventing intradialytic hypotension
 - Means: diet, residual kidney function, hemodialysis, time
 - Stepwise approach
5. Take home message

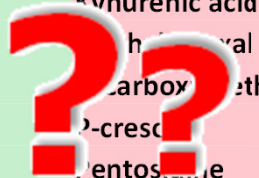
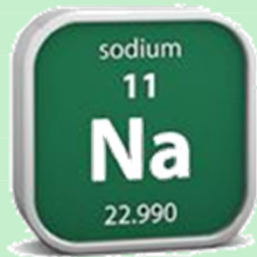
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Uremic Toxins

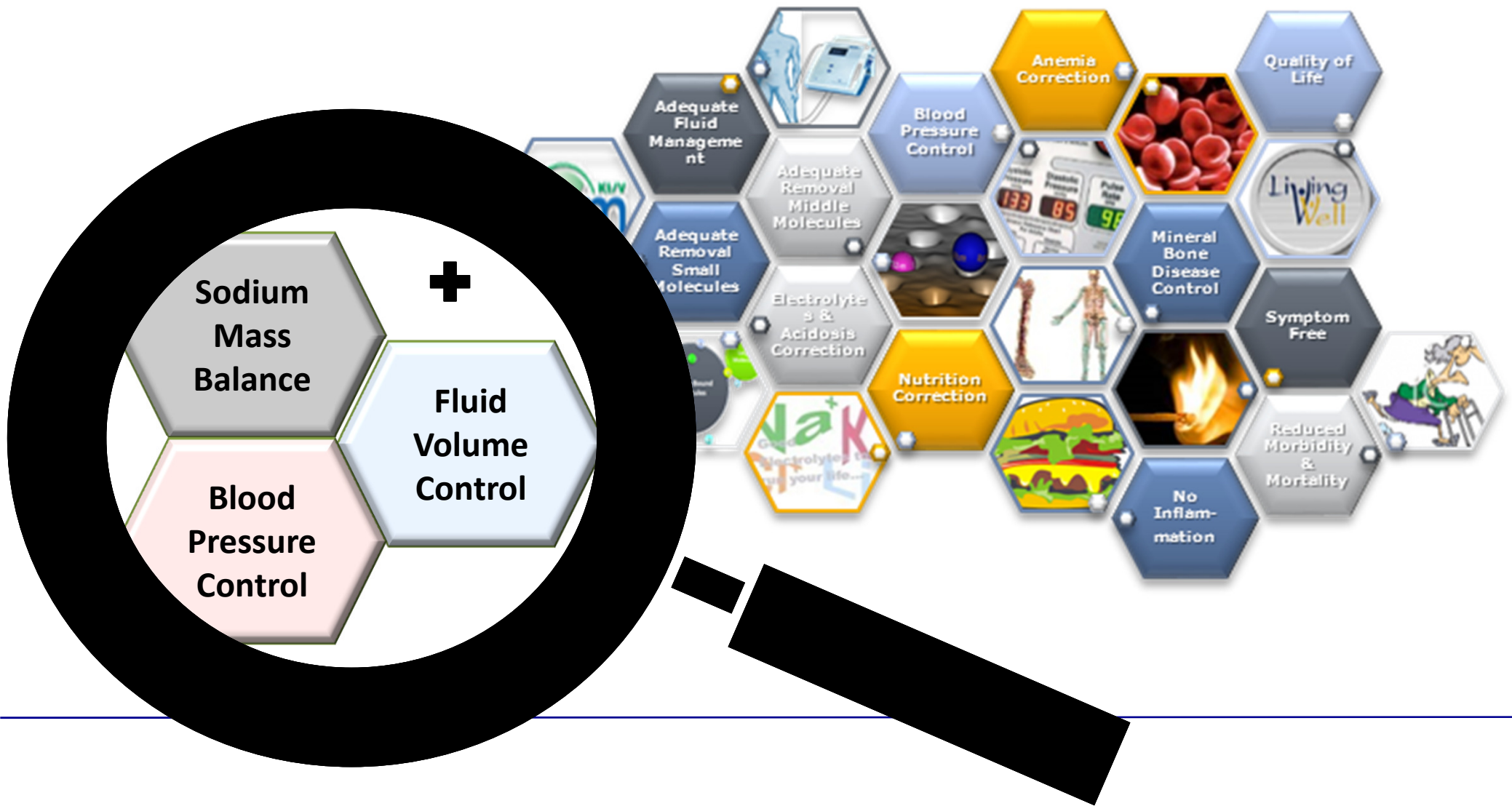
Sodium and Fluid Are Forgotten

| Small water soluble solutes < 500 Daltons (n = 45) | Protein-bound solutes 500 - 22000 Daltons (n = 25) | Middle molecules > 500 Daltons (n = 22) > 12 Daltons (n = 12) |
|---|---|--|
| Asymmetric dimethylarginine | 3-Deoxyglucosone | Adrenomedullin |
| Benzylalcohol | Carboxy-Methyl-Propyl-Furanpropionic Acid | Atrial natriuretic peptide |
| β-Guanidinopropionic acid | Fructoselysine | β2-Microglobulin |
| β-Lipotropin | Glyoxal | β-Endorphin |
| Creatinine | Hippuric acid | Cholecystokinin |
| Cytidine | Homocysteine | Clara cell protein |
| Guanidine | Hydroquinone | Complement factor D |
| Guanidinoacetic acid | Indole-3-acetic acid | Cystatin C |
| Guanidinosuccinic acid | Indoxyl sulfate | Degranulation inhibiting protein I |
| Hypoxanthine | Kinurenine | Delta-sleep-inducing peptide |
| Malondialdehyde | Kynurenic acid | Endothelin |
| Methylguanidine | h...al | Hyaluronic acid |
| Myoinositol | Carbox...eth | Interleukin 1β |
| Orotic acid | 2-cresc... | Interleukin 6 |
| Orotidine | entosome | Kappa-Ig light chain |
| Oxalate | Phenol | Lambda-Ig light chain |
| Pseudouridine | P-OHhippuric acid | Leptin |
| Symmetric dimethylarginine | Quinolinic acid | Methionine-enkephalin |
| Urea | Spermidine | Neuropeptide Y |
| Uric acid | Spermine | Parathyroid hormone |
| Xanthine | | Retinol Binding Protein |
| | | Tumor Necrosis Factor Alpha |



Renal Replacement Therapy Adequacy

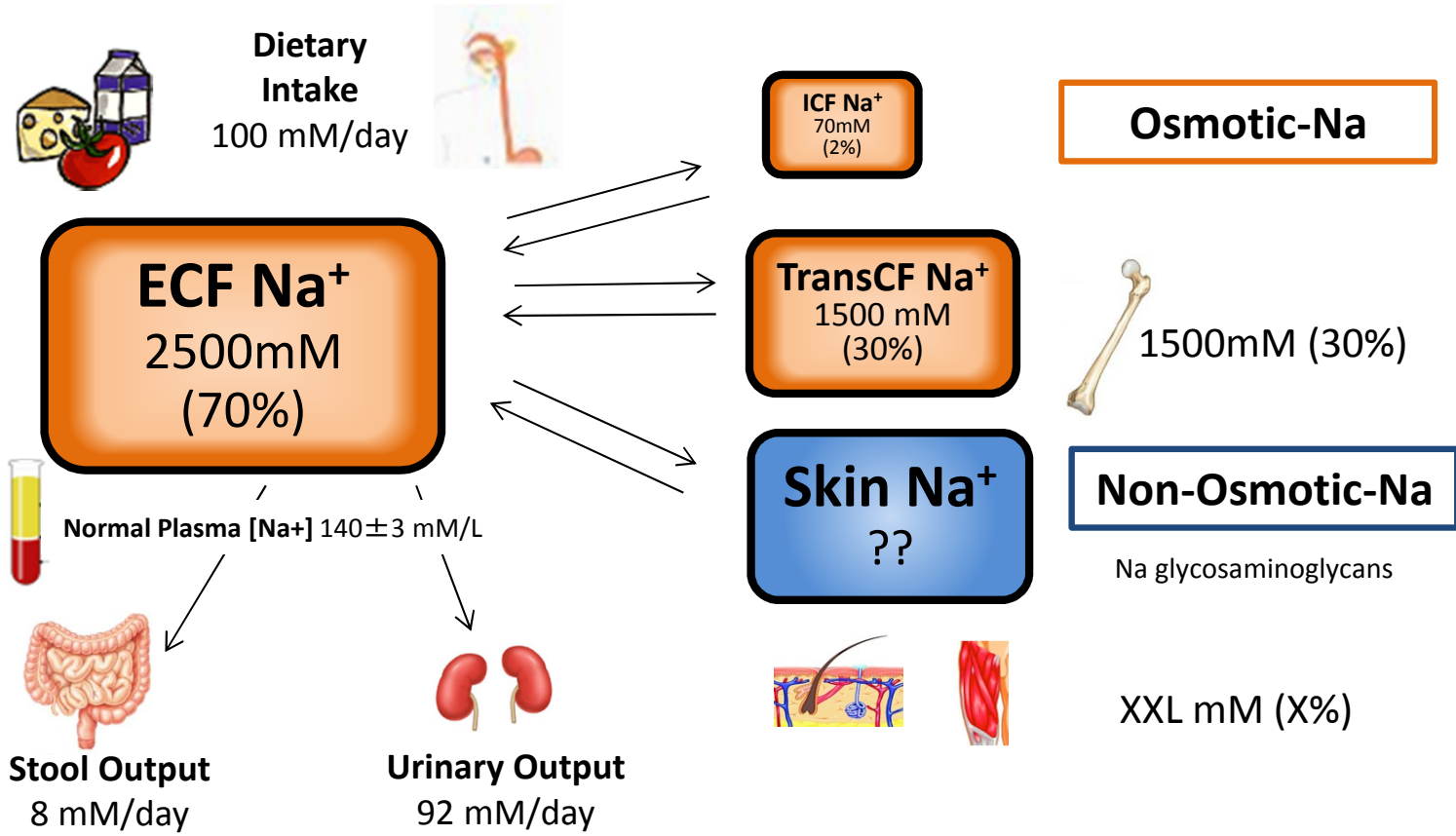
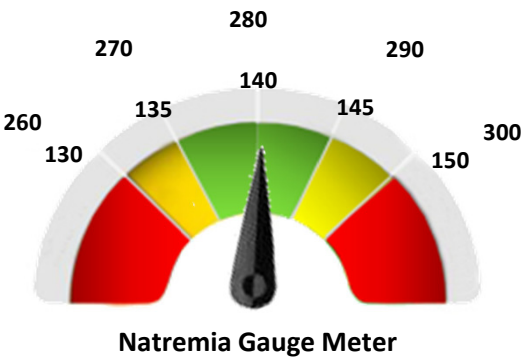
Na Mass Balance, Fluid Control & Blood Pressure: Neglected Component



Sodium Mass Balance in Normal Subject

Sodium Homeostasis – Zero Balance

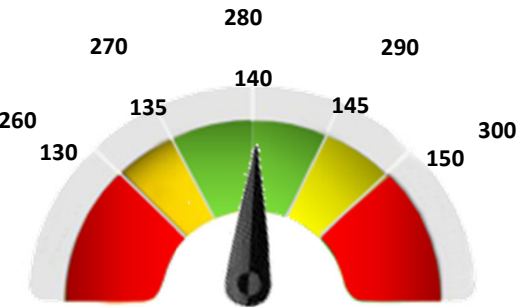
[Osmostat] mosm/Kg



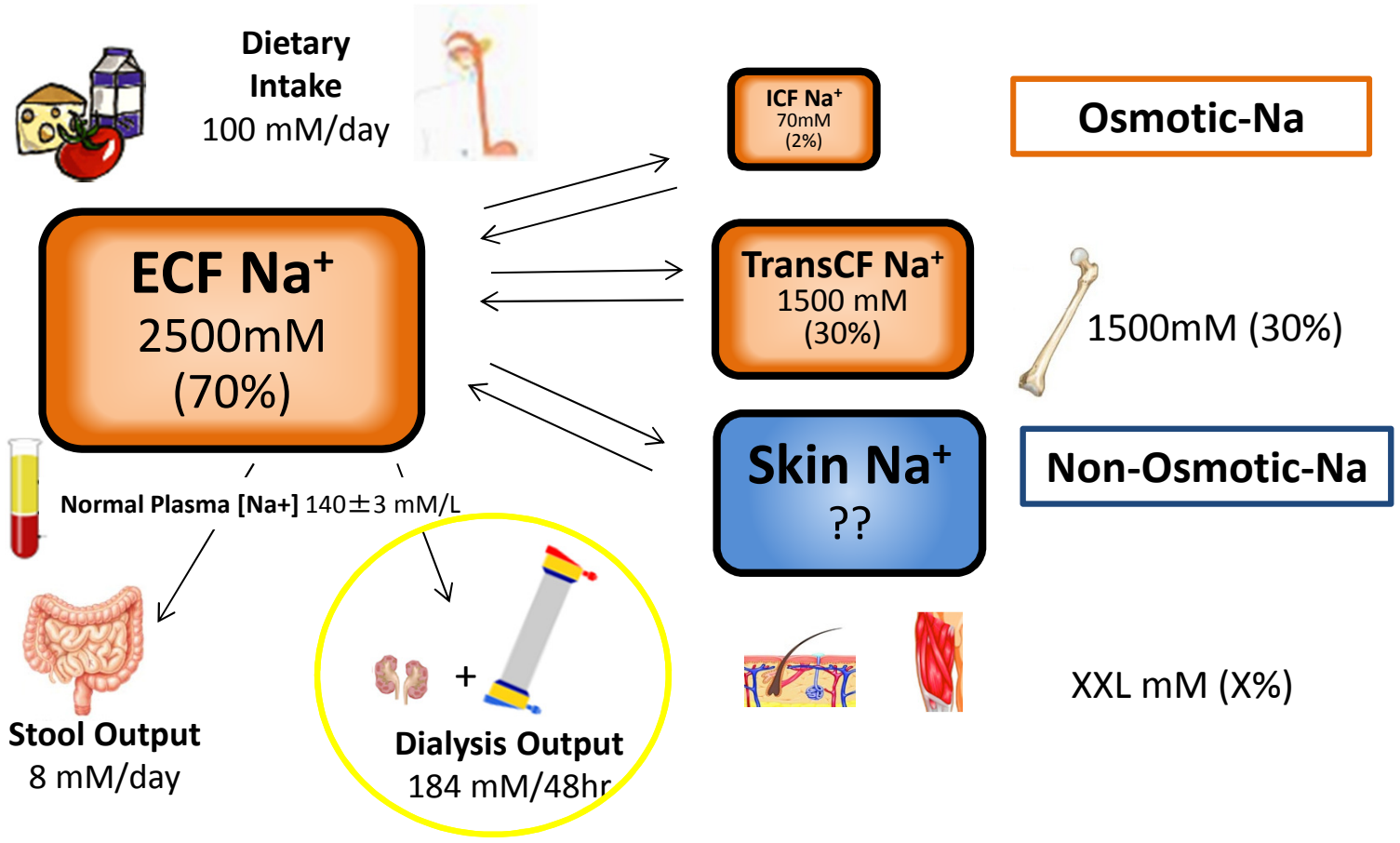
Sodium Mass Balance in Hemodialysis Patient

Restore Sodium Homeostasis

[Osmostat] mosm/Kg

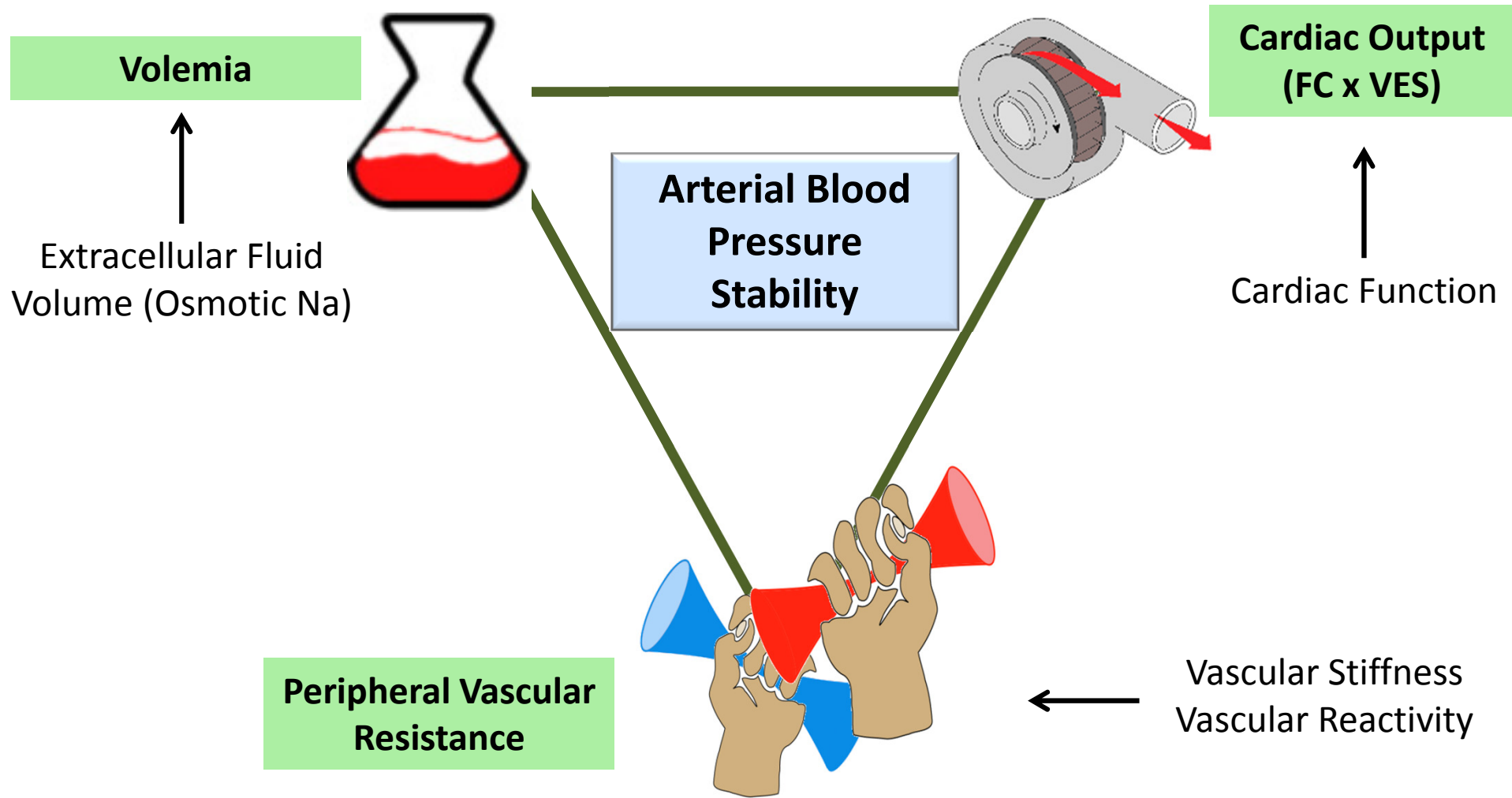


Natremia Gauge Meter



Arterial Blood Pressure Equilibrium

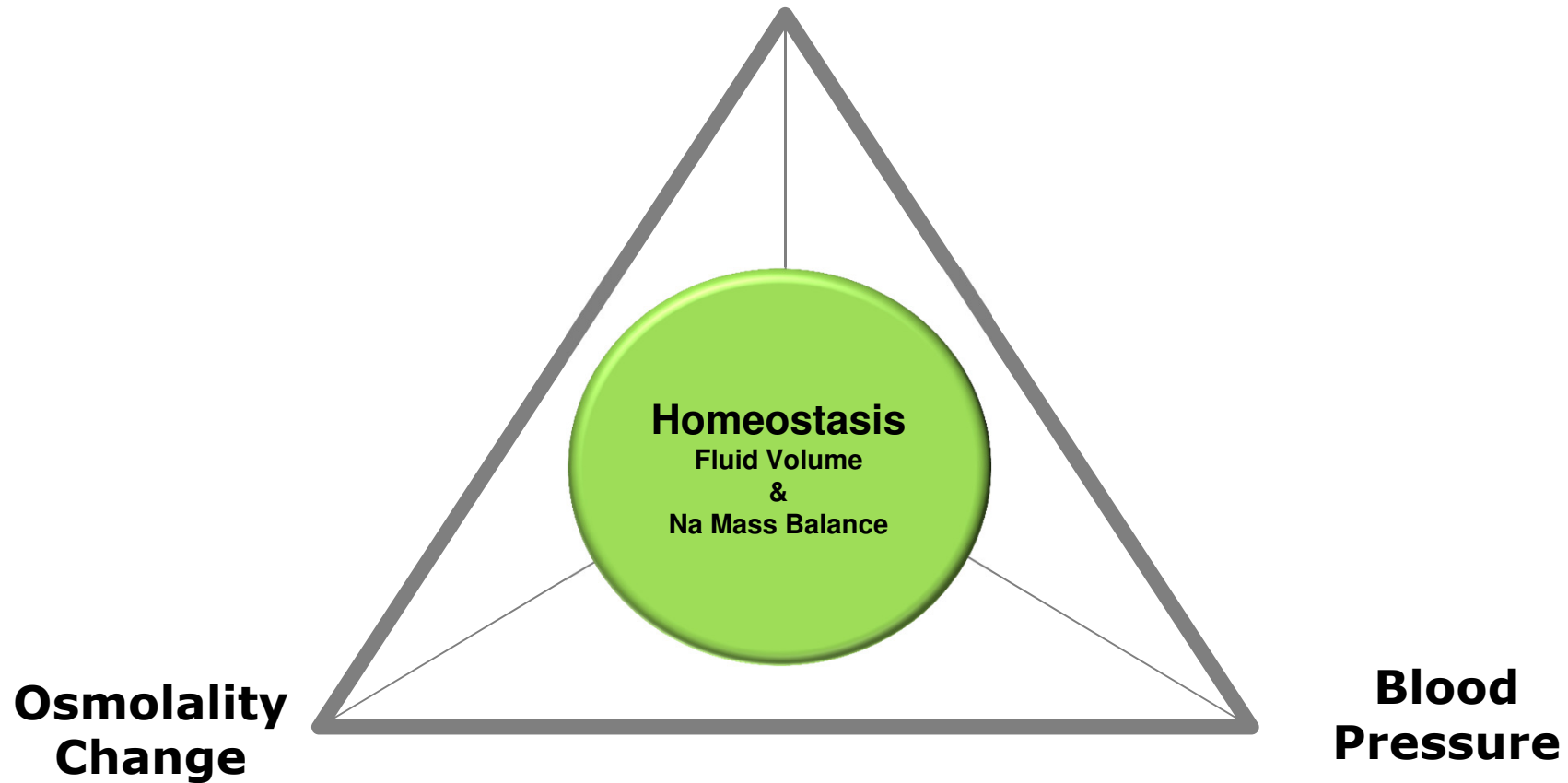
Mechanistic Approach



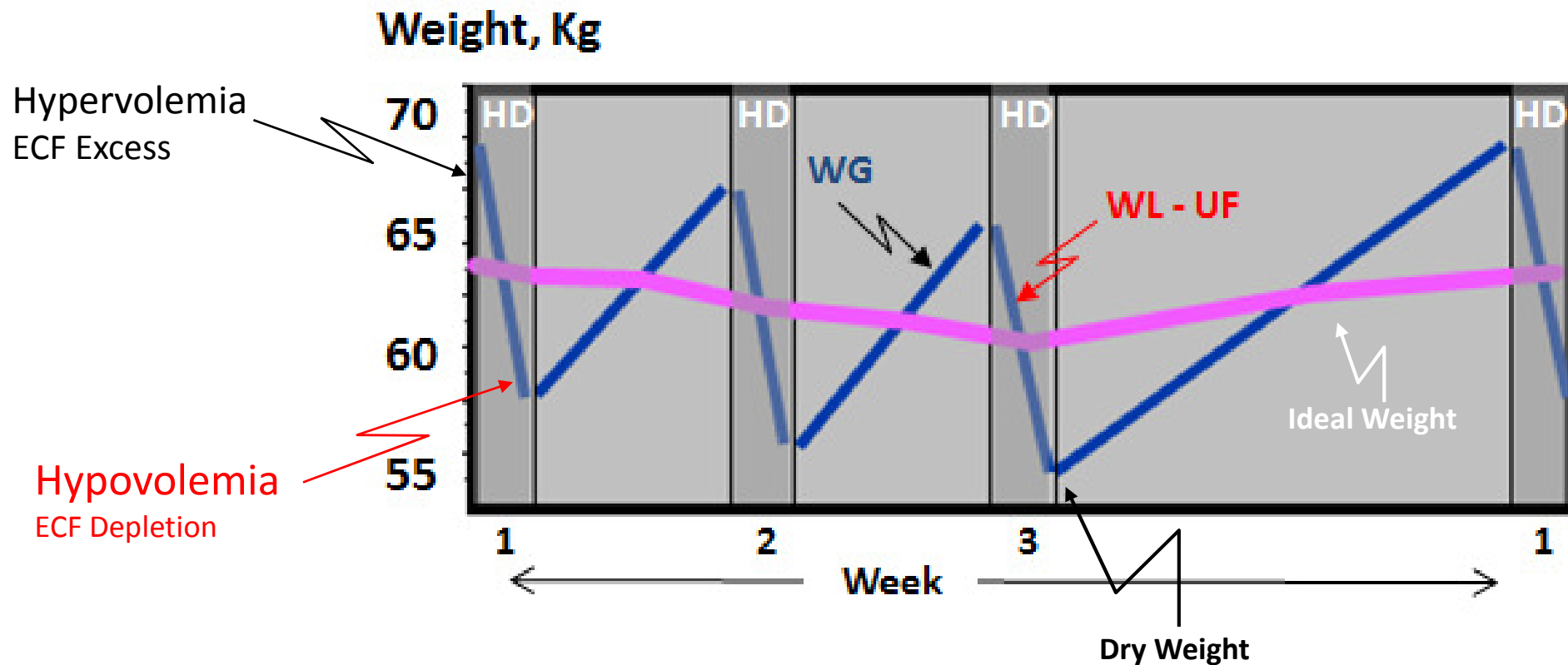
Management of Na Mass Balance & Fluid Volume

'Challenging Situation' with Intermittent Treatment

Na & Fluid Mass Balance
Extracellular Volume (volemia)



Weight Changes During HD Cycles

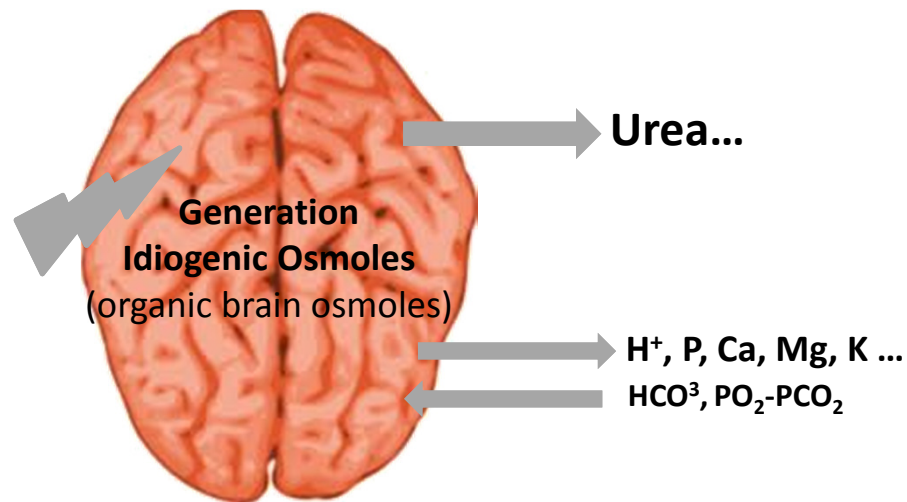


Osmolality Changes During HD Cycles

Brain Consequences

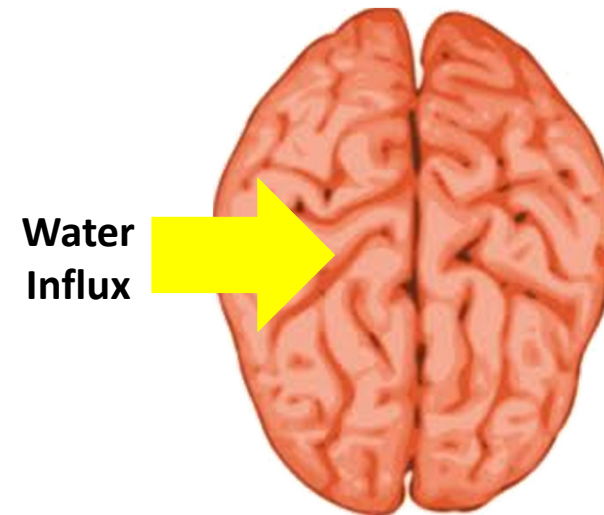
Disequilibrium Syndrome = osmolality, water shift and brain changes

Osmolality Changes
ECF/CSF/ICF



Brain during Hemodialysis

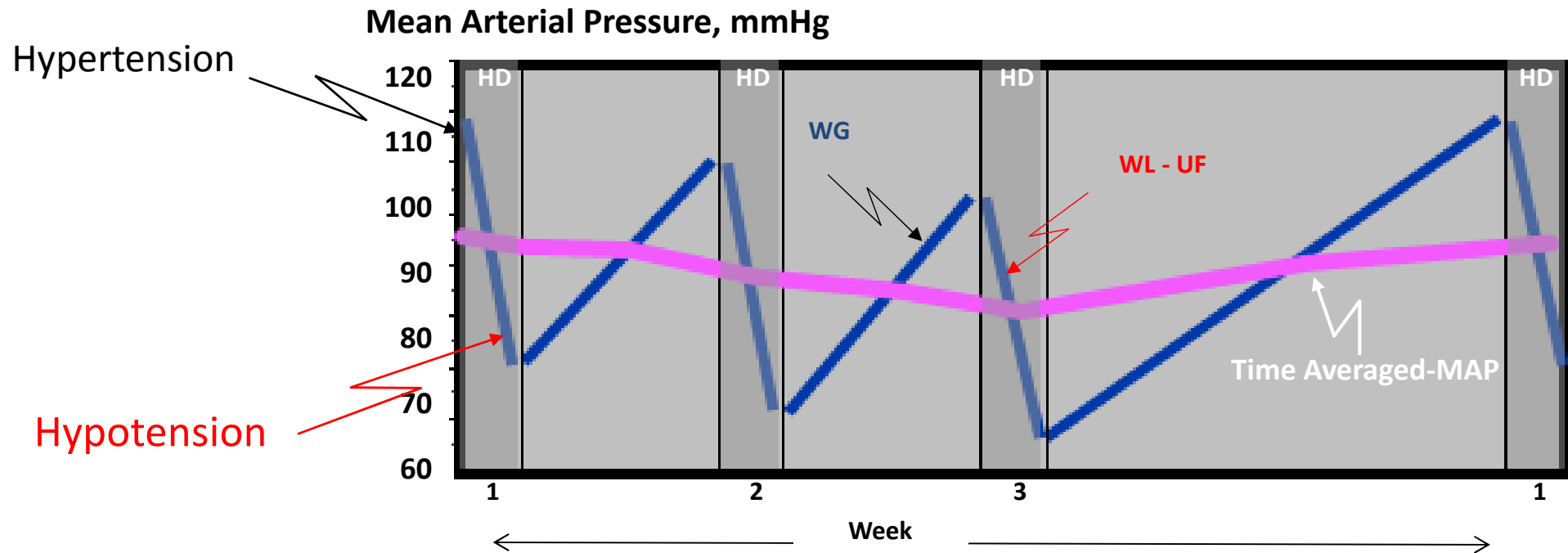
Osmolality Changes
Water Shift



Brain Edema

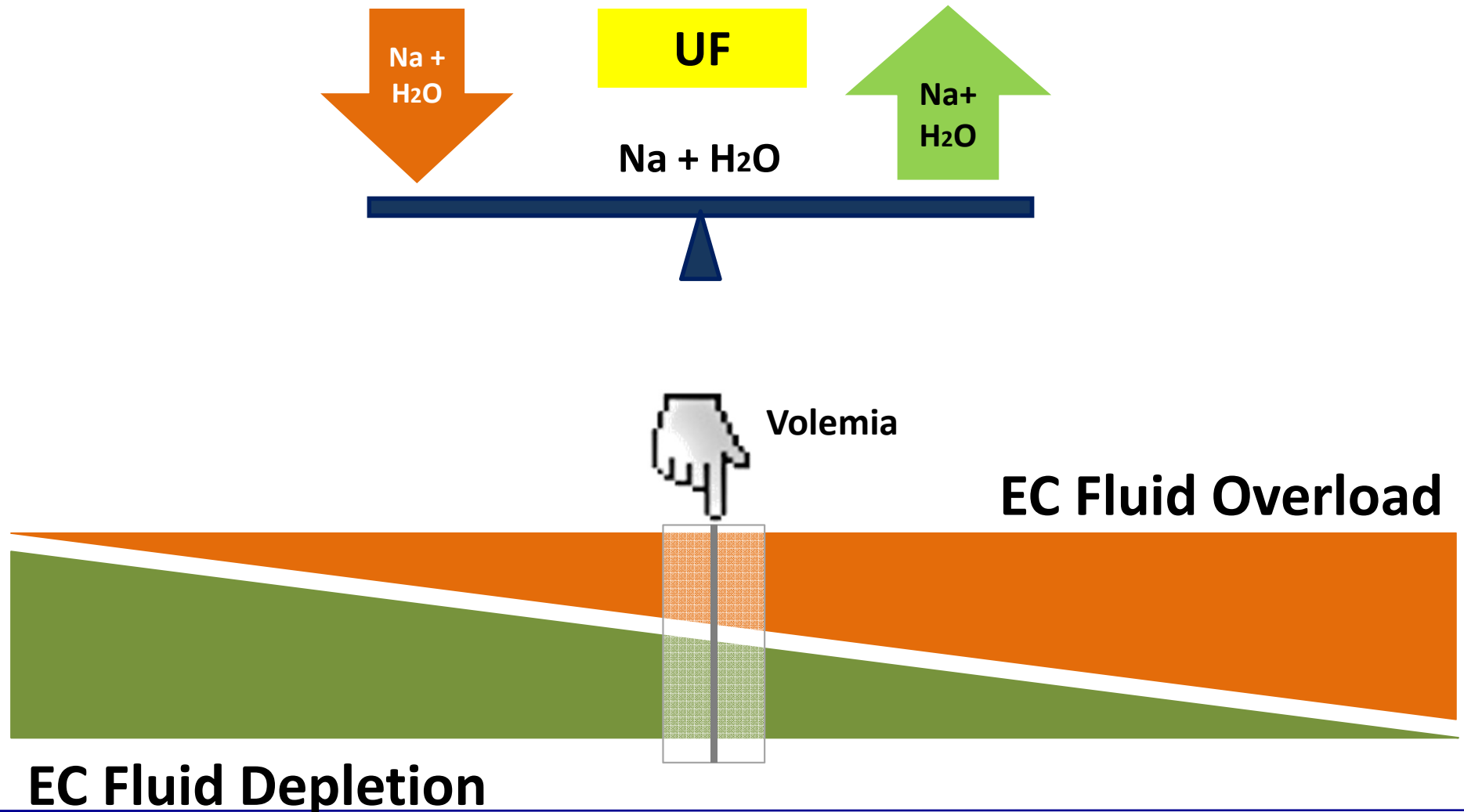
Arterial Blood Pressure Changes During HD Cycles

Mean Arterial Pressure



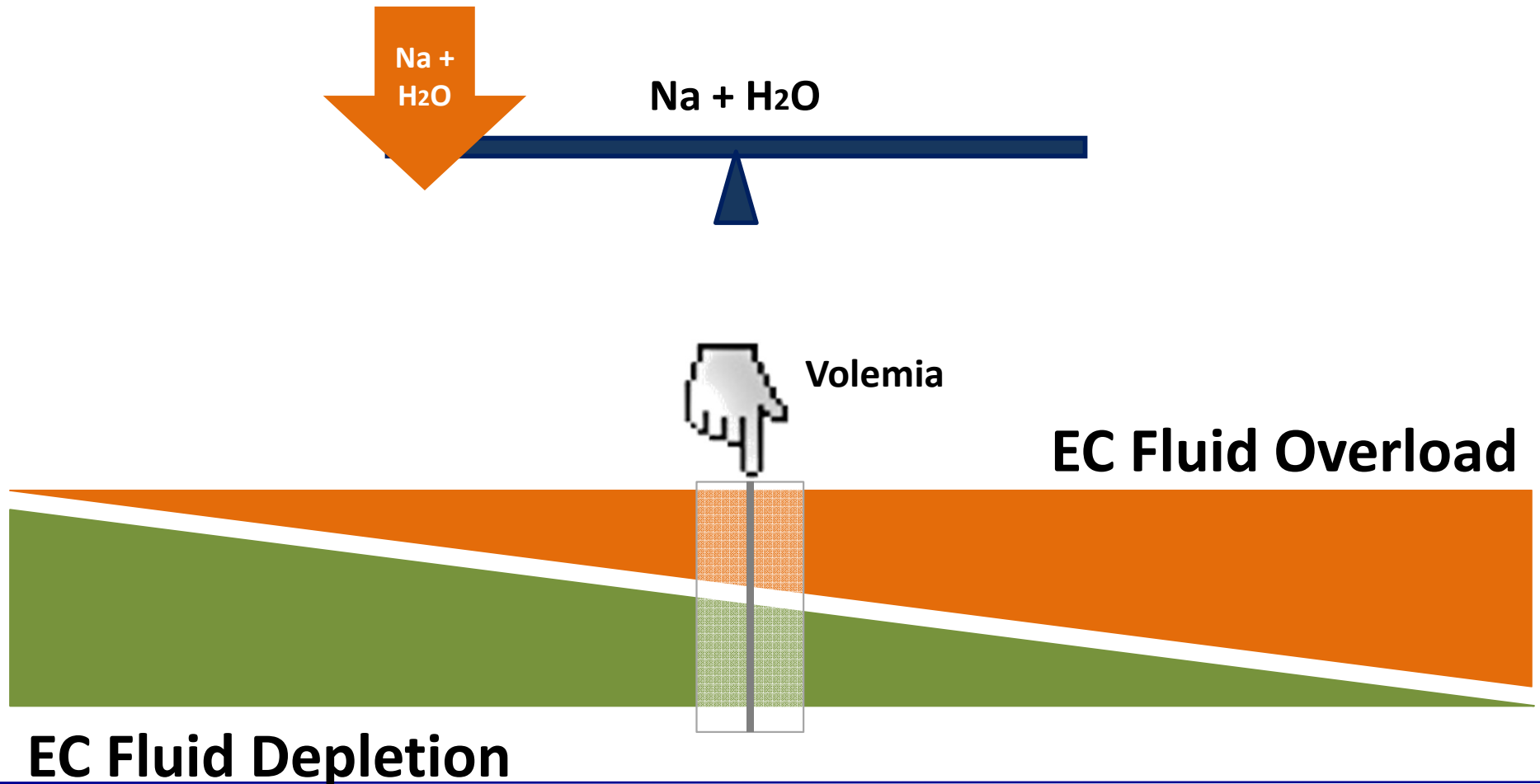
Na & Fluid Mass Balance in Intermittent HD

A Trade-Off Situation



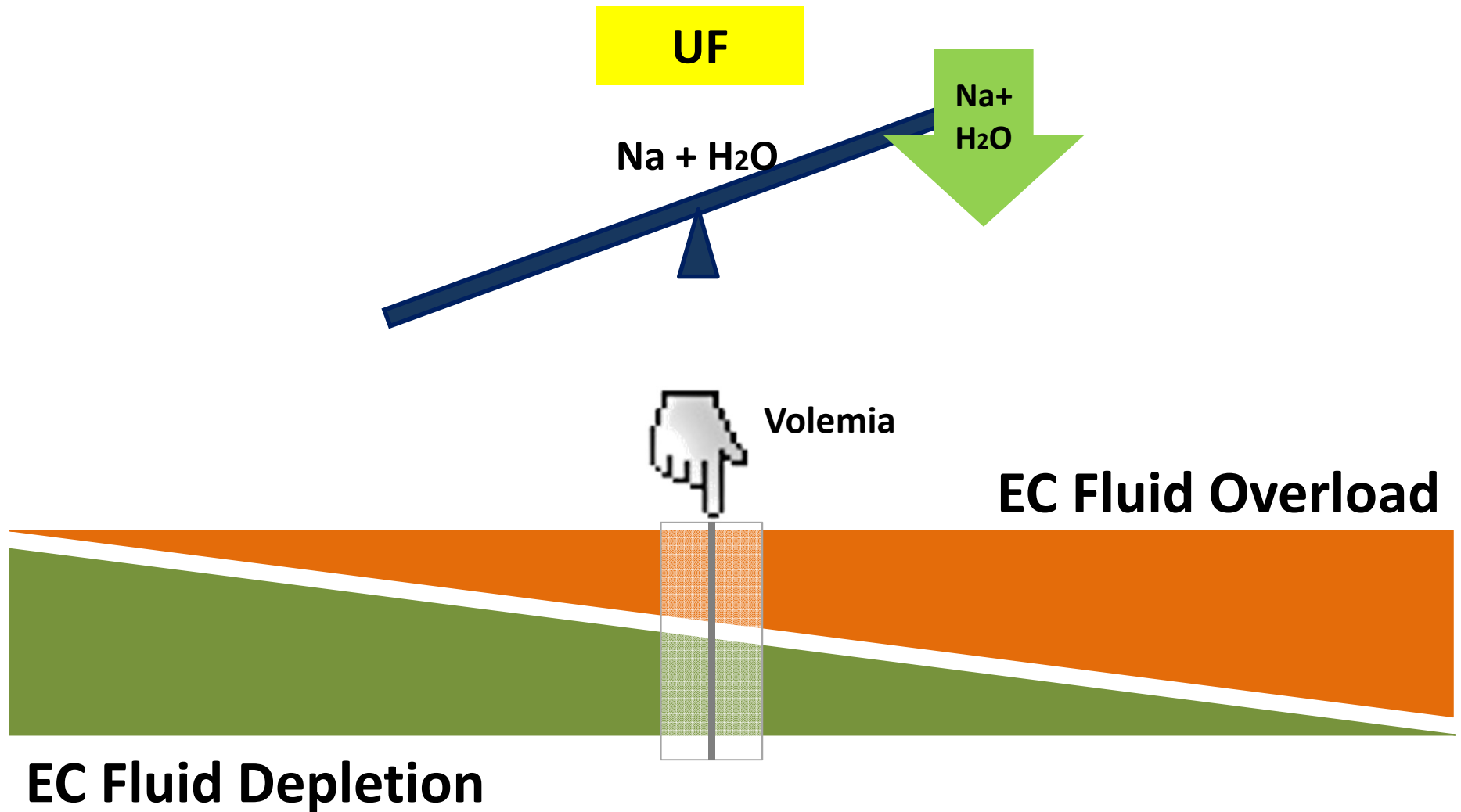
Na & Fluid Mass Balance in Intermittent HD

Interdialytic Period = Na and Fluid Gain



Na & Fluid Mass Balance in Intermittent HD

Intradialytic Period = Na and Fluid Depletion



Volemia Changes

Unphysiologic State

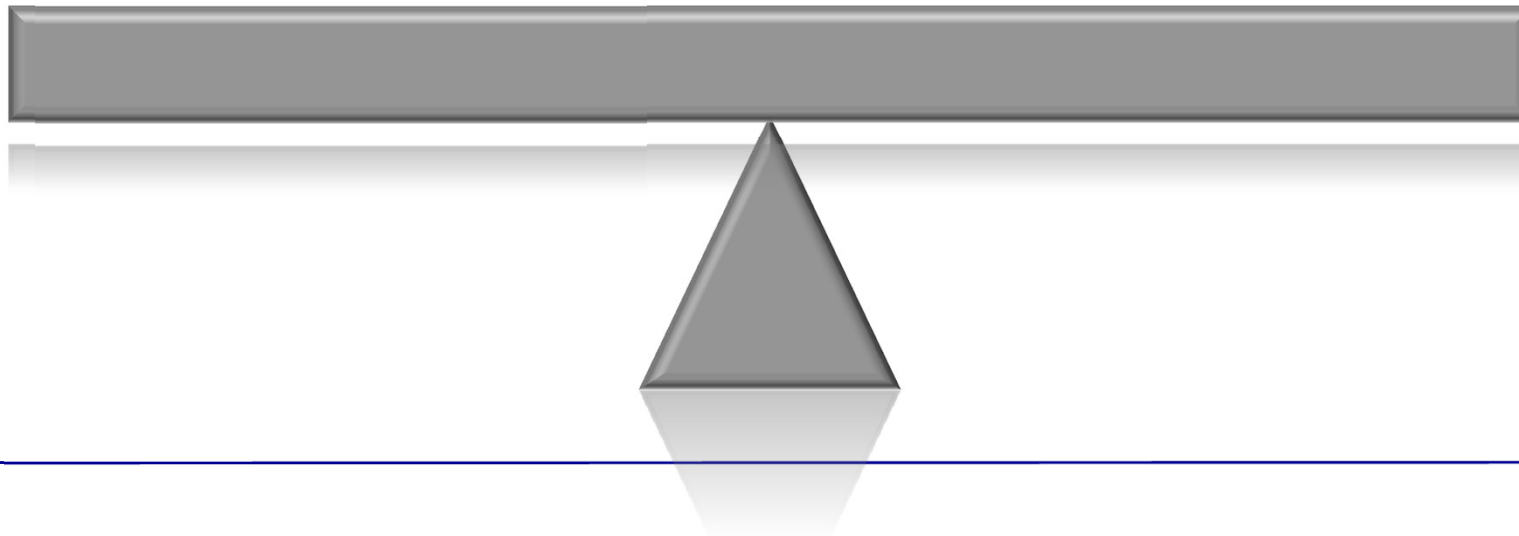
Interdialytic

=

Intradialytic

Hypervolemia

Hypovolemia

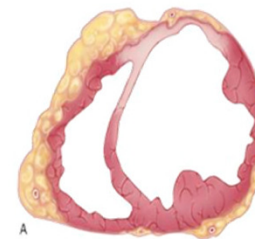


EC Fluid Overload : Consequences

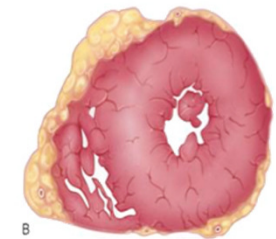
- Hypertension
- Cardiac remodeling :
 - Dilation – Hypertrophy
- Arterial vascular remodeling :
 - Stiffness – Endothelial dysfunction
- Lung edema :
 - Lung hypertension - Fibrosis
- Additional side effects :
 - Inflammation – Anemia
 - Malnutrition...



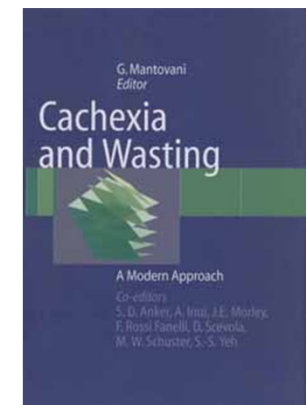
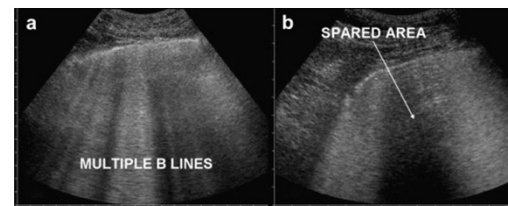
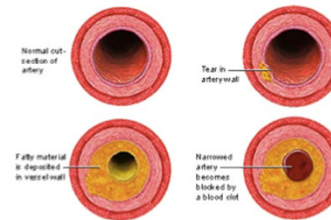
Hypertension
Na Mass Excess...



A Dilated cardiomyopathy



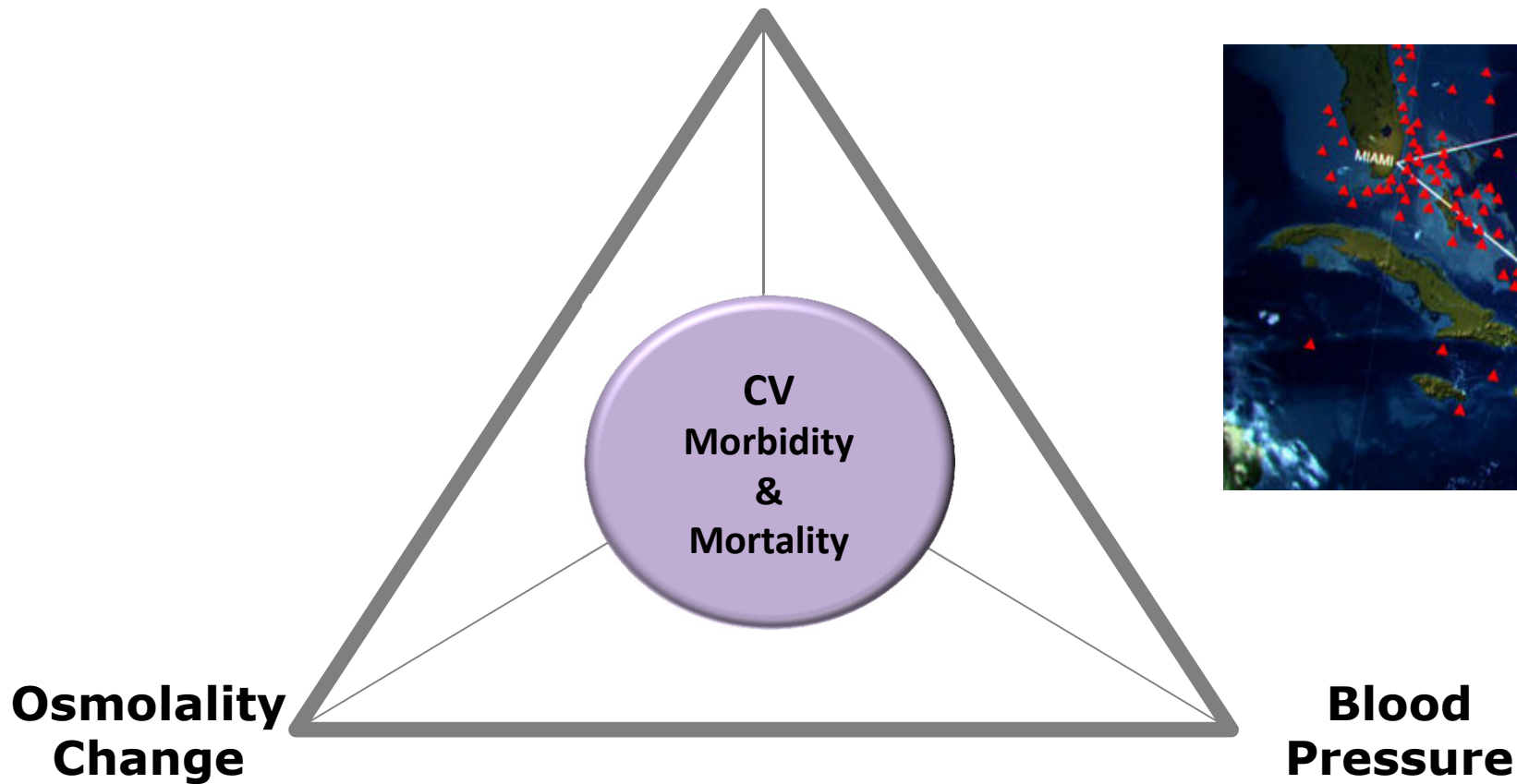
B Hypertrophy cardiomyopathy



Management of Na Mass Balance & Fluid Volume

'Bermuda Triangle' for HD Patient

Na & Fluid Mass Balance
Extracellular Volume (volemia)



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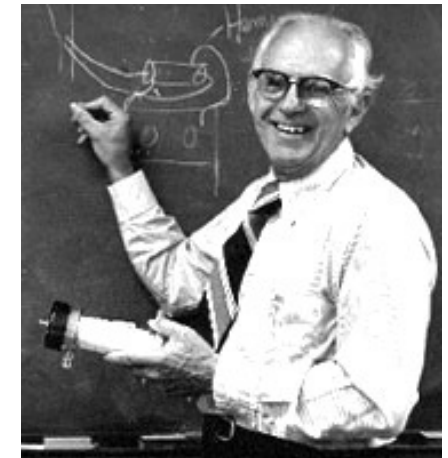
Intra Dialytic Hypotension (IDH)

Definition of Symptomatic Hypotension

- Various definitions in scientific studies have created lot of confusion in research studies.
- European Best Practice Guidelines (EBPG) define intradialytic hypotension (IDH) as **both a fall in blood pressure and the occurrence of symptoms needing an intervention.**
- A **fall in SBP by at least 20mmHg** or a decrease in mean arterial pressure by at least 10mmHg is required to qualify for the diagnosis of hypotension.

Intra Dialytic Hypotension

A Quite Common Phenomenon in the Pioneering Phase of Dialysis

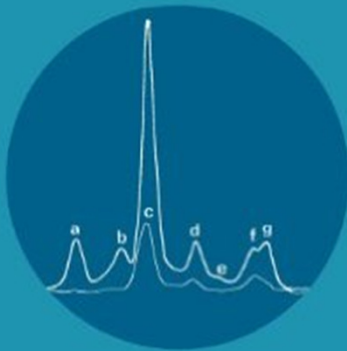


Scribner BH, Buri R, Caner JEZ, Hegstrom R, Burnell JM. The treatment of chronic uremia by means of intermittent hemodialysis: a preliminary report. *Trans Am Soc Artif Intern Organs.* 1960;6:114-122.

IntraDialytic Hypotension Reduced Over Time

replacement of renal function by dialysis

edited by William Drukker, Frank M. Parsons and John F. Maher



Martinus Nijhoff 1979

Hypotension

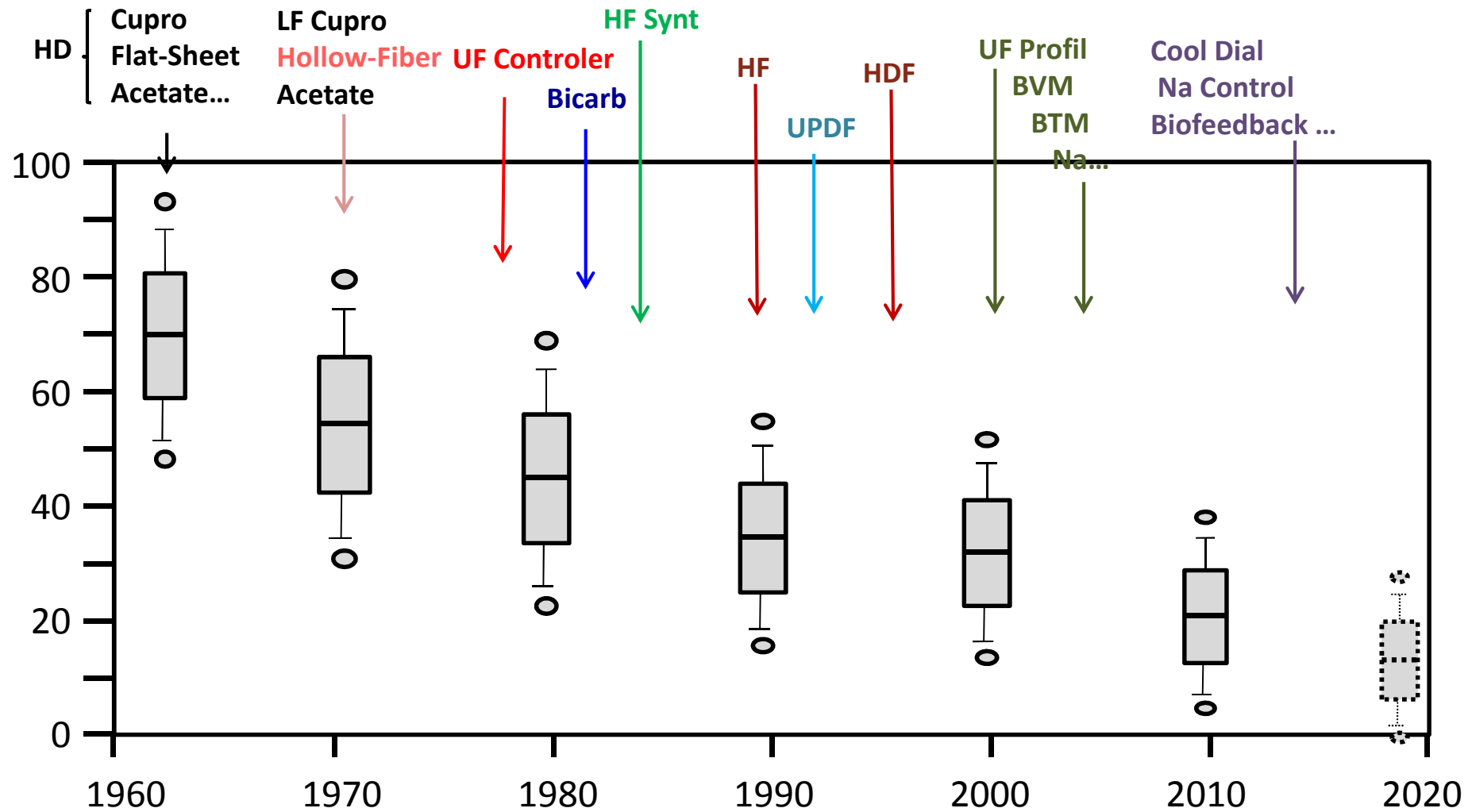
Episodes of hypotension occur in 20% to 30% of all hemodialyses (5, 6), and relate to various factors affecting cardiac output and systemic vascular resistance (7, 8). Cardiac output depends on myocardial contractility and filling volume, which in turn relates to vascular volume and heart rate. the increase (systemic vas

The role of acetate and hypoxemia

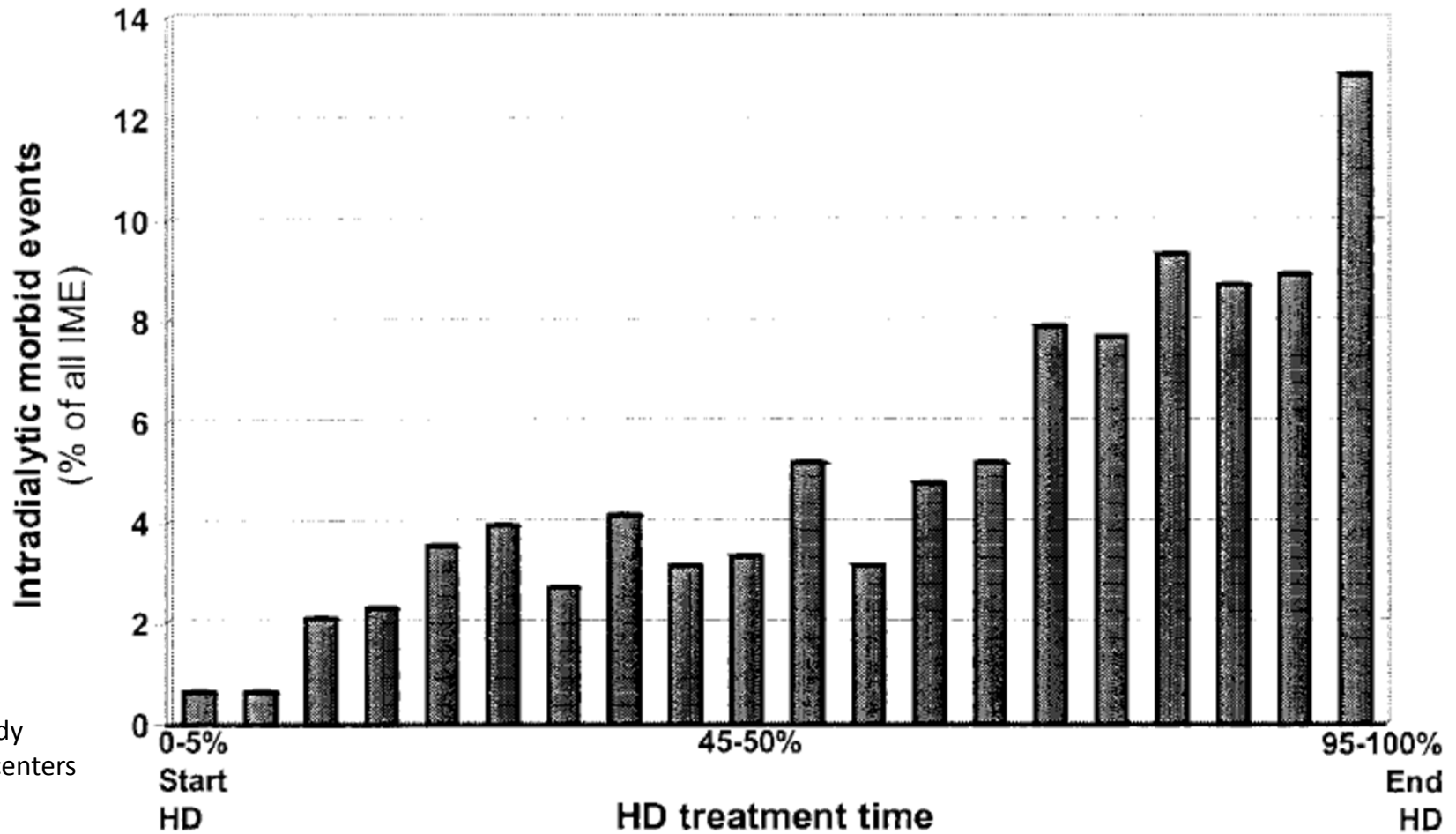
With development of automated single-pass dialysis equipment in the 1960s, acetate became the standard anion in dialysate, replacing bicarbonate because of the need to prevent precipitation of calcium and magnesium (18). Acetate is readily metabolized in the body, resulting in the regeneration of bicarbonate from carbon dioxide (19).

More recently, with larger surface area dialyzers and more rapid dialysis, transport of acetate into blood can occur at a rate exceeding the capacity of the body to metabolize it, and this is associated with hypotension (20, 21). Acetate ion is a vasodilator (22), and during dialysis the drop in systemic

Incidence of Intradialytic Hypotension



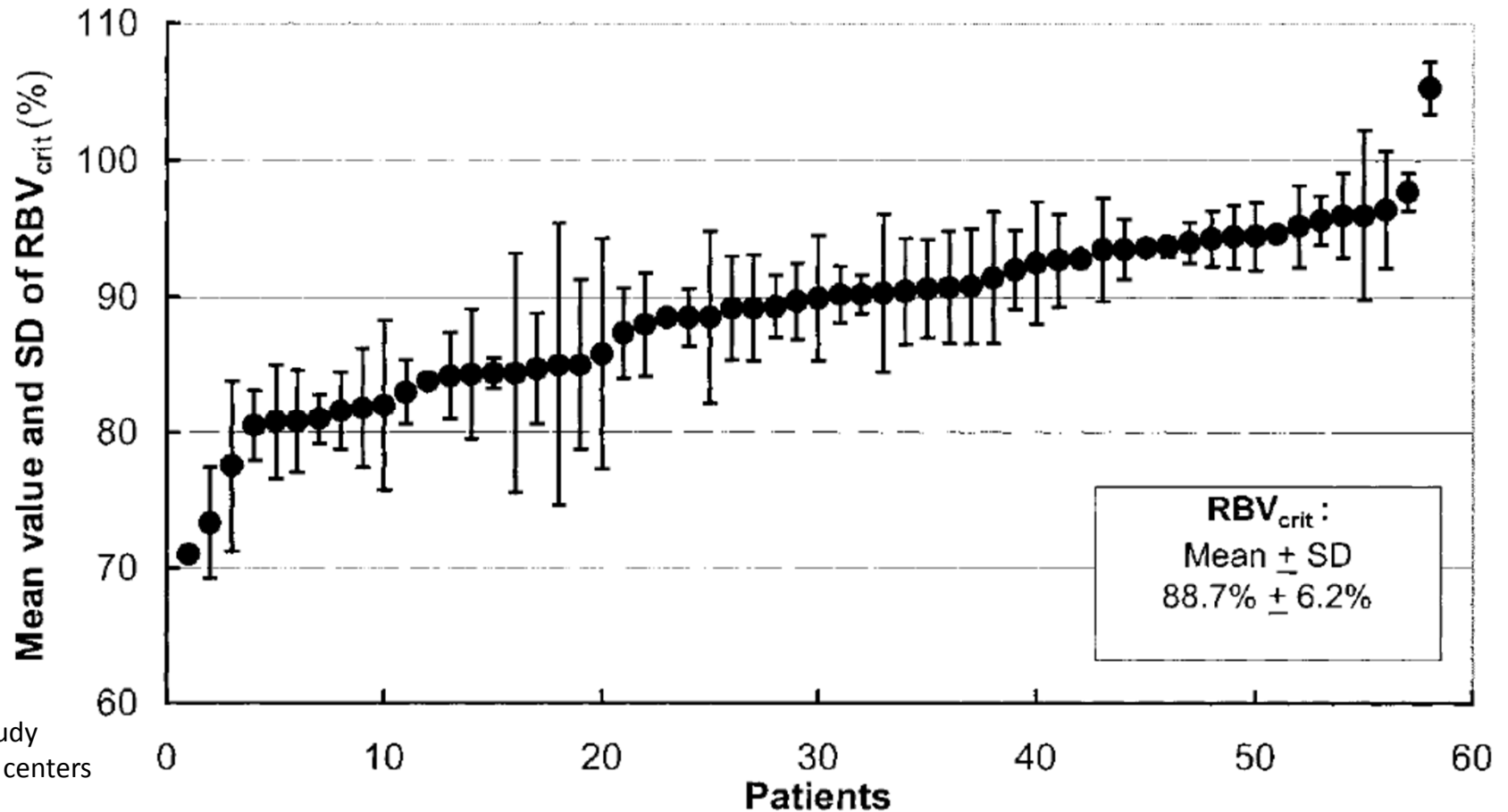
Distribution of IDH Over HD Session



Prospective multicenter study
60 IDH prone pts 9 dialysis centers
Monitored 21 HD sessions
No intervention
RBV changes monitored

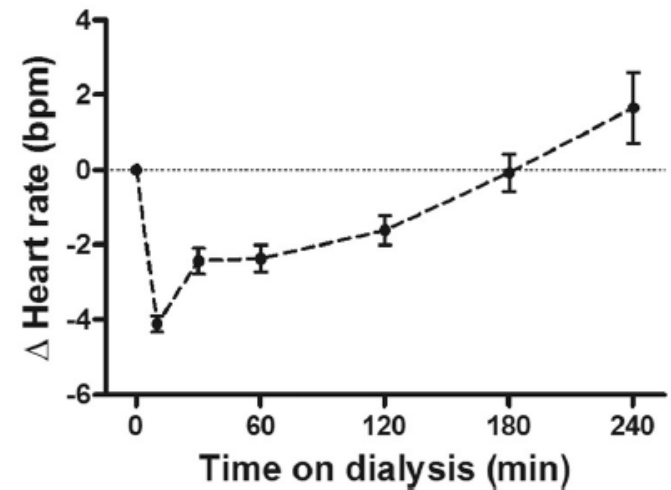
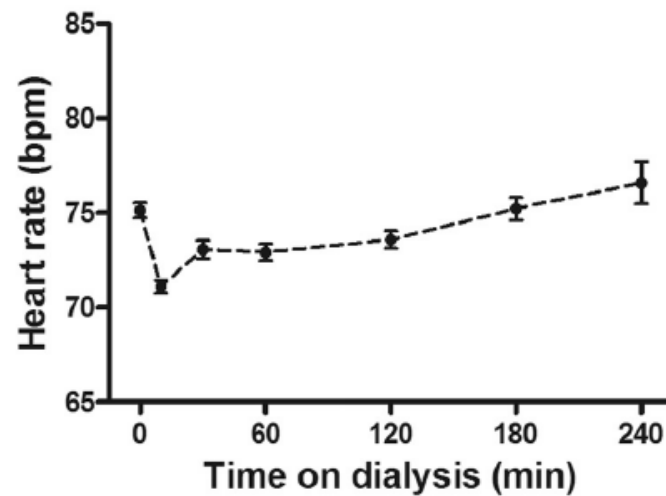
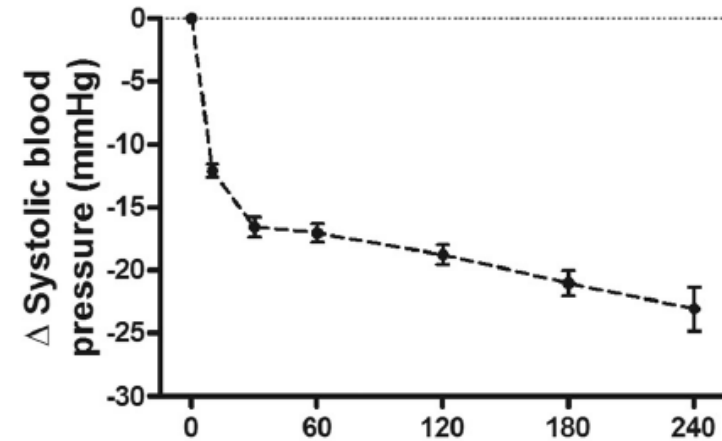
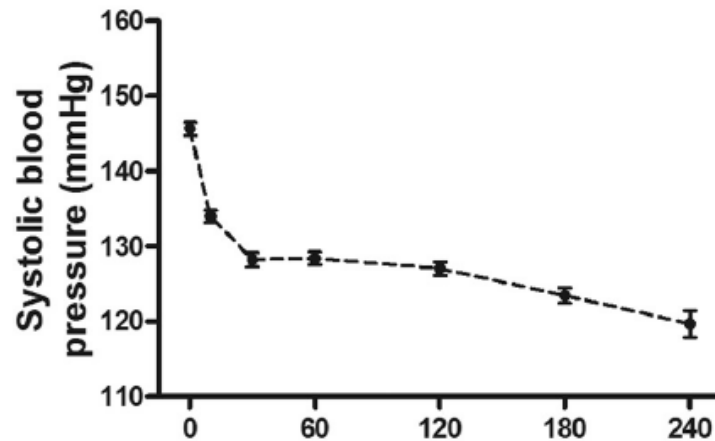
Individual Relative Blood Volume Changes

Relative Critical Volume is Individual



Prospective multicenter study
60 IDH prone pts 9 dialysis centers
Monitored 21 HD sessions
No intervention
RBV changes monitored

Hemodynamic Changes Occurring During HD Sessions



University Medical Center Groningen
Incenter Dialysis Unit – 3 mo prospective study

Hemodynamic data - EBPG definition
124 adult HD pats – 3818 HD sessions

Prevalence of Intradialytic Hypotension, Clinical Symptoms and Nursing Interventions

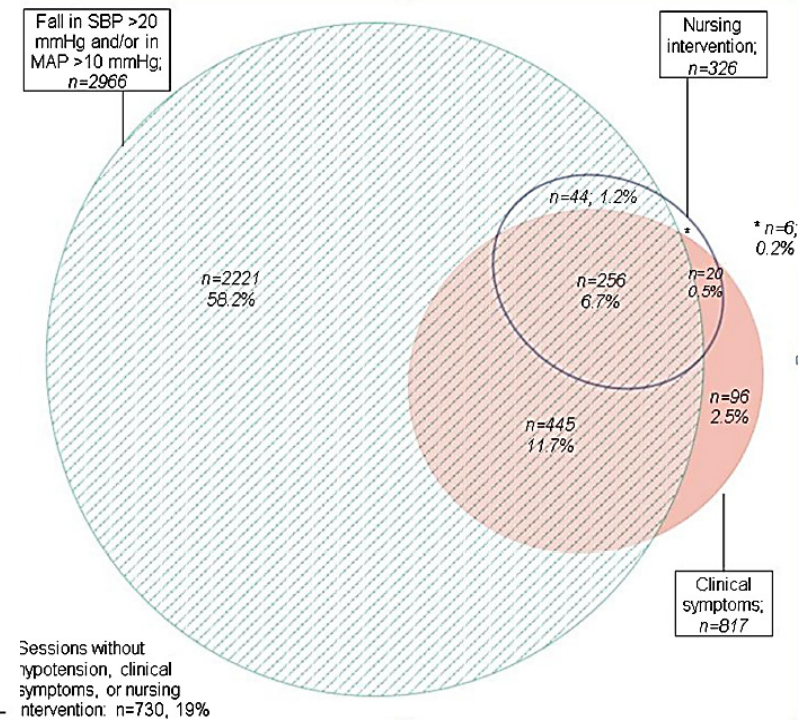
| | Nr of dialysis sessions (%) |
|--|-----------------------------|
| Blood pressure drop | |
| Decrease in SBP ≥ 20 mmHg | 2434 (63.8) |
| Clinical events | |
| Any clinical event | 817 (21.4) |
| Nursing interventions | |
| Any nursing intervention | 326 (8.5) |
| Decrease in SBP ≥ 20 mmHg or MAP ≥ 10 mmHg | 21.4 |
| Clinical symptoms | 8.5 |
| Nursing interventions | 8.5 |
| Any combination with a nursing intervention | 610 (16.0) |
| Decrease in SBP ≥ 20 mmHg | 285 (7.5) |

Prevalence(%)

Decrease in SBP ≥ 20 mmHg or MAP ≥ 10 mmHg : 21.4

Clinical symptoms : 8.5

Nursing interventions : 8.5



Values are given as number (percentage). The total number of patients with clinical events and nursing interventions is lower than the separate items since some patients had more than one clinical event and/or intervention
 Abbreviations: BP blood pressure, SBP systolic blood pressure, MAP mean arterial blood pressure

University Medical Center Groningen
 Incenter Dialysis Unit – 3 mo prospective study Hemodynamic
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 124 adult HD pats – 3818 HD sessions

Causes of Intradialytic Hypotension

Dialysis-Related Factors

Acetate Buffer

Bioincomp-
-atibility

Dialysate Contamination

Thermal Balance

Osmolality Change

Hypovolemia

Hypoxemia

Electrolytes
Ca, Mg

Cardiac Impairment

Intradialytic Hypotension

Treatment Time

Vascular Impairment

High Ultrafiltration

Autonomic Dysfunction

Medications

Renal Residual Function

Imbalance UFR/RR

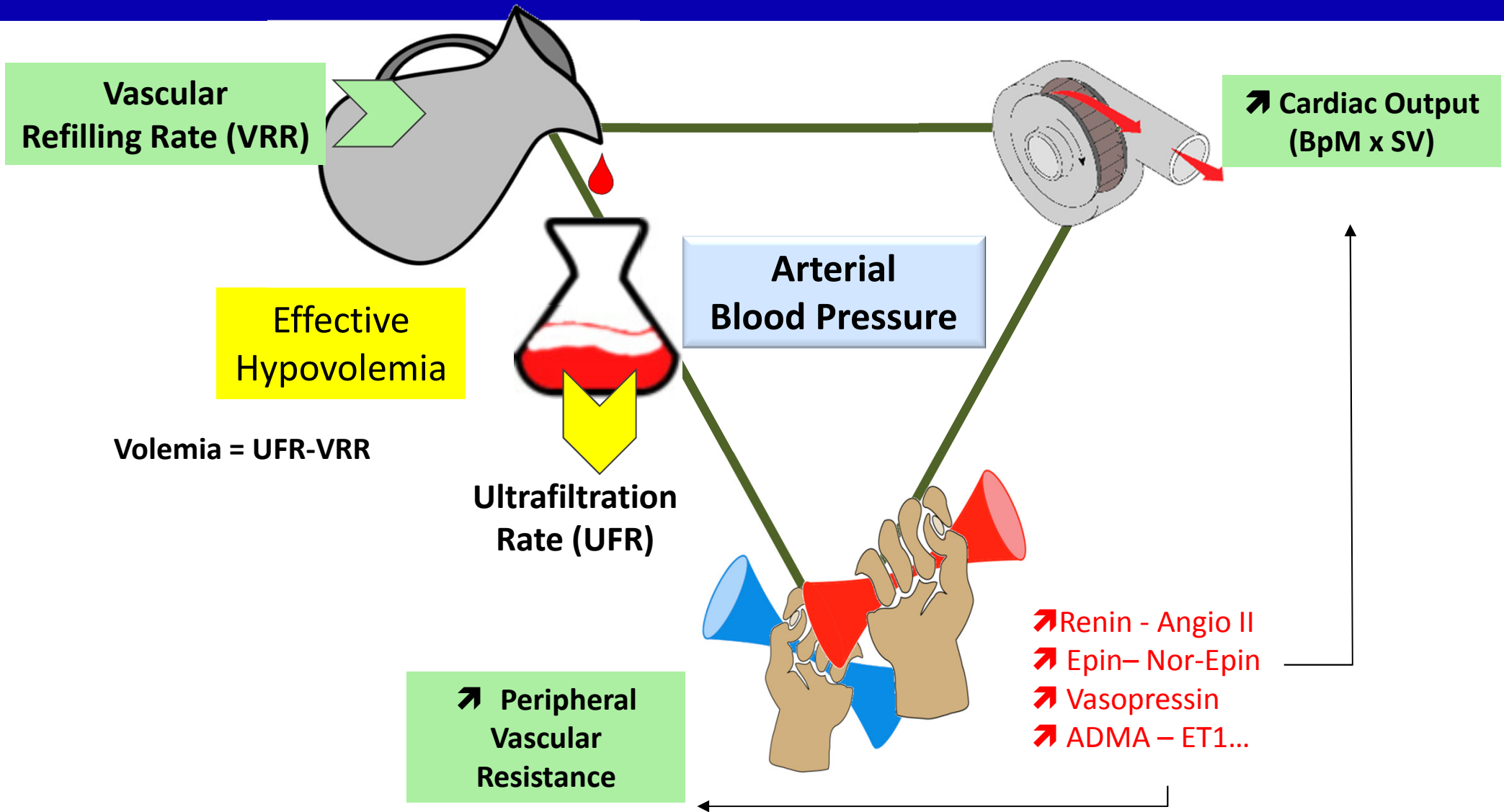
Hemodynamic Reserve

Control Uremia

Patient-Related Factors

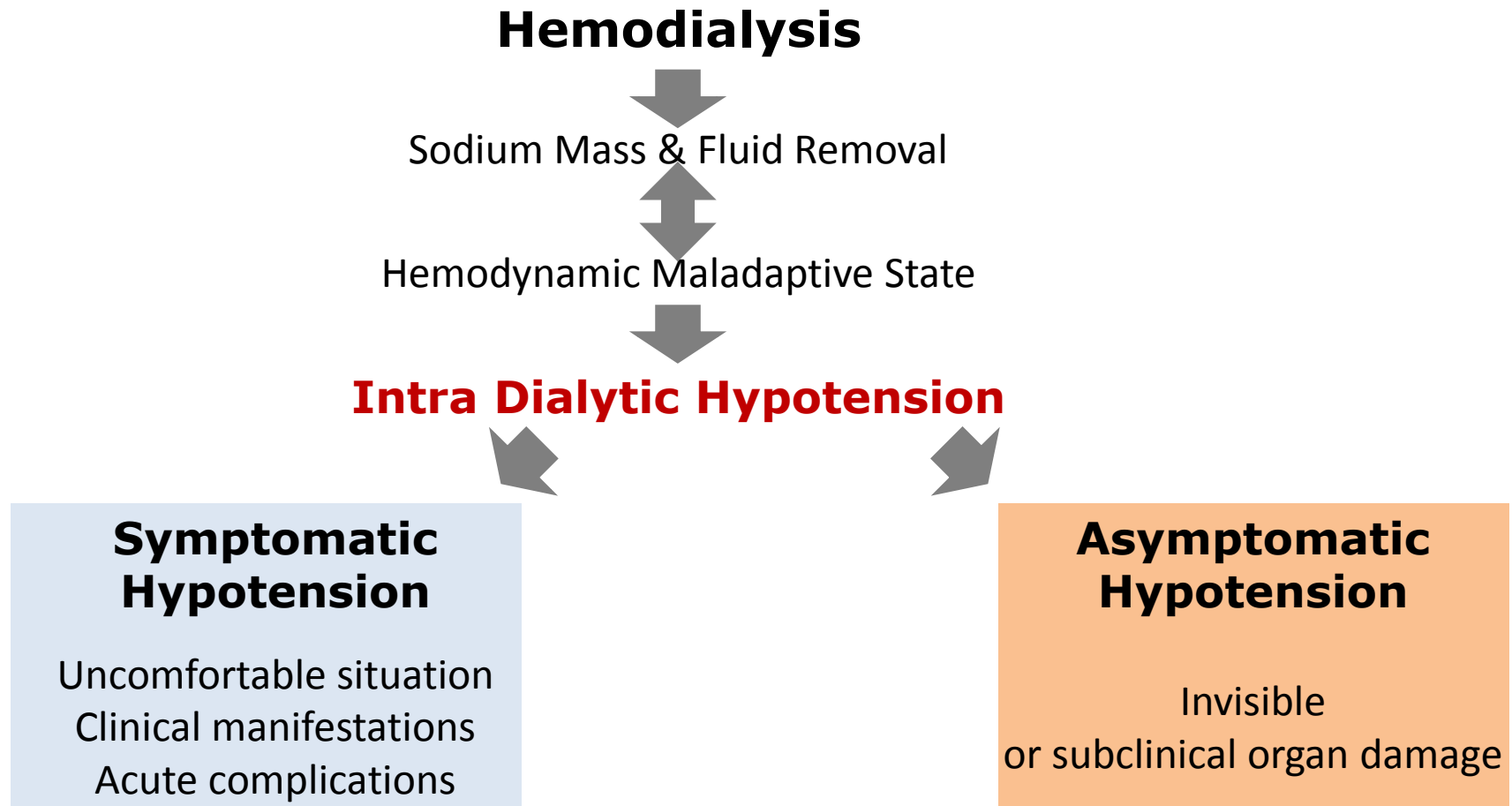
Prescription-Related Factors

Factors Preserving Hemodynamic Stability during HD with Ultrafiltration

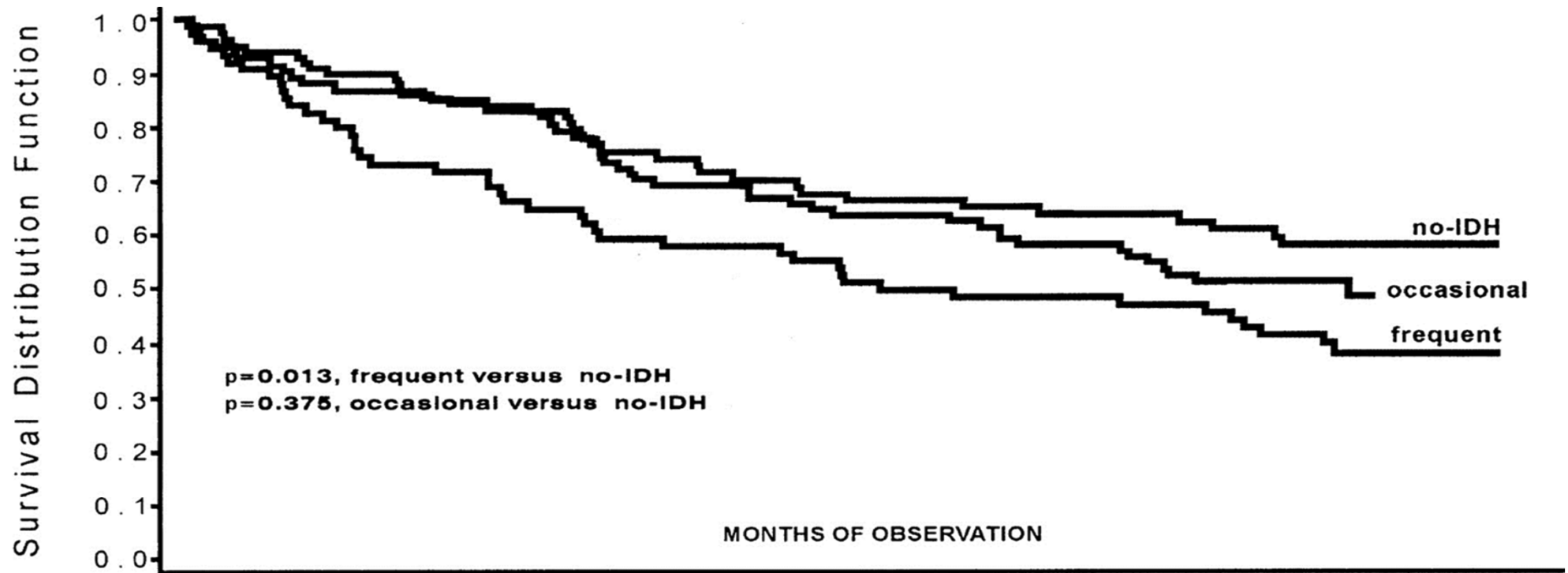


Intra Dialytic Hypotension

Maladaptive State

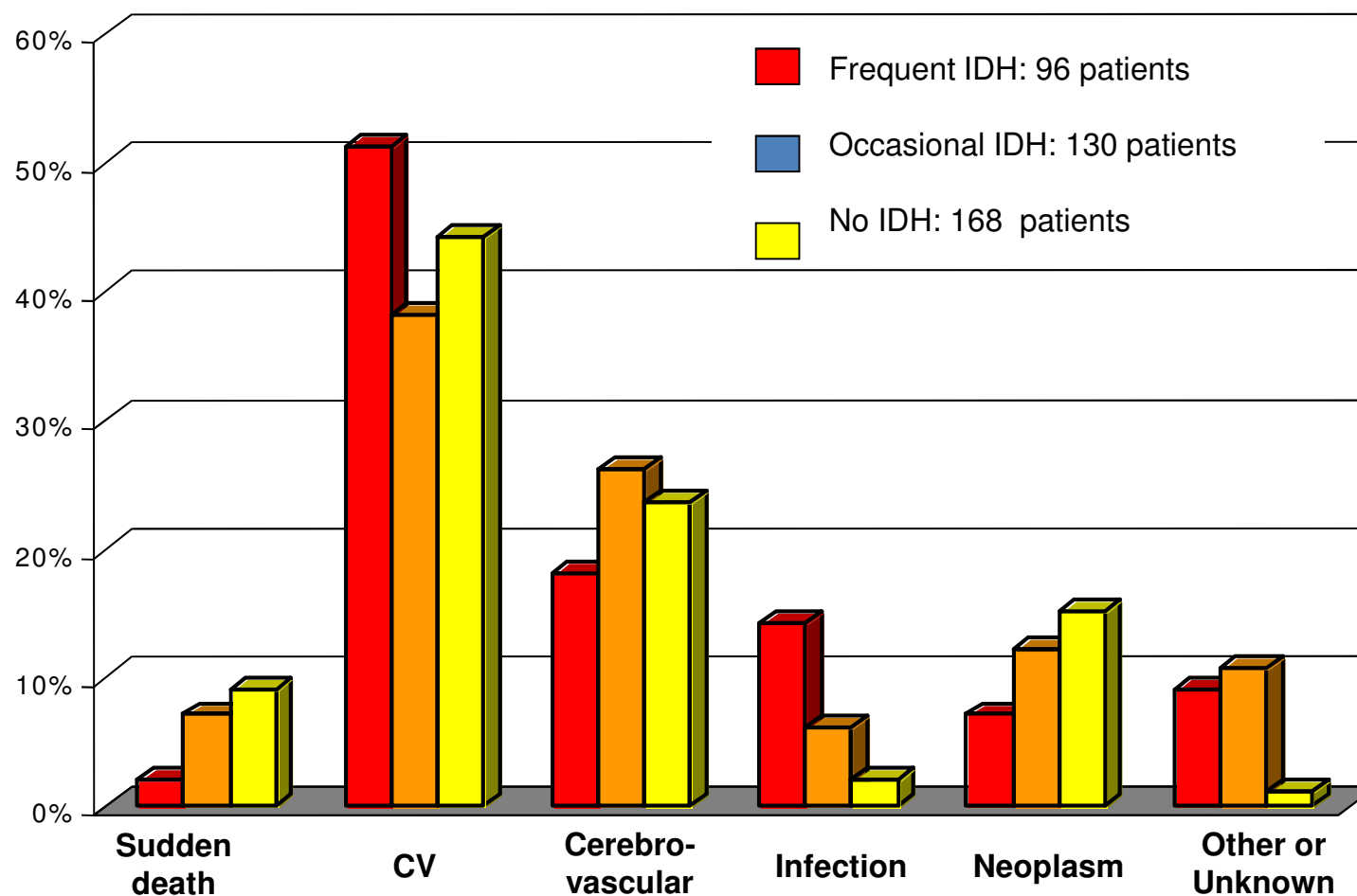


Survival Curves of Patients With Frequent, Occasional or No IntraDialytic Hypotension

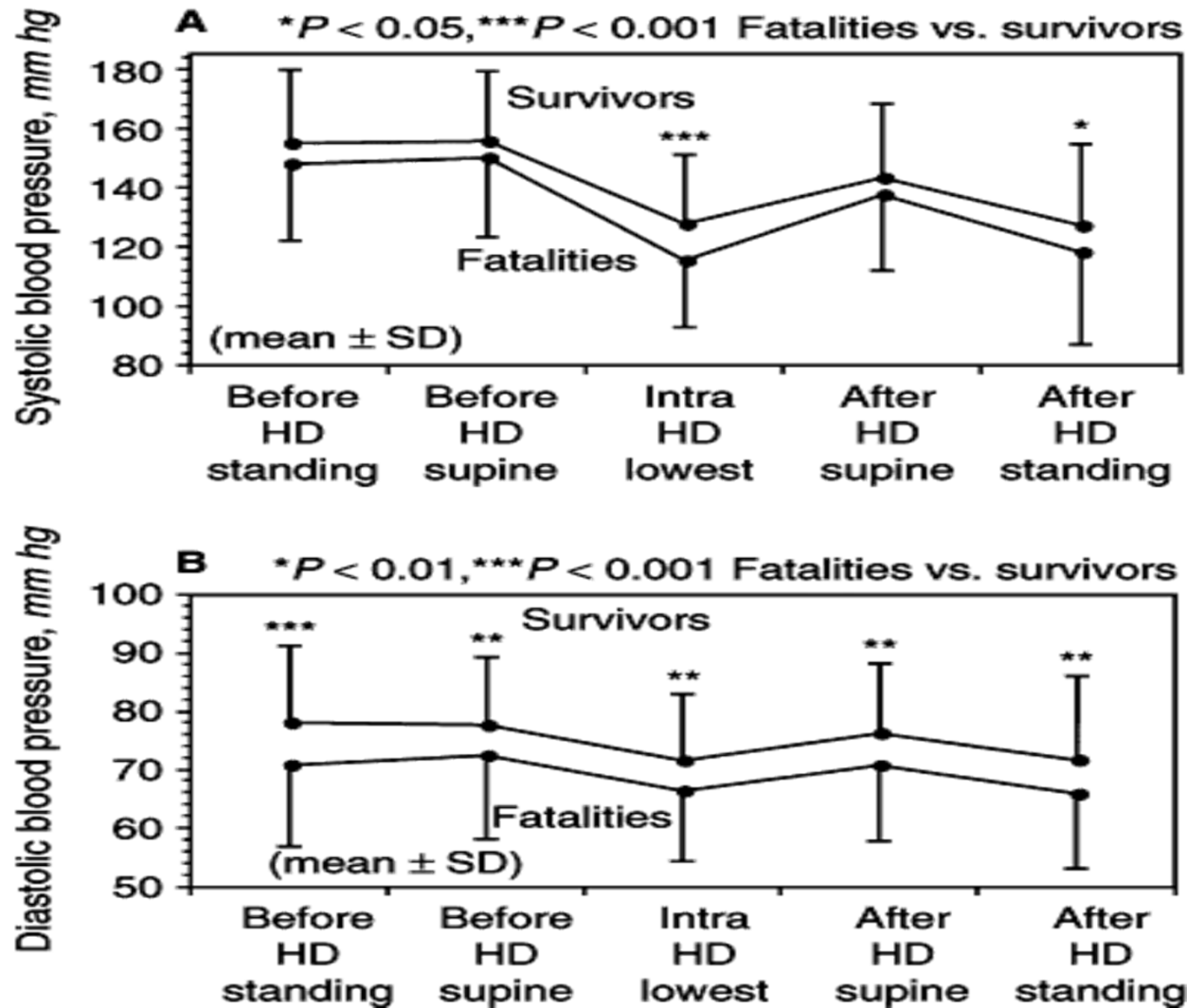


| | 0 | 5 | 10 | 15 | 20 | 25 | 30 | 35 |
|------------|-----|----|----|----|----|----|----|----|
| no-IDH | 85 | 72 | 68 | 55 | 51 | 48 | 45 | 42 |
| occasional | 101 | 30 | 81 | 65 | 58 | 51 | 45 | 19 |
| frequent | 77 | 56 | 47 | 42 | 36 | 35 | 32 | 20 |

Causes of Death in Patients With Frequent, Occasional and No IDH

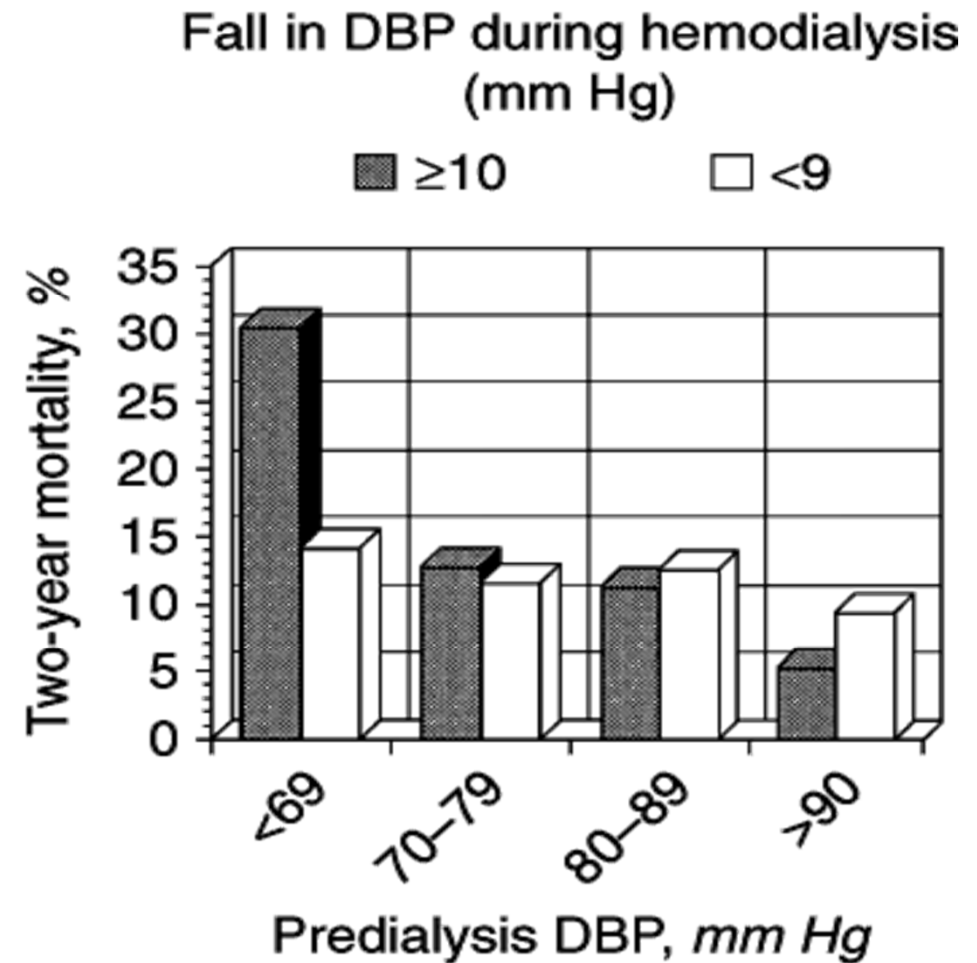
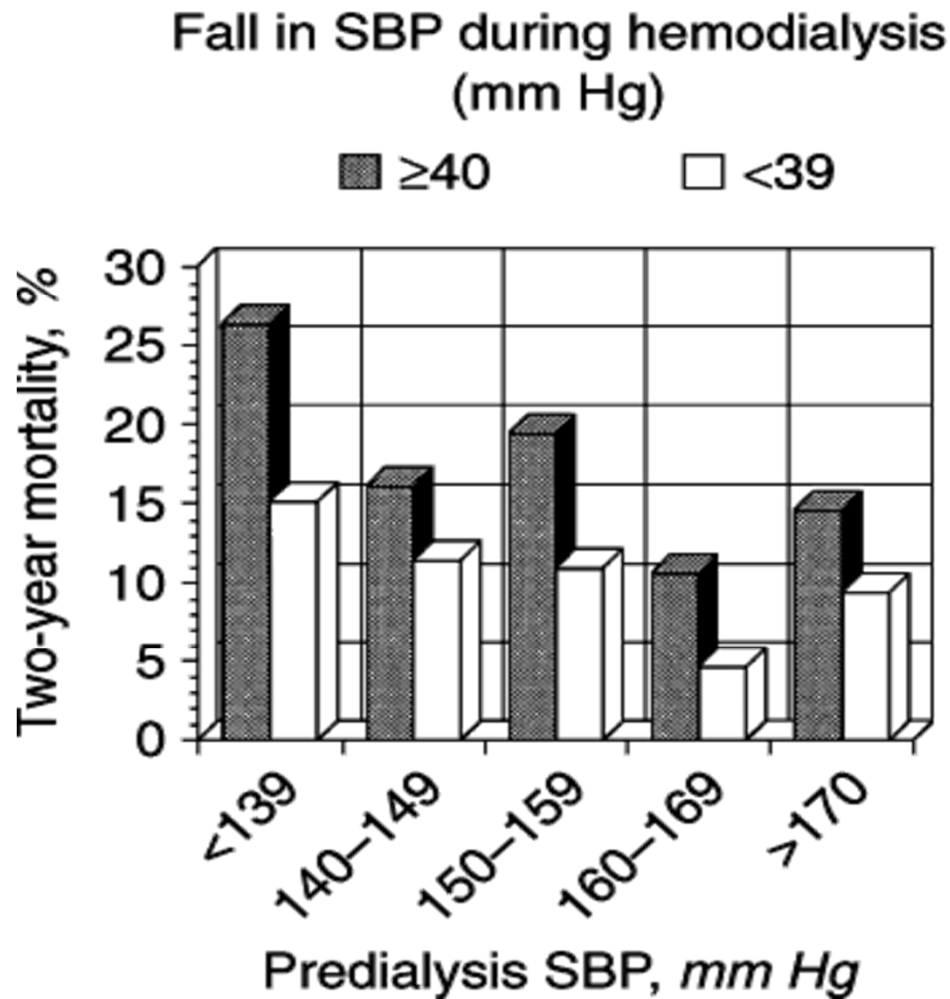


Impact of Intradialytic Hypotension on Mortality

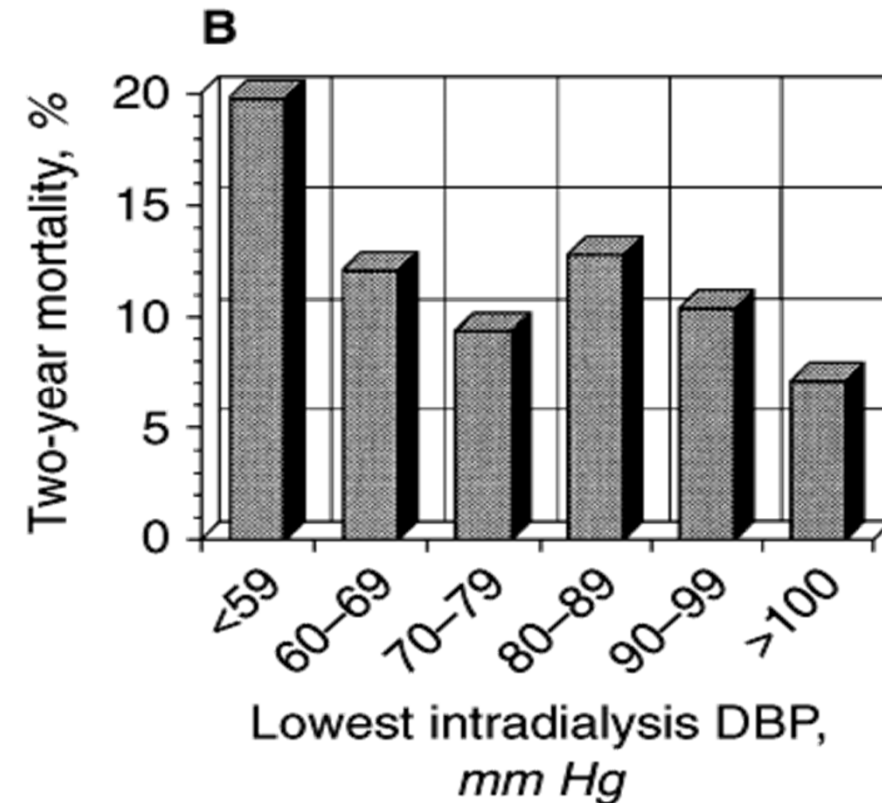
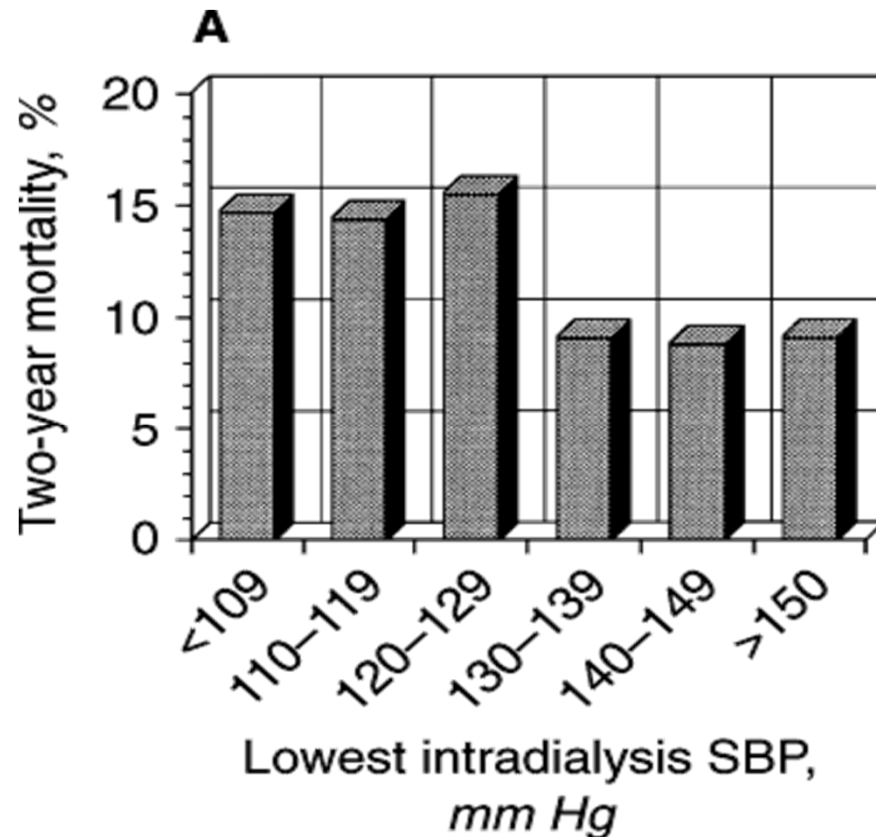


Japanese study
1244 HD patients
28 HD units
2 years follow-up

Two-Years Mortality Associated with Predialysis Blood Pressure and Fall During Hemodialysis



Two-year mortality is associated with a low intradialytic blood pressure



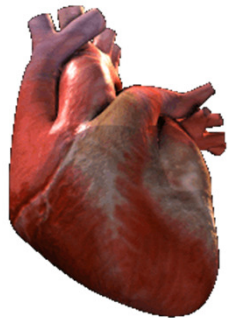
Intra Dialytic Hypotension Induces Hemodynamic Stress



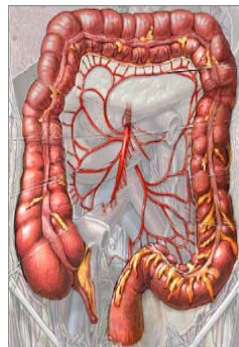
Intradialytic Hypotension



Cardiac ischemia
Stunning



Gut ischemia
Endotoxin translocation



Brain ischemia
Leukoaraiosis



Stroke



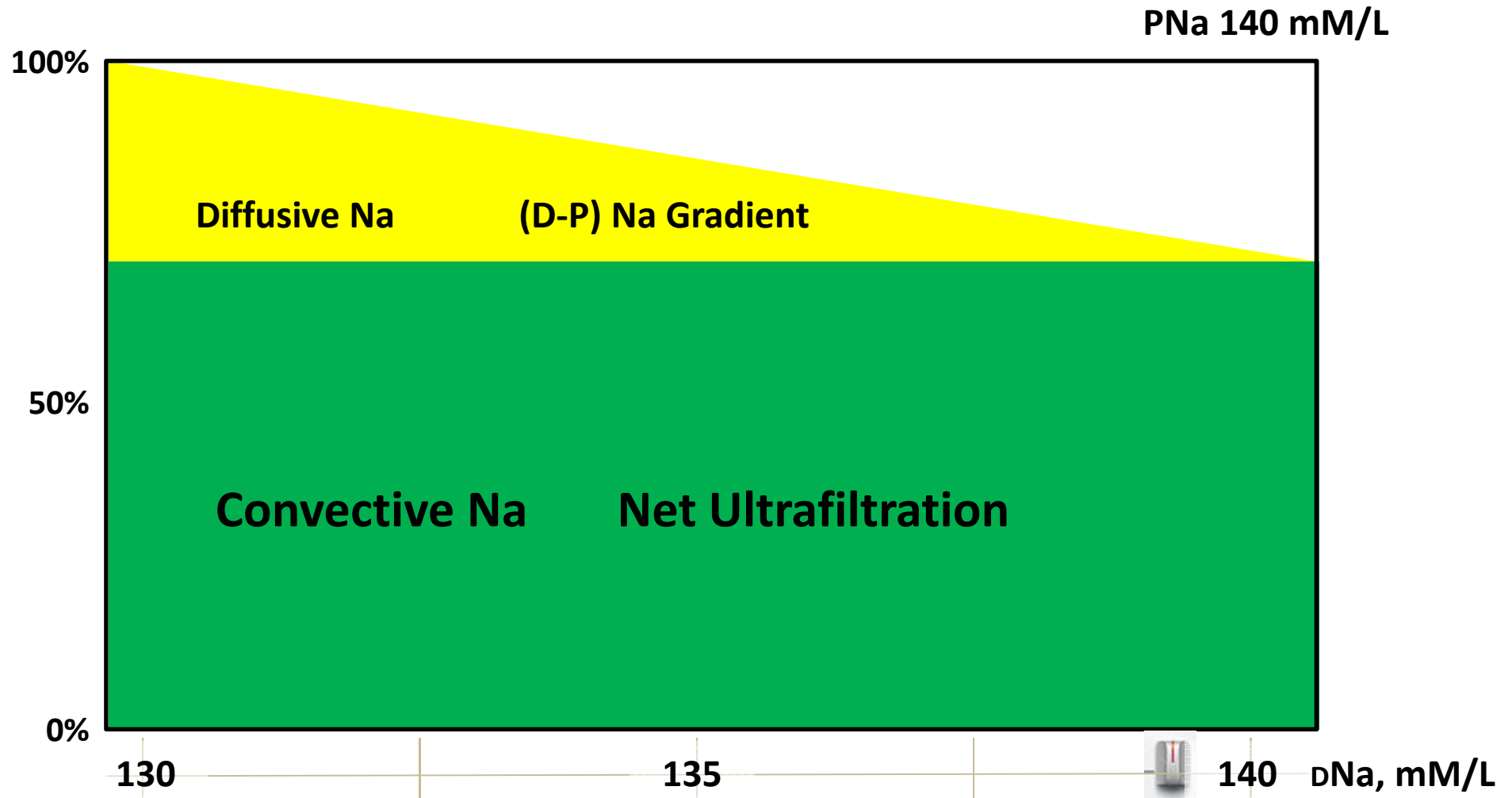
Liver stress
Redistribution flow from portal to artery



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Relative Contribution of Diffusion and Convection to Sodium Mass Balance



Sodium Mass Balance

Convective Removal, Ultrafiltrate

Ultrafiltrate

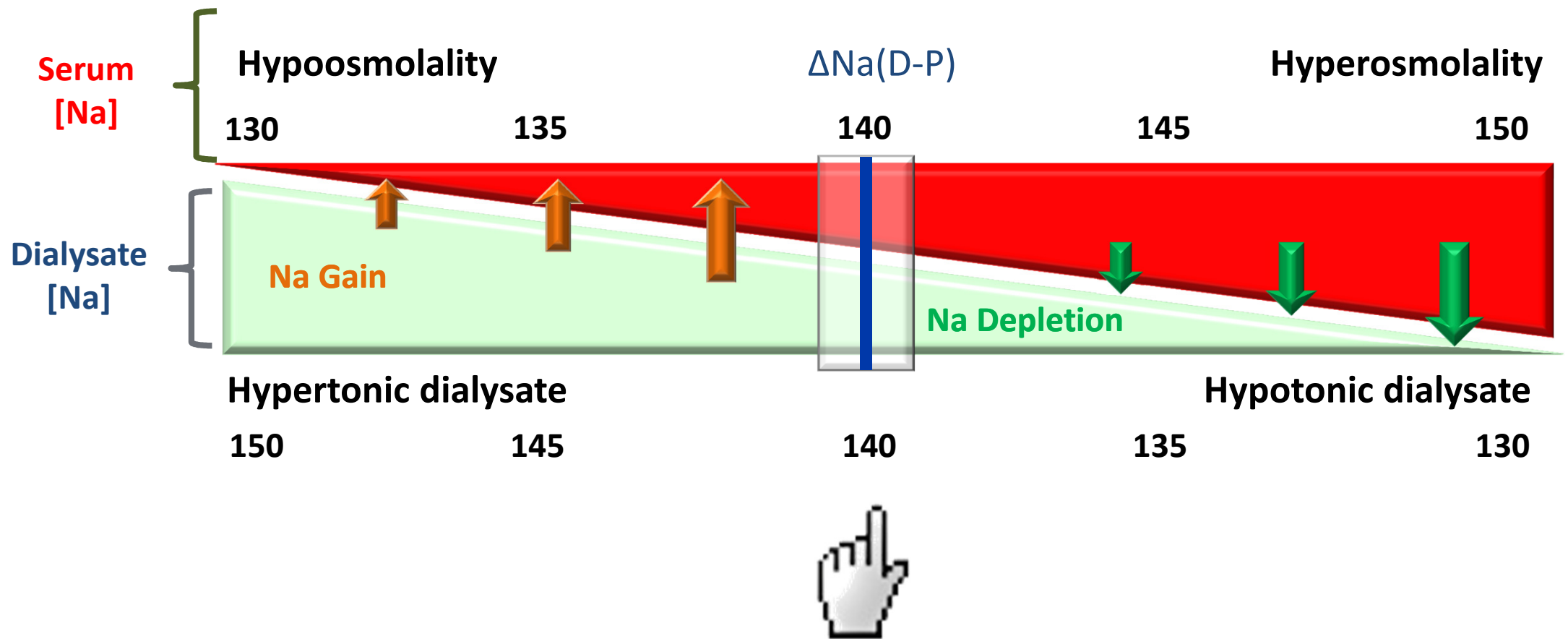


140 mmol/l

9 g NaCl per liter

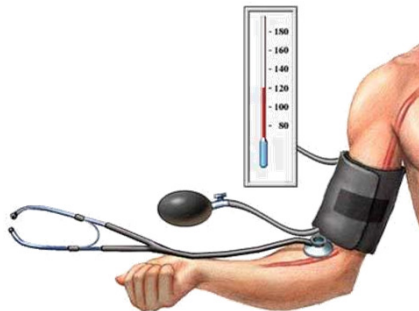
Sodium Mass Balance

Diffusive Na



Extracellular Fluid Management:

Old Fashion - Clinical Tools for Probing Dry Weight



Ambulatory Blood Pressure

New Tools Provide More Appropriate Assessment of ABP



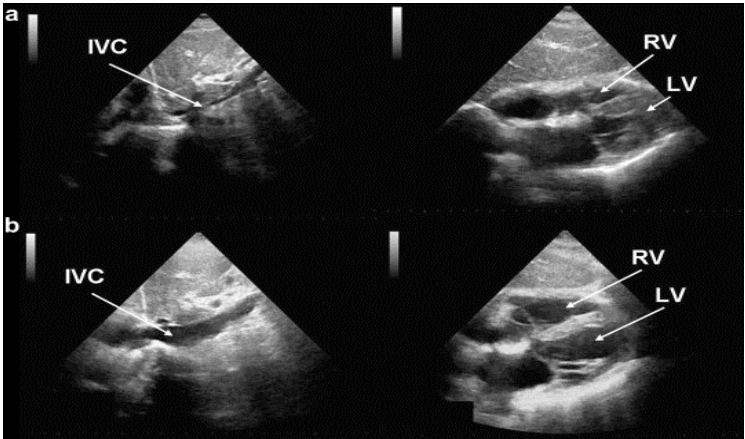
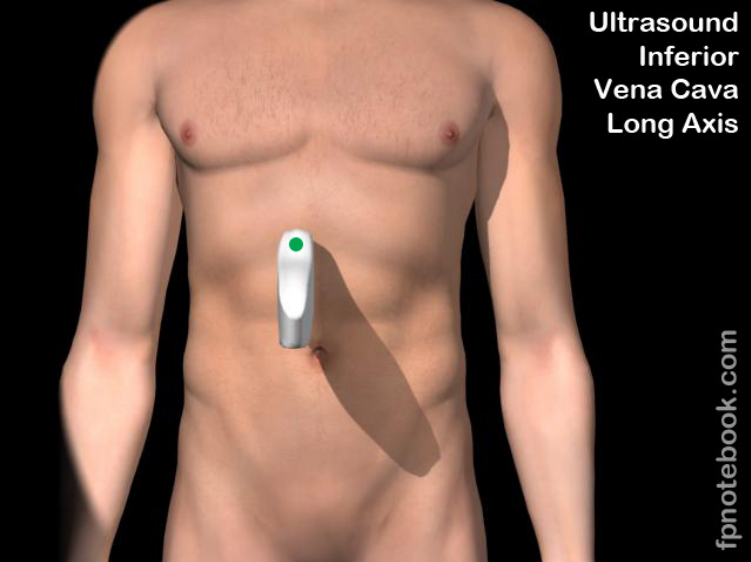
iHealth



Extracellular Fluid Management

New Tools for Fluid Assessment & Management

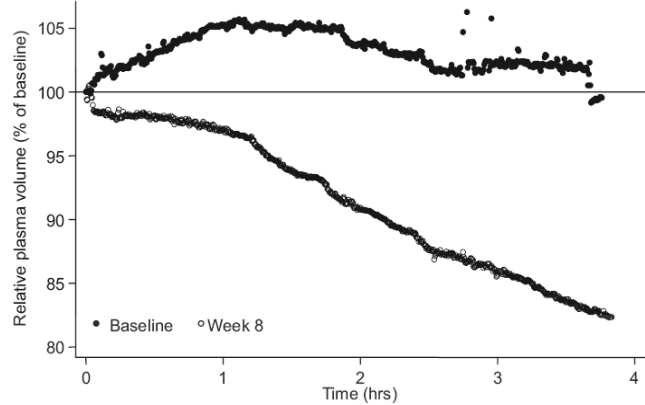
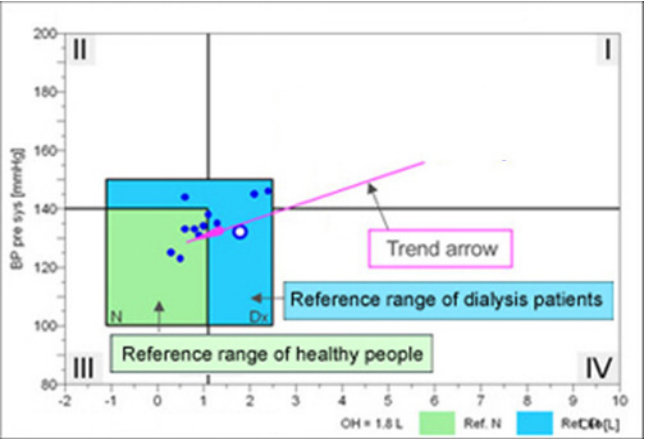
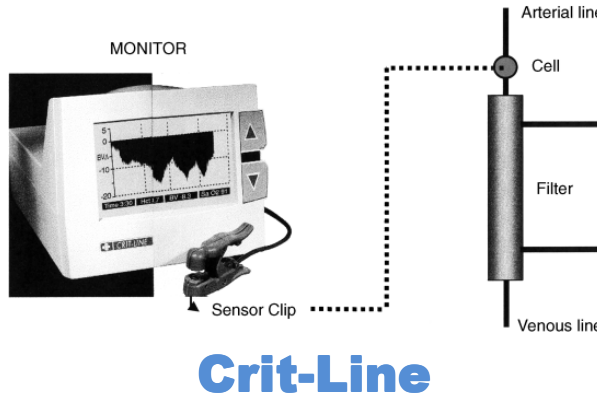
Volemia



ECF/ICF



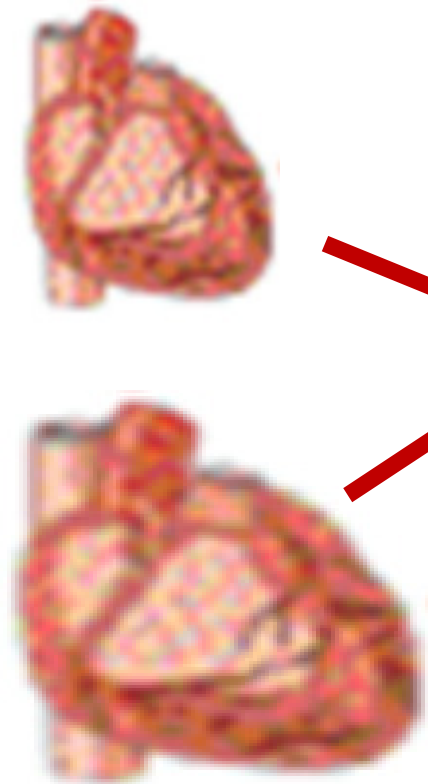
Relative Blood Volume Monitor



Extracellular Fluid Management

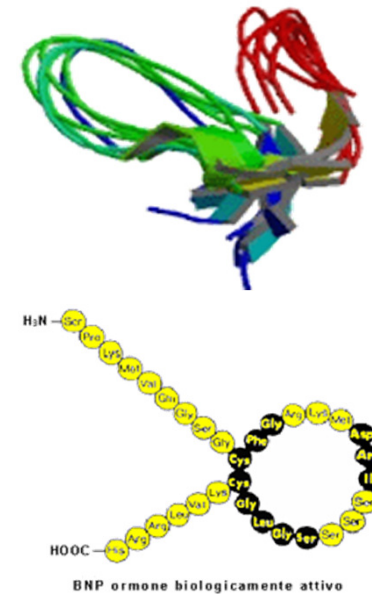
New Cardiac Biomarkers

Confounding factors : ECF overload and/or myocardial abnormalities ?



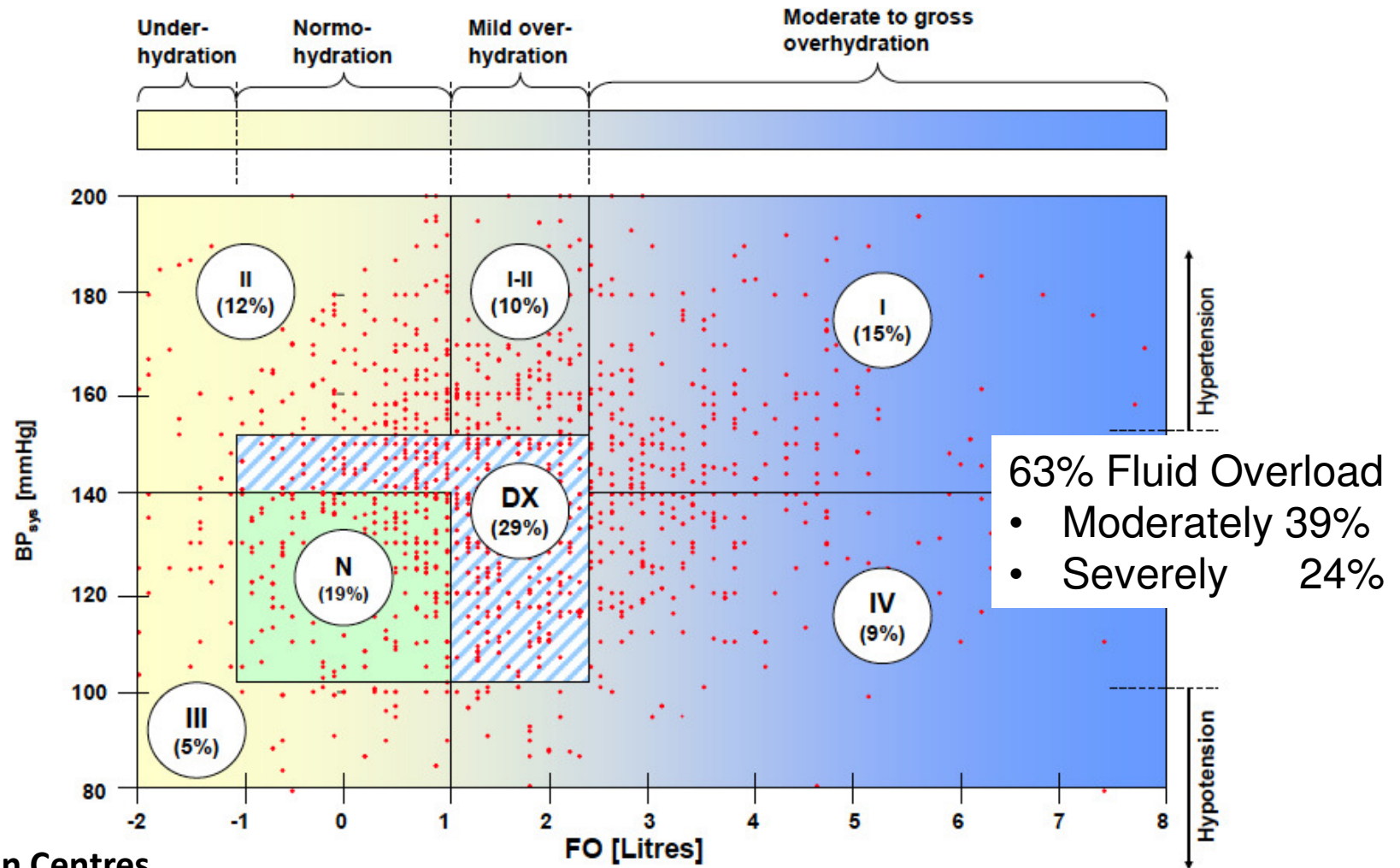
ANP
BNP
NT-ProBNP
Copeptin

■■■



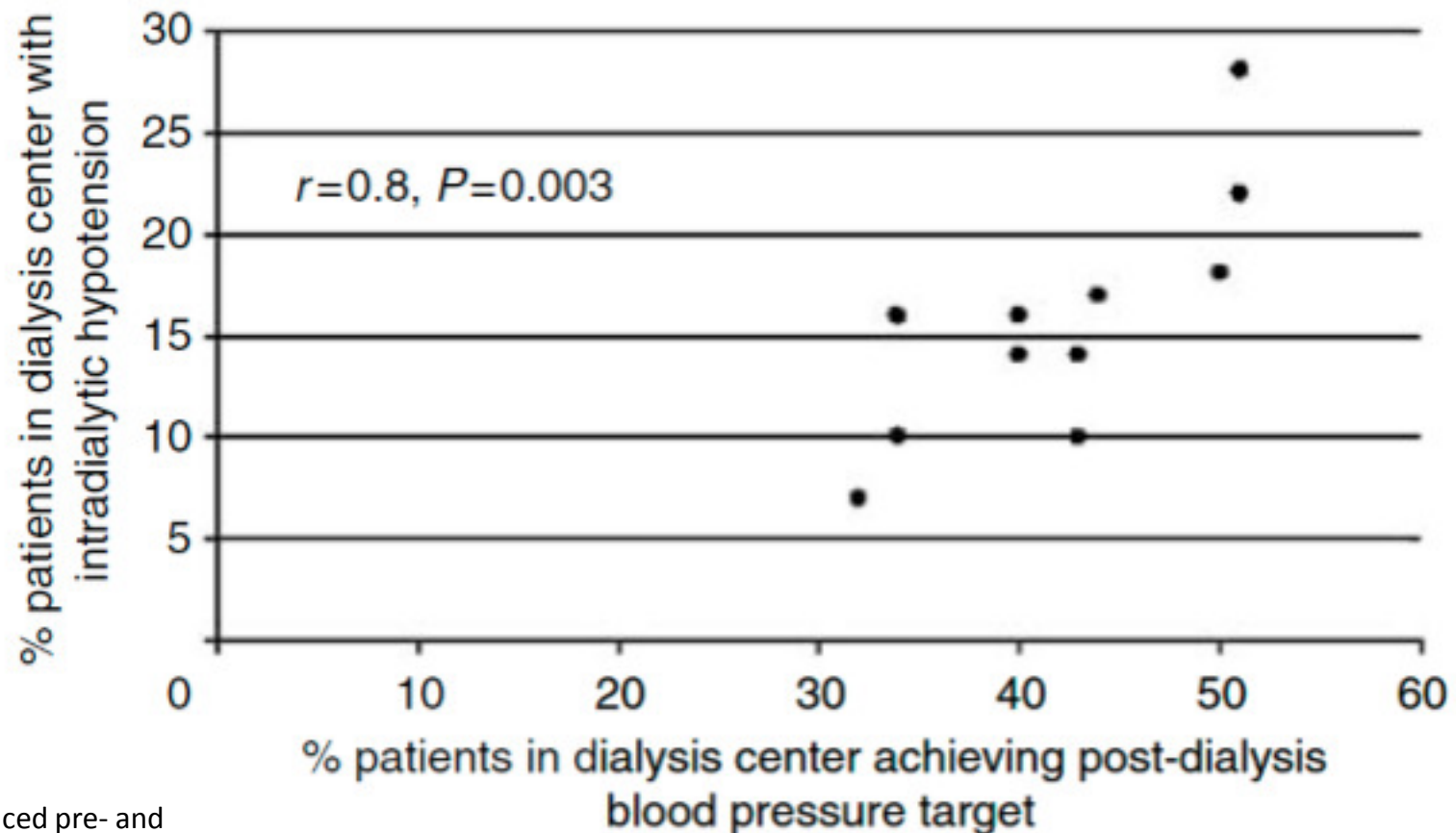
EC Fluid Status in HD Patients

Bioimpedence MultiFrequency (BCM)



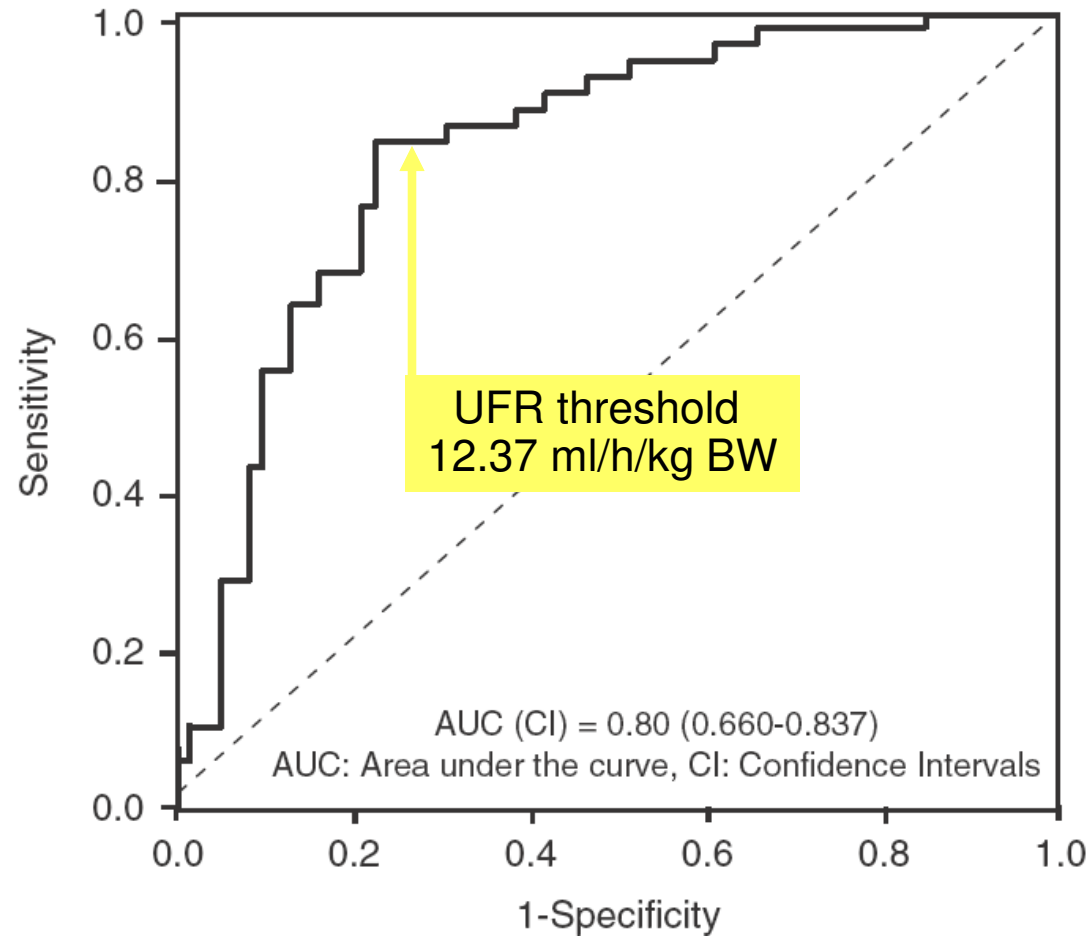
NephroCare 22 European Centres
1500 Prevalent Hemodialysis patients

Achieving Dry Weight and Post-Dialysis Blood Pressure Target Increases Incidence of IDH



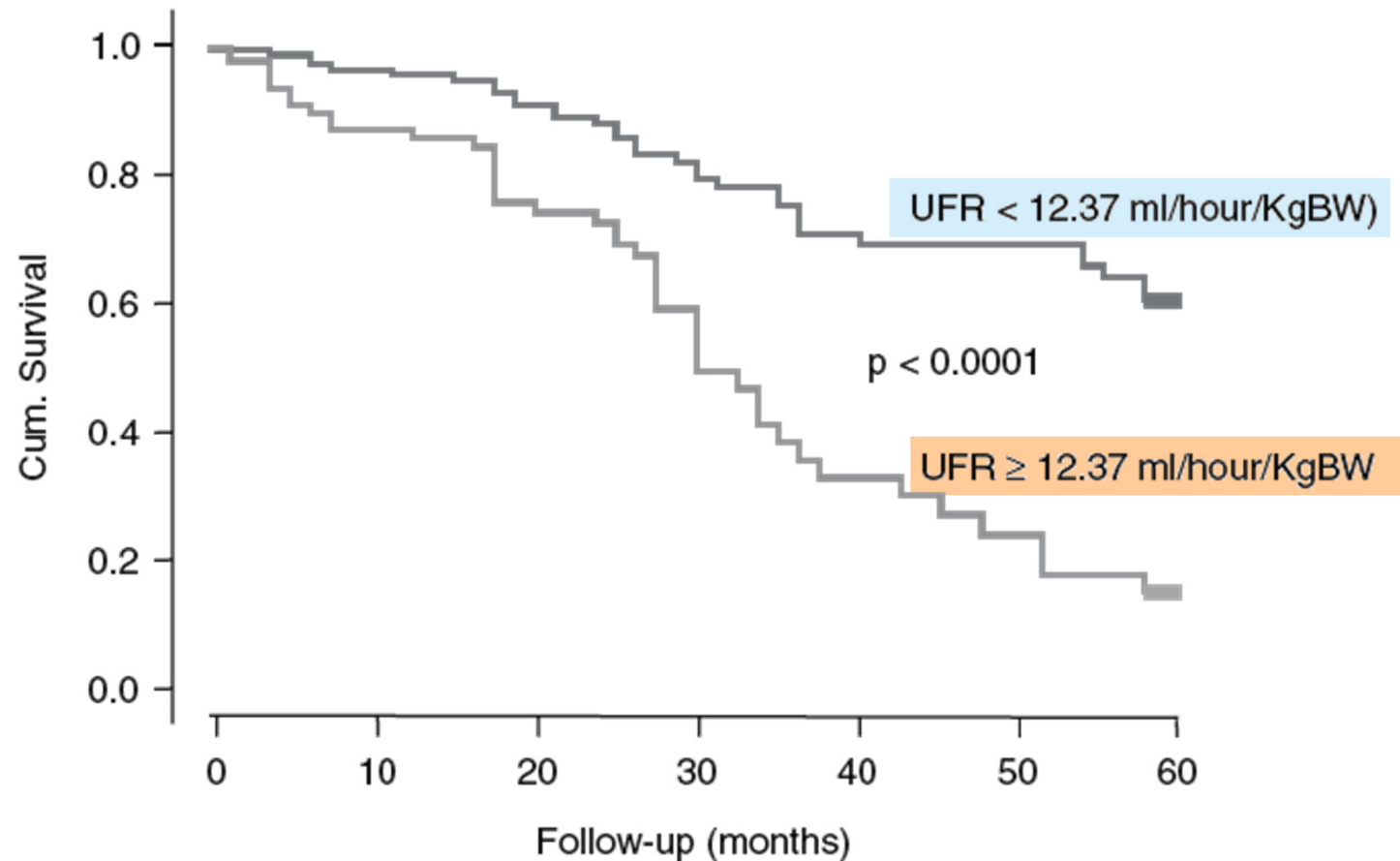
UK Renal Association introduced pre- and postdialysis target BP <140/90 & <130/ 80mmHg.
Audit Greater London - 2630 HD patients
Symptomatic IDH requiring fluid resuscitation

High UFR is associated with an increased risk of mortality at 5 year



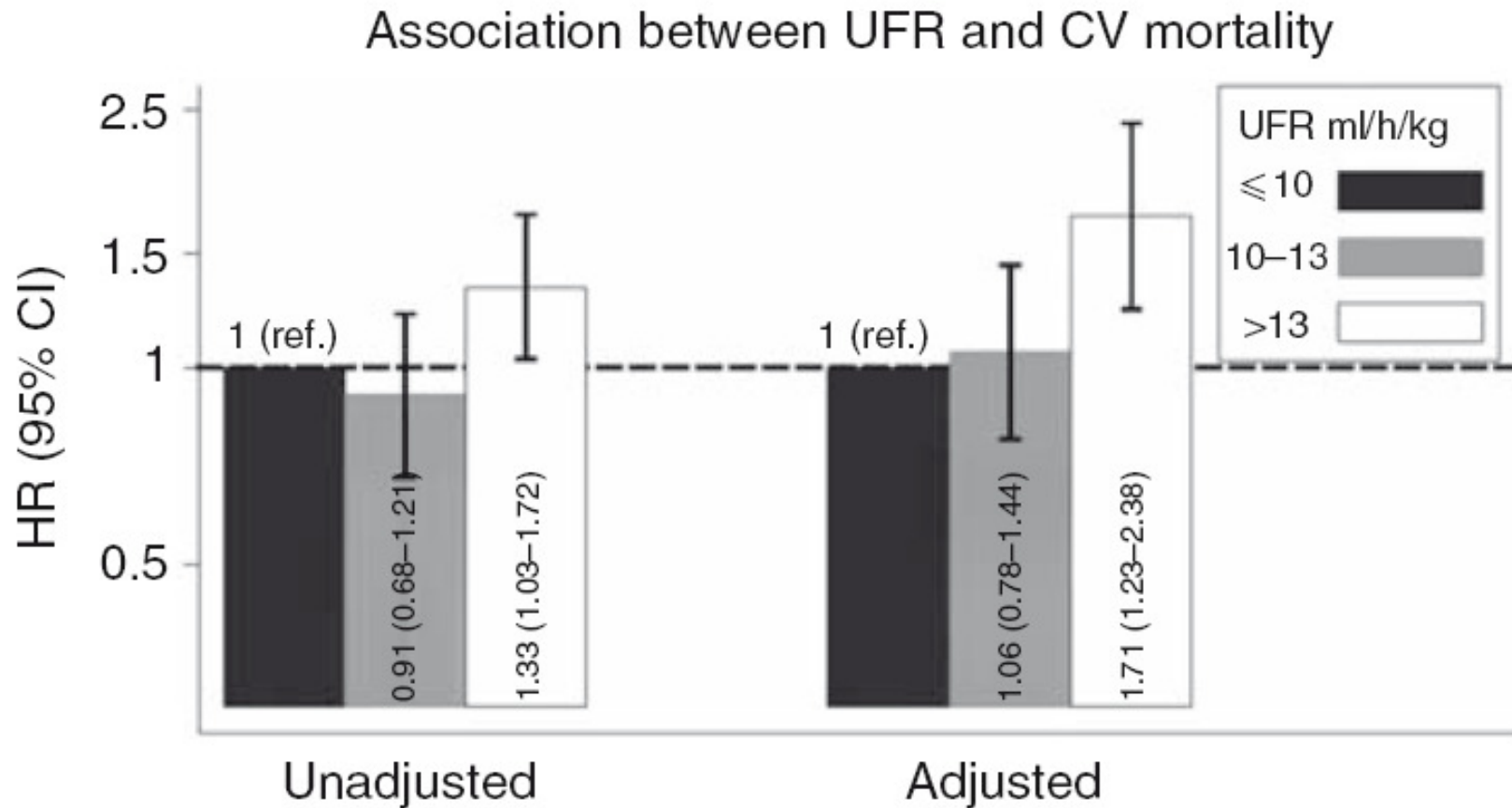
5 year prospective observational multicentre study
287 prevalent CKD HD patients (65 M, 122 F)
1 January 2000 to 31 December 2005
BW 62 ± 13 Kg; Kt/V 1.27 ± 0.13 ; PCRn 1.11 ± 0.20 g/kg/d

High UFR is associated with an increased risk of mortality



Ultrafiltration Rate and CV Mortality:

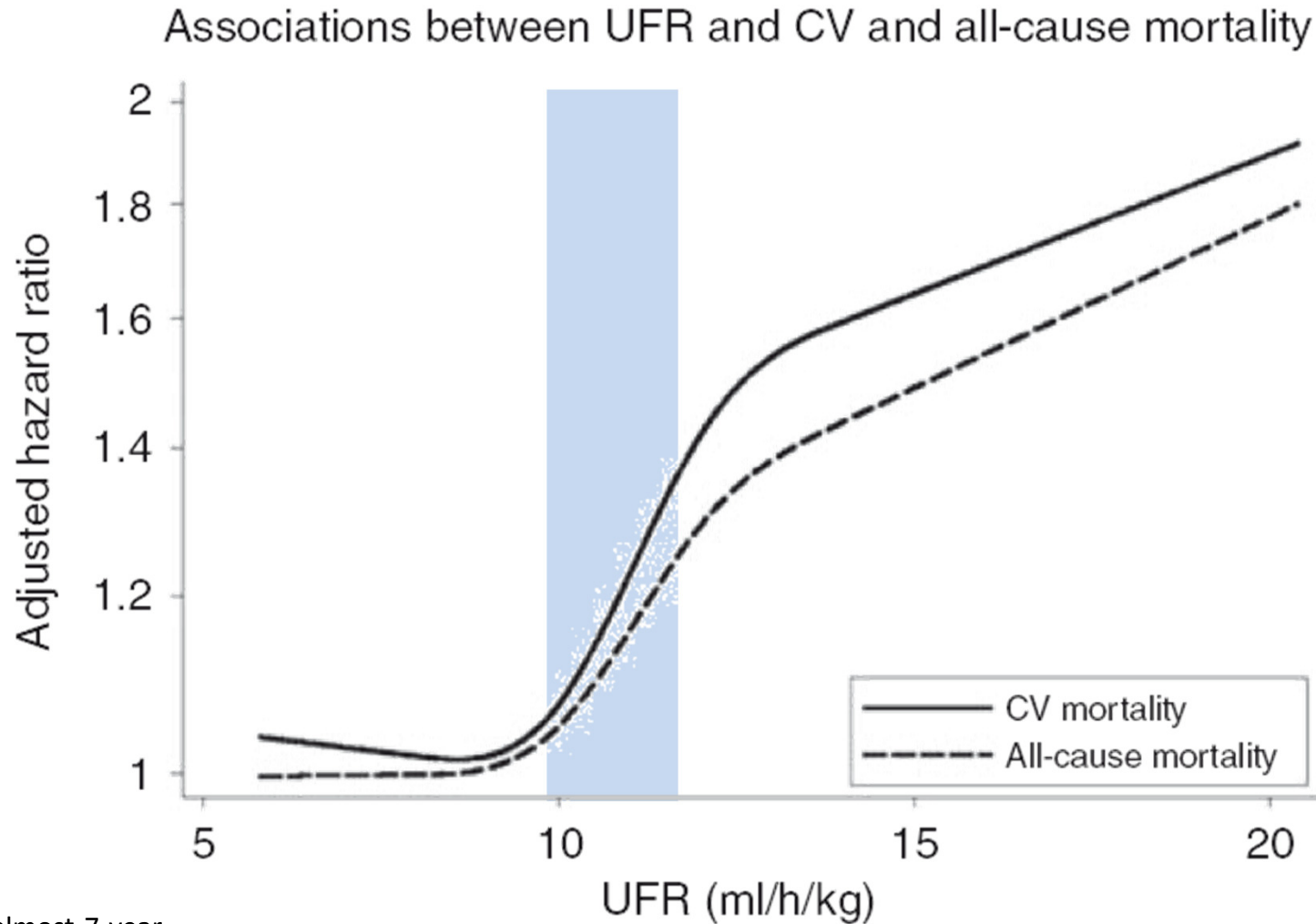
High UFR >13ml/h/kg is Associated with Higher CV Mortality



Hemodialysis Study, an almost-7-year
Randomized clinical trial of 1846 patients

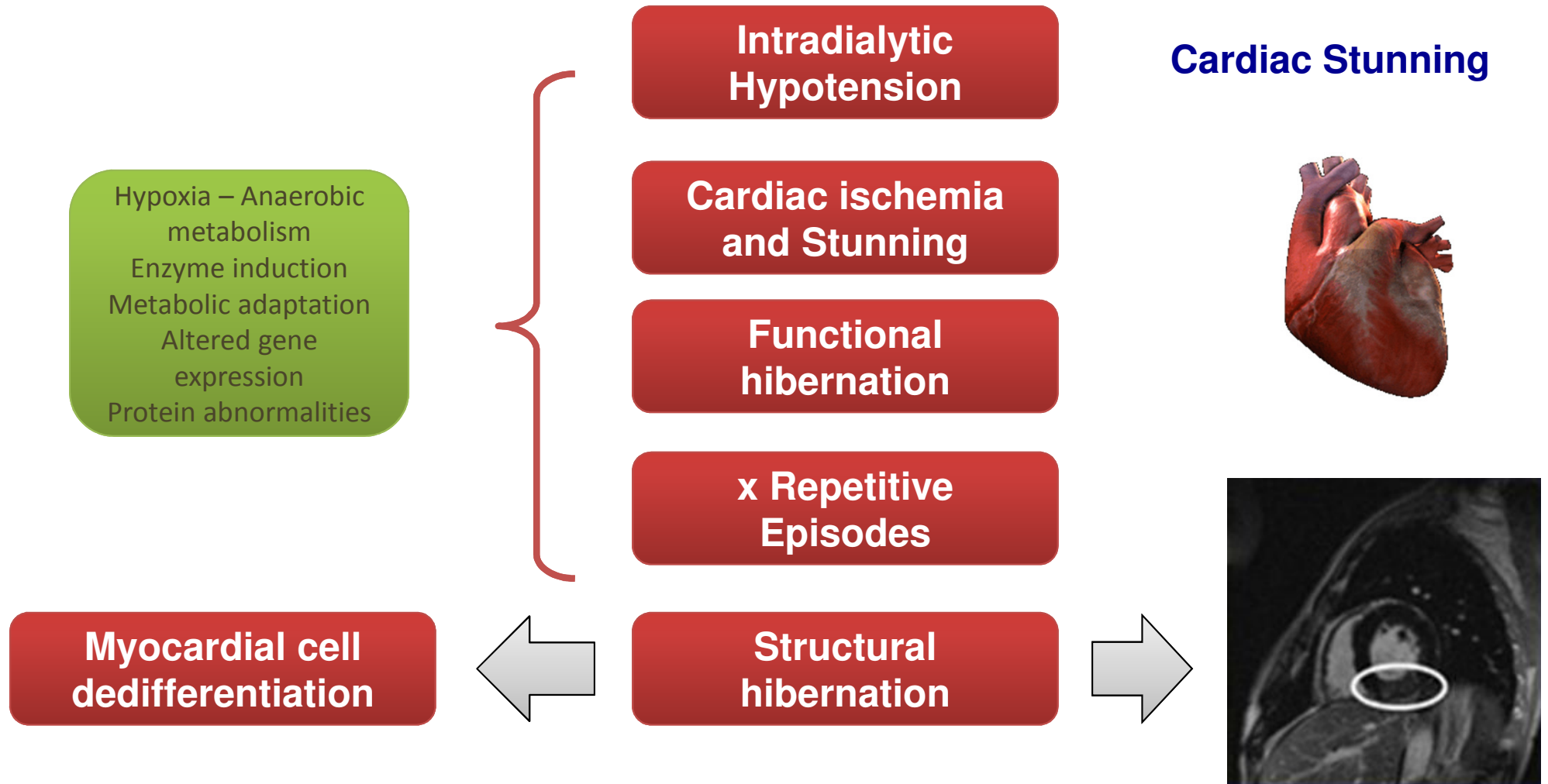
Ultrafiltration Rate and CV Mortality:

UFR > 10 ml/h/kg is Associated with Increased CV and All-Cause Mortality

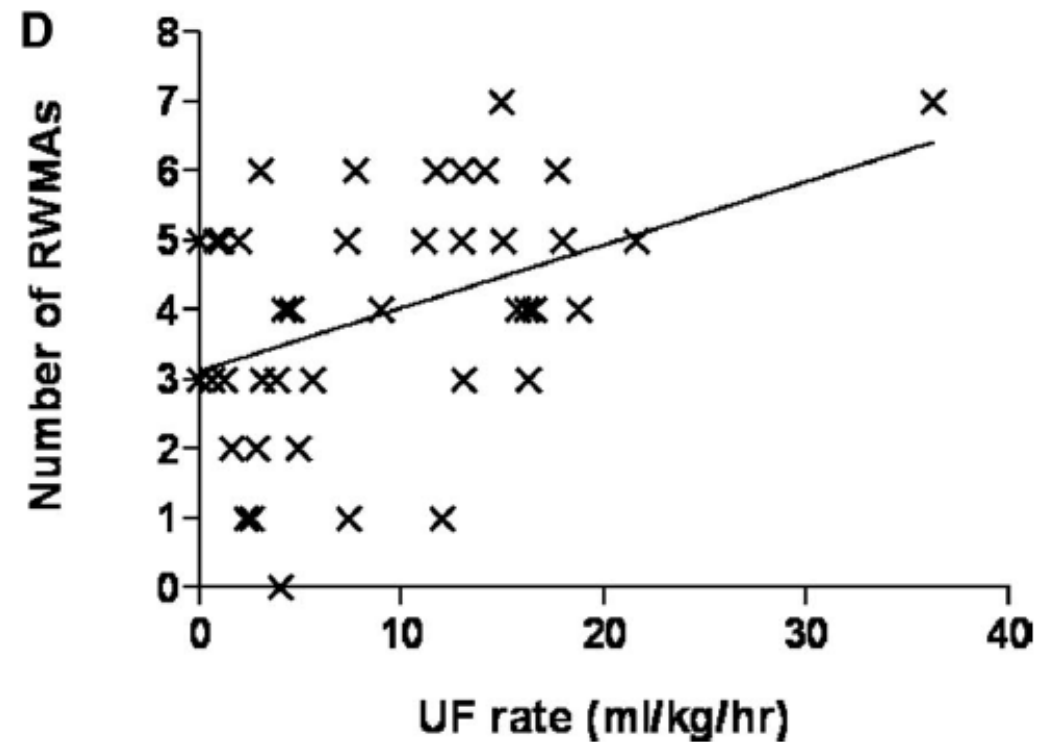
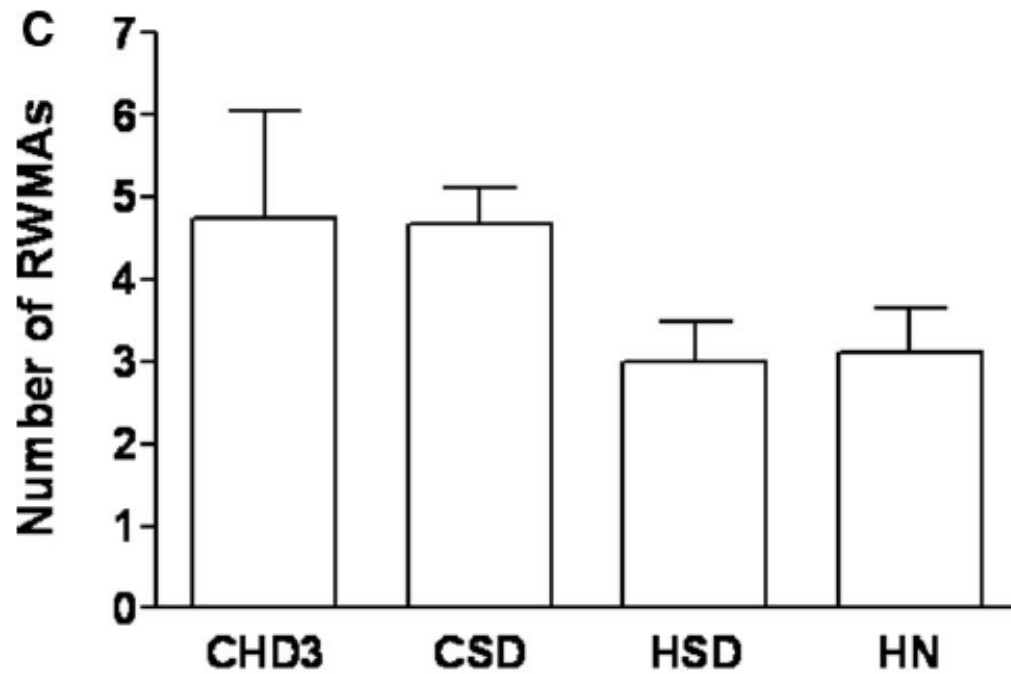


Hemodialysis Study, an almost-7-year
Randomized clinical trial of 1846 patients

Severe hypotensive episodes are responsible for repetitive cardiac insults and cardiac stunning

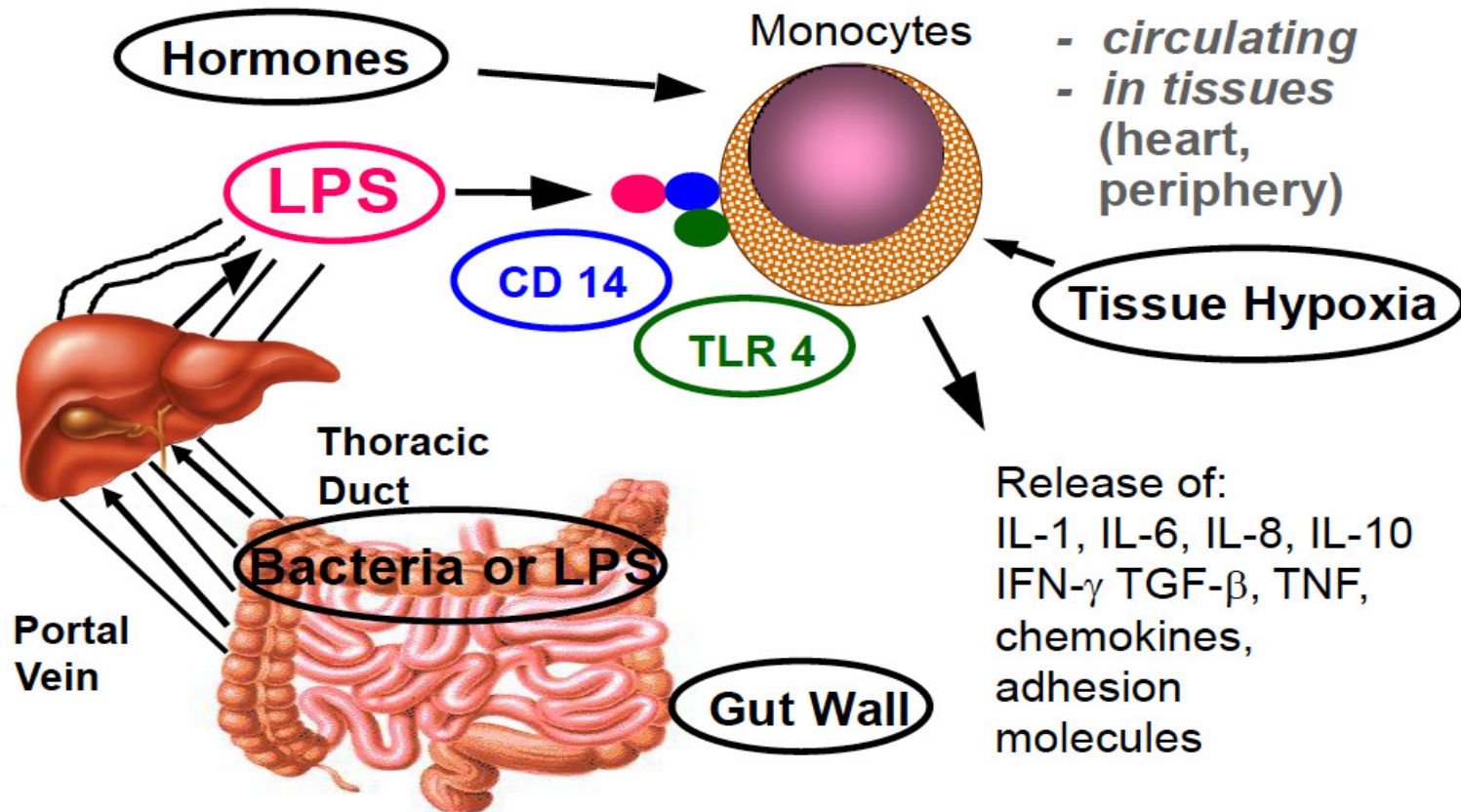


Frequent Hemodialysis Schedules Are Associated with Reduced Levels of Dialysis-induced Cardiac Injury



Repetitive gut ischemia contributes to inflammation

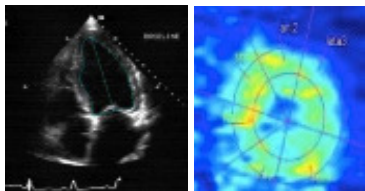
Gut ischemia - Translocation



Clinical and Subclinical Manifestations of Hemodynamic Instability

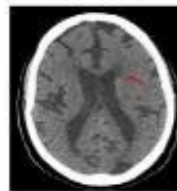
Intra Dialytic Hypotension

Cardiac
Stunning



Burton JO et al.
CJASN 2009

Leuko-
-araiosis



McIntyre CW et al.
JASN 2014

Gut Trans-
-location



Jefferies HJ et al
Nephron Clin Pract. 2014

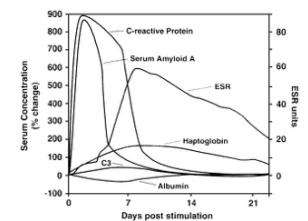
Distal
Necrosis



Games FL et al,
Nephron Clin Pract. 2013

Inflam-
-mation

Stenvinkel P et al.
NDT 2002



McIntyre CW et al.
CJASN 2011

Outlook of the Presentation

1. Sodium & fluid volume homeostasis in CKD5 HD patient
 - Basics of physiology – Challenges for nephrologist & care giver
2. Intradialytic hypotension:
 - Definition – Frequency – Causes – Consequences
3. Sodium & fluid management in HD
 - Diffusive/Convective Na
 - Ultrafiltration
- 4. Preventing intradialytic hypotension**
 - **Means: diet, residual kidney function, hemodialysis, time**
 - **Stepwise approach**
5. Take home message

Restore Sodium Mass Balance in HD Patient

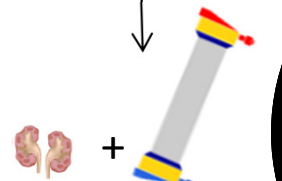
↘ **Salt diet**


Dietary Intake
 50 mM/day
 3g NaCl



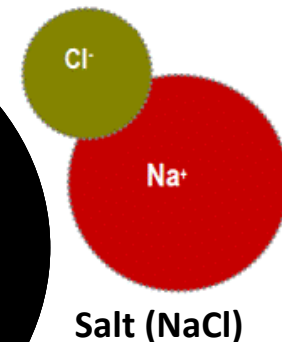
ECF Na⁺
 2500mM
 (70%)

**= Residual
Kidney Function**


 +
Dialysis Output
 100 hr

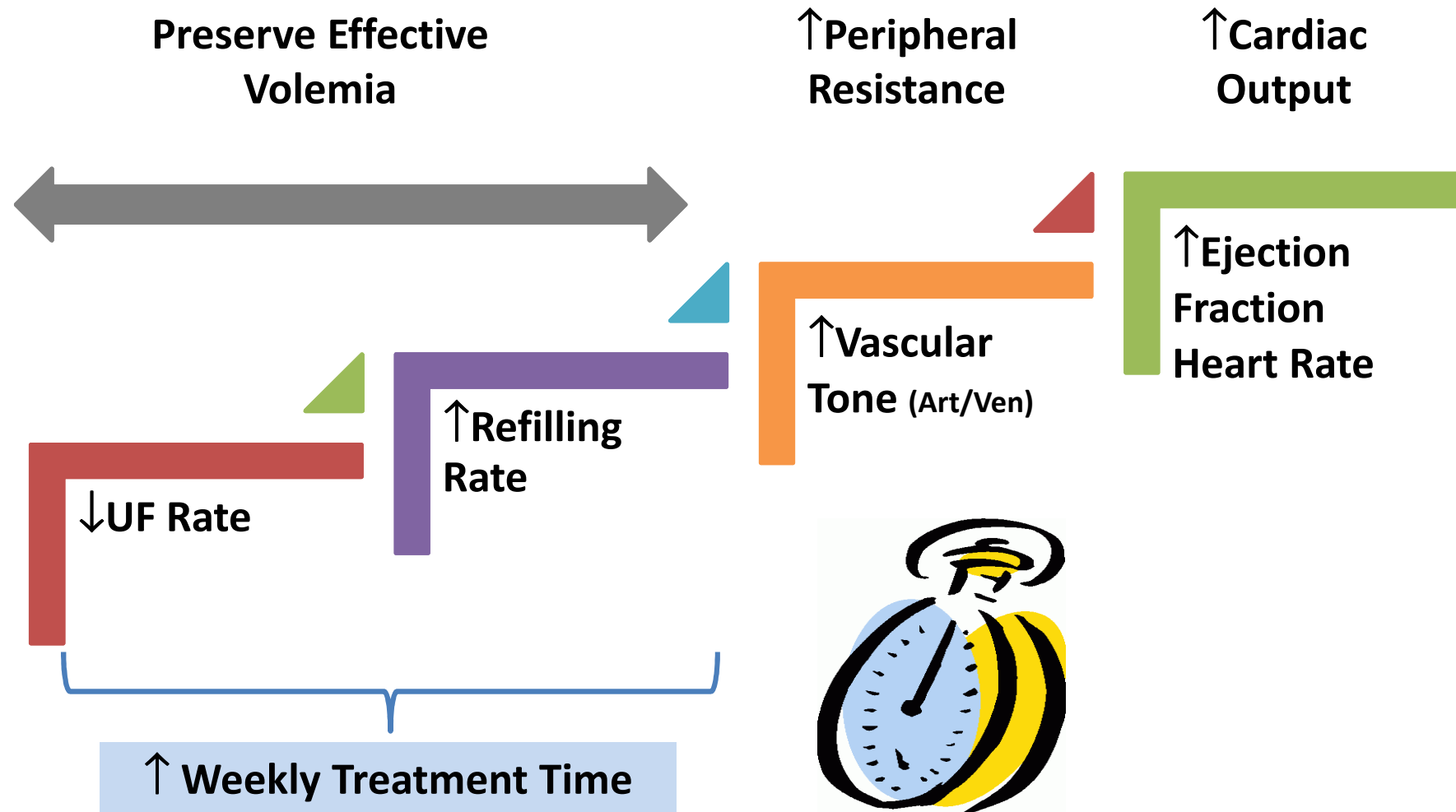


↗ **Sodium Mass
Removal**

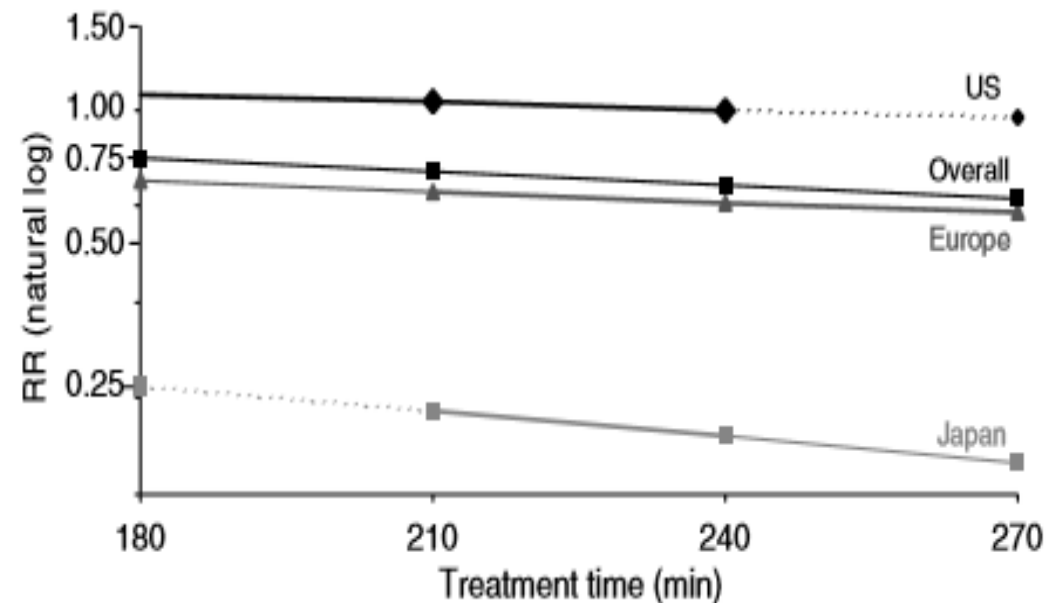
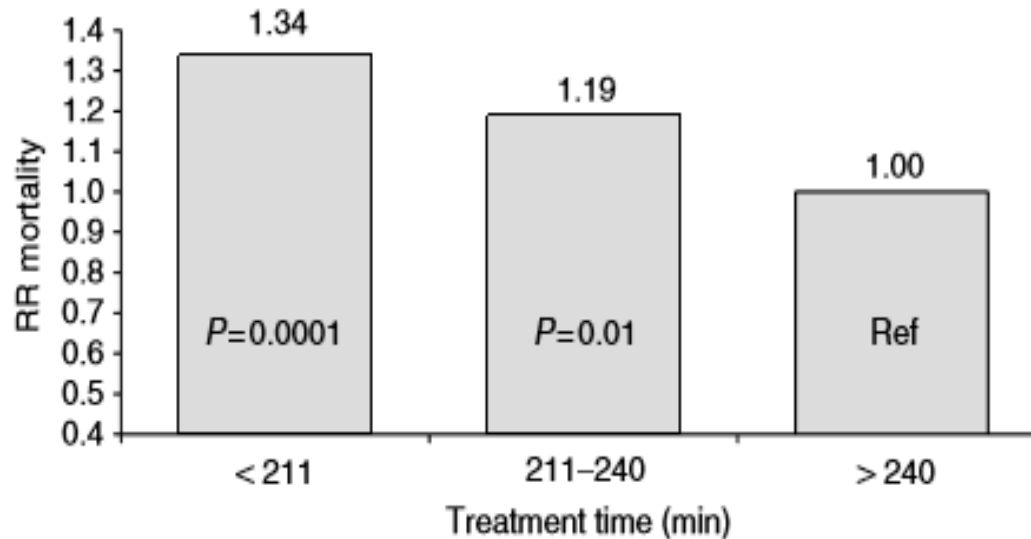


| Salt In grams | Sodium In mg x2,5 | This is roughly equivalent to |
|---------------|-------------------|--------------------------------|
| 1 | 400 | Good pinch of salt |
| 1.25 | 500 | One-quarter of a teaspoon salt |
| 2.3 | 920 | One-third of a teaspoon salt |
| 2.5 | 1000 | Half a teaspoon salt |
| 4 | 1600 | ¾ of a teaspoon salt |
| 5 | 2000 | One teaspoon salt |
| 6 | 2400 | 1¼ teaspoons salt |
| 10 | 4000 | 2 teaspoons salt |
| 12 | 4800 | 2½ teaspoons salt |

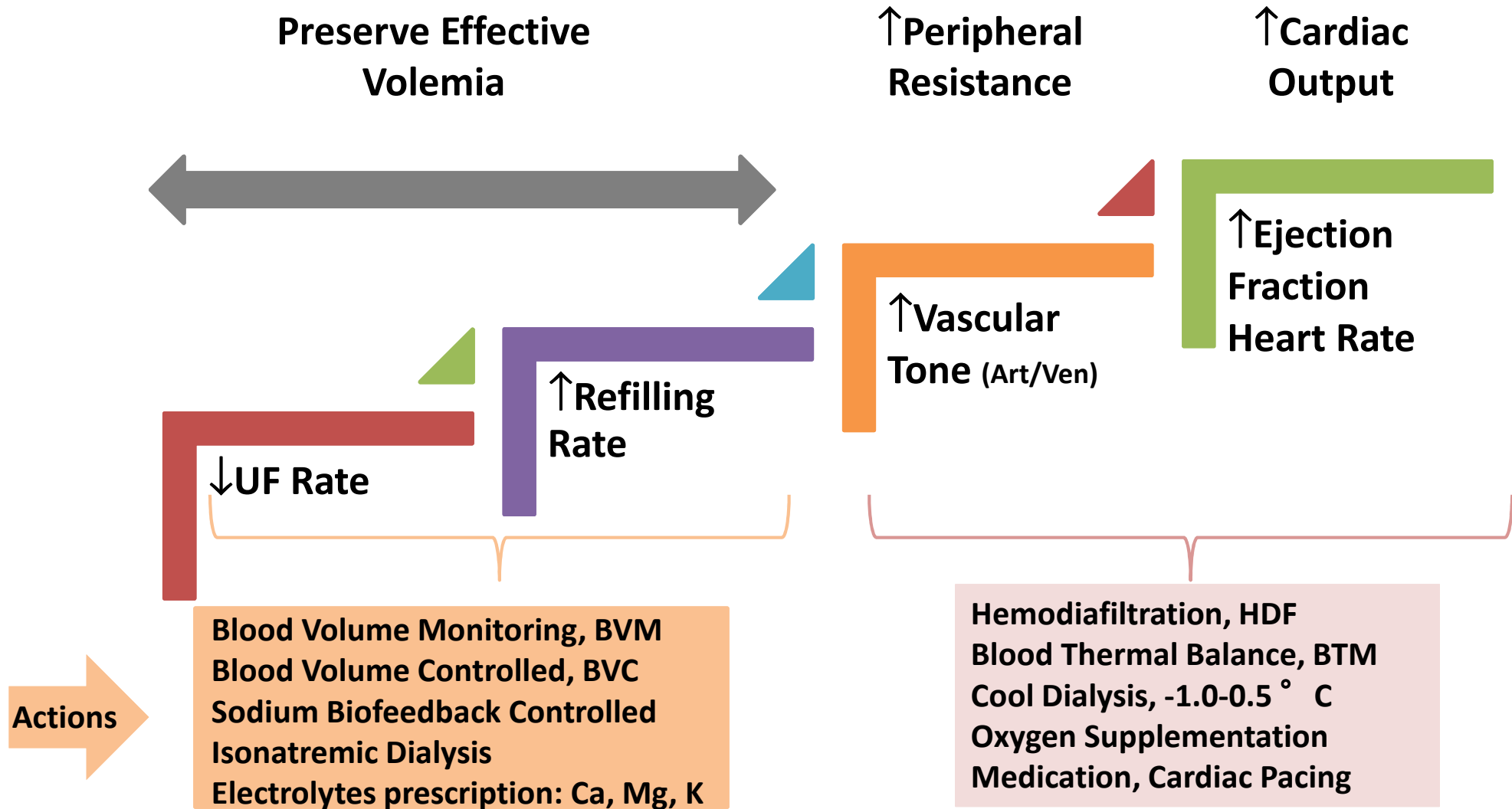
Preventing Intra Dialytic Hypotension



Longer Treatment Time is Associated with Lower UFR and Better Survival



Preventing Intra Dialytic Hypotension



Hemodynamic Tolerance Is Improved By HDF

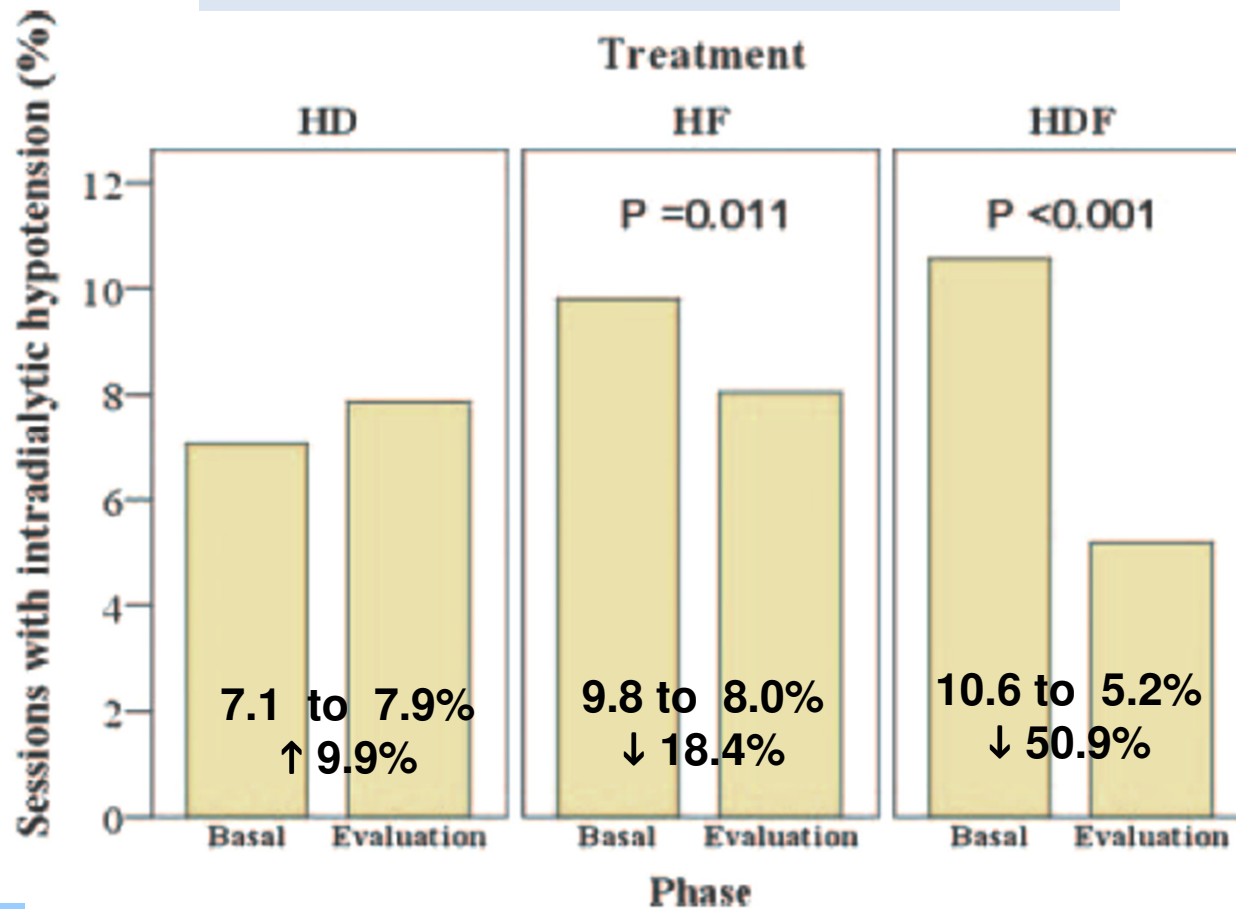
Prospective Controlled Study

| Condition | HFHD (Baseline) | On-line HDF | | | |
|--------------|-----------------|-------------|-------------|-------------|-------------|
| | | 6 months | 1 year | 2 years | 3 years |
| Hypotension | 20.2 ± 17.1 | 10.4 ± 17.6 | 11.8 ± 16.1 | 10.0 ± 13.8 | 12.4 ± 16.1 |
| Hypertension | 2.9 ± 4.7 | 2.2 ± 7.7 | 2.4 ± 5.7 | 0.1 ± 0.4 | 0.9 ± 2.1 |
| Muscle cramp | 7.8 ± 9.5 | 5.3 ± 7.7 | 2.0 ± 2.1 | 3.0 ± 3.7 | 1.9 ± 2.3 |
| Headache | 1.7 ± 2.6 | 1.3 ± 3.2 | 0.4 ± 1.1 | 0.4 ± 1.1 | 0.3 ± 0.9 |

Prospective Controlled Cohort Study
 Thailand Monocenter Study
 22 pts - HDHF/HDF

Hemodynamic Tolerance Is Improved By HDF Randomized Controlled Study

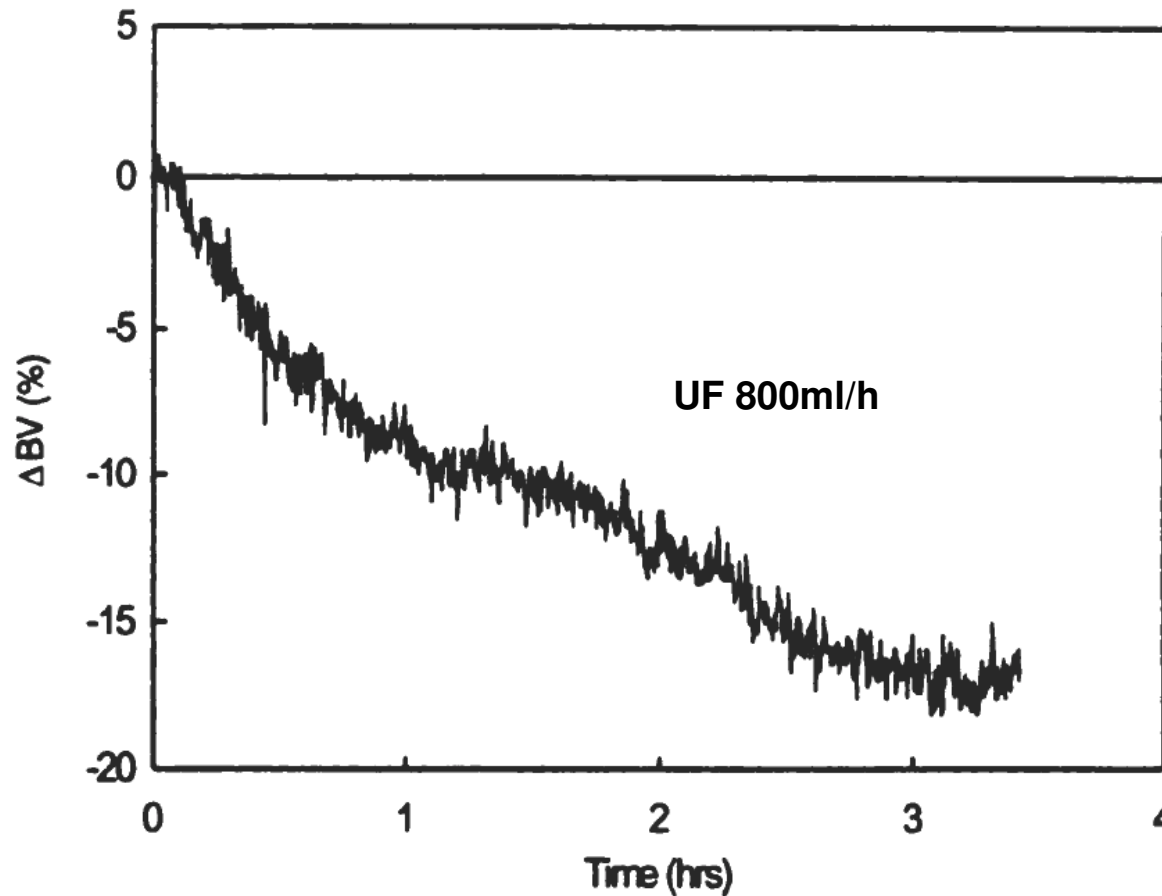
Total incidence of ISH 7.5% 28950 sessions



Italian Multicentric Study RCT
LFHD, HF, HDF Ratio 2/1/1

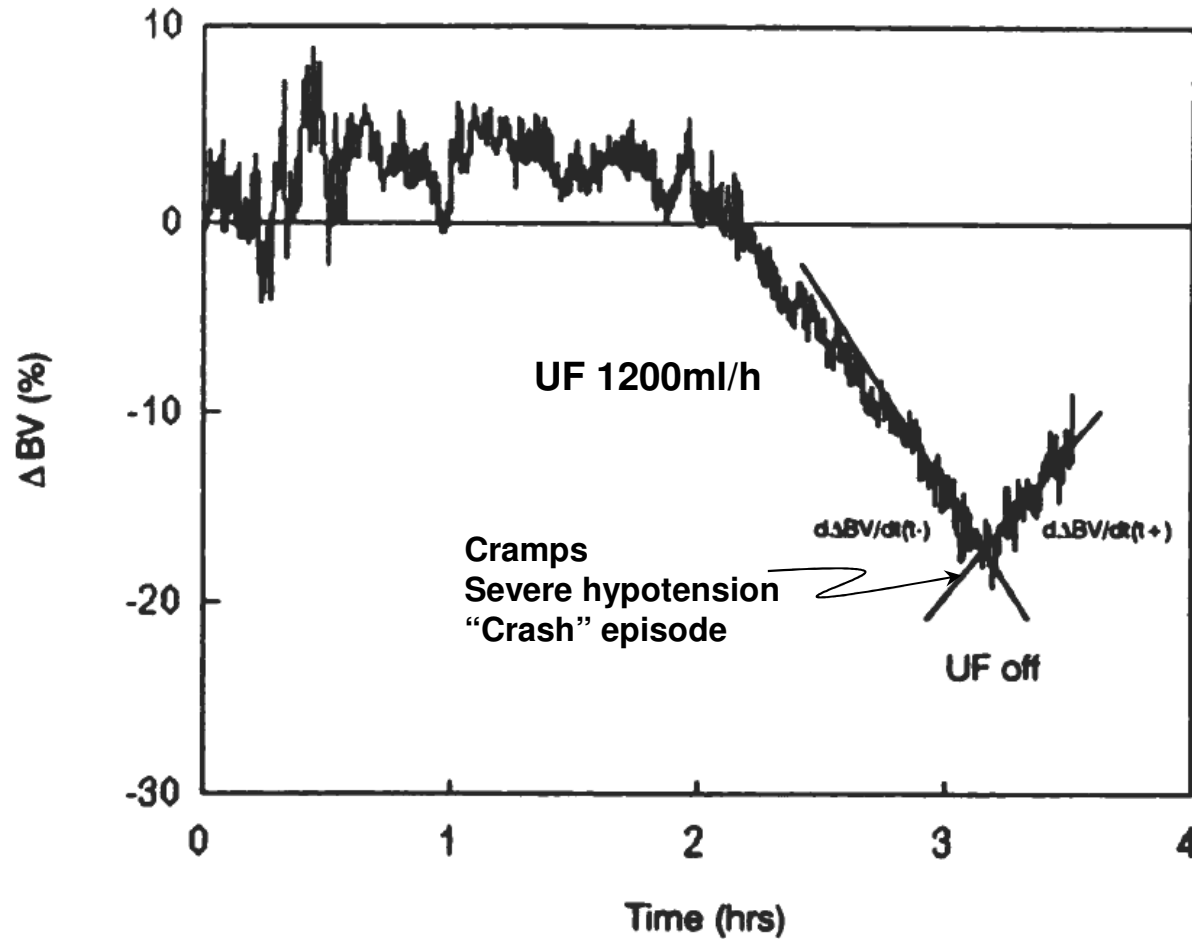
Residual Blood Volume Monitoring

Probing Refilling Rate Capacity



Residual Blood Volume Monitoring

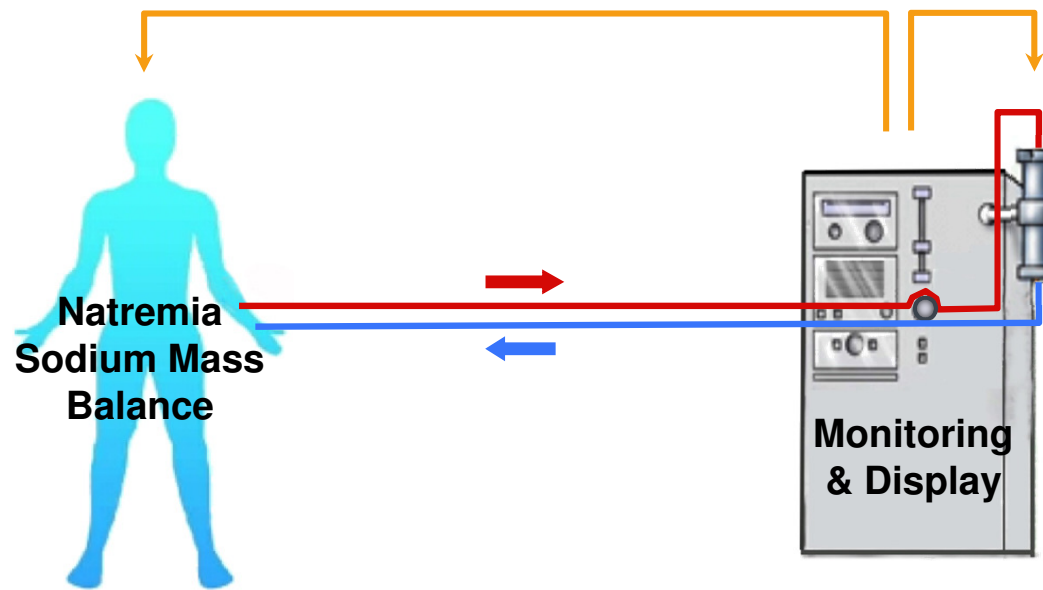
Defining Individual Critical Volume



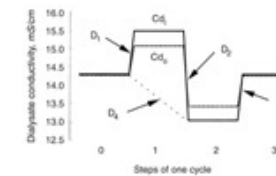
Sodium Mass Balance & Osmolality Control

Na Mass Management

Na Dialysate Adjustment

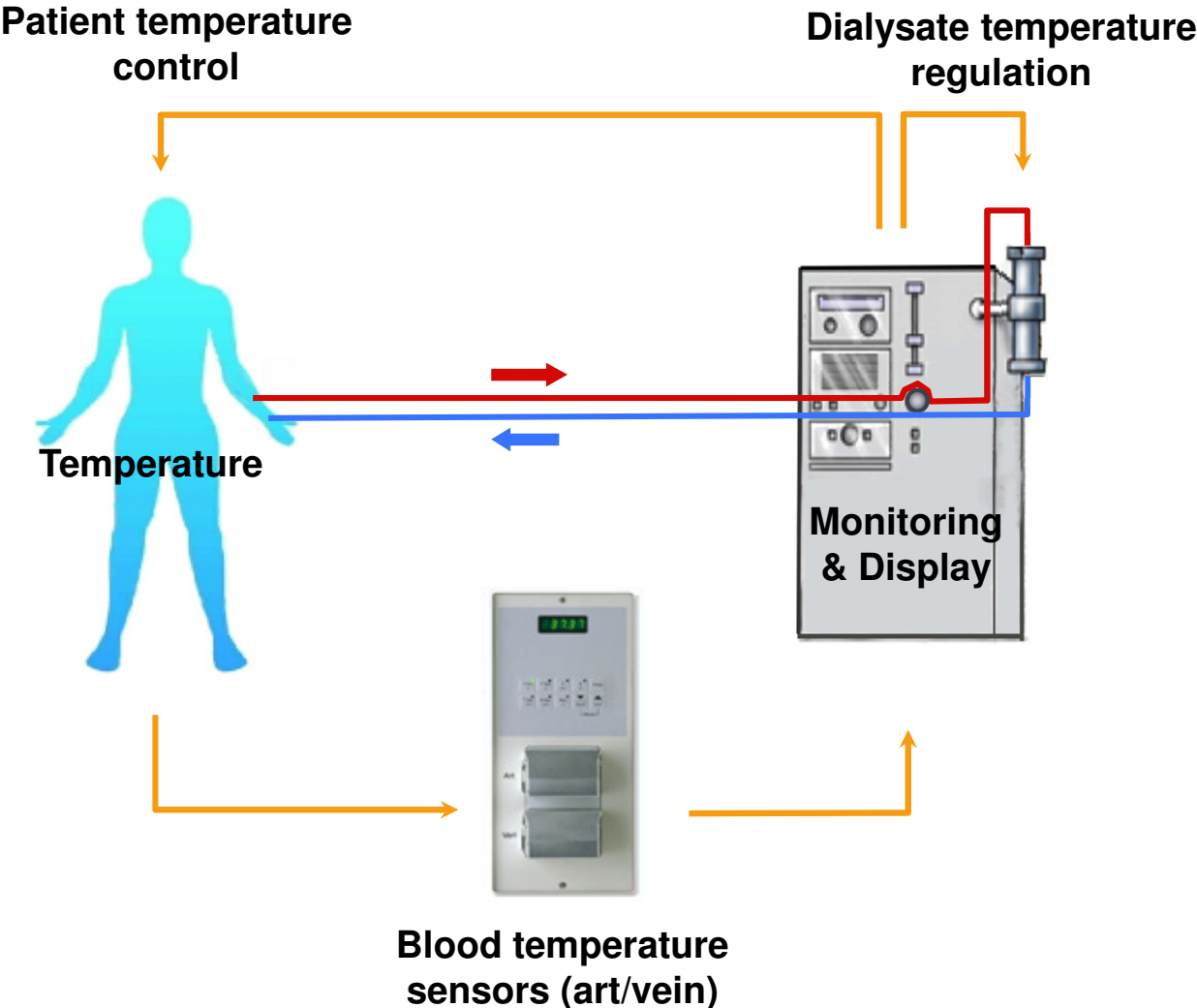


Conductivity changes

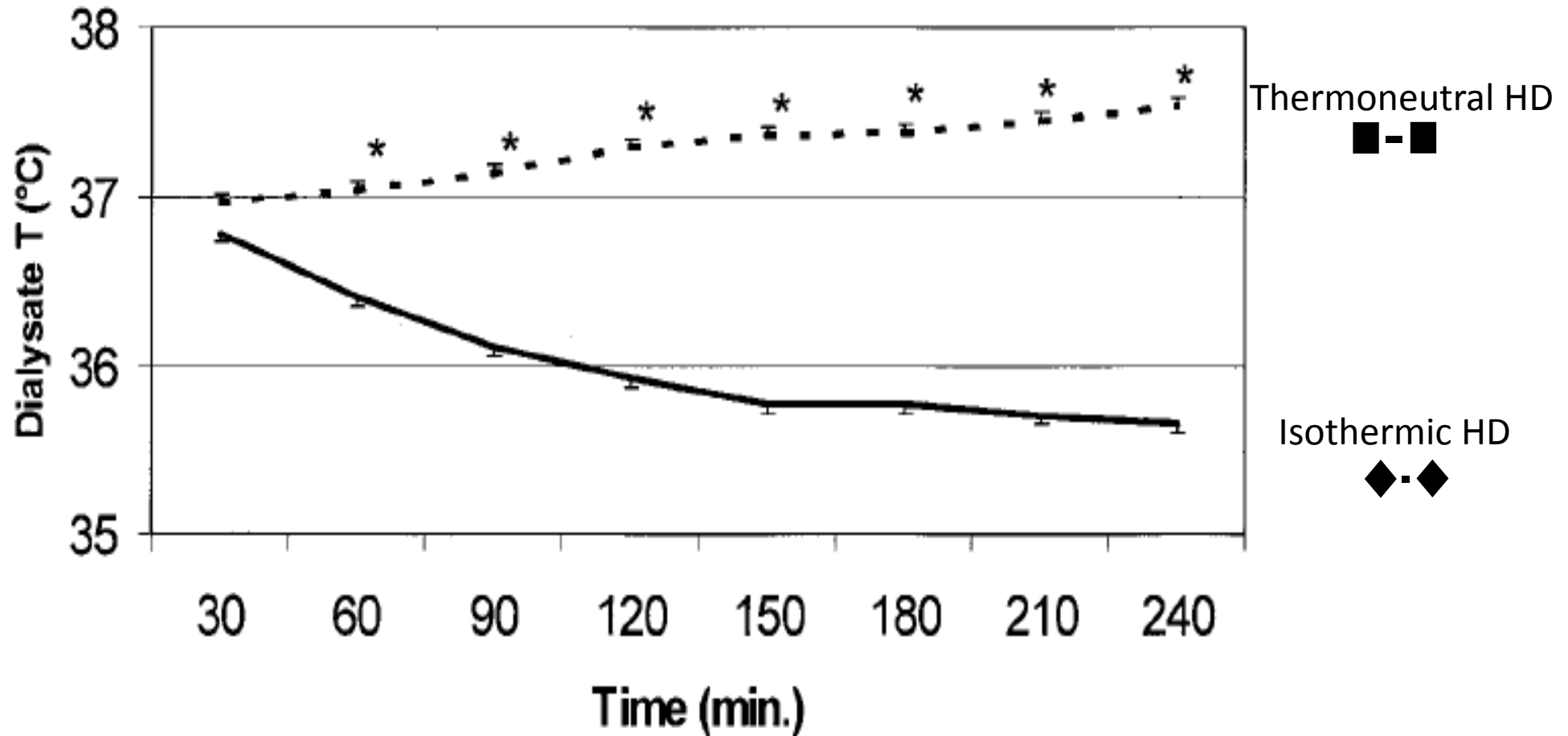


Conductivity sensors
on dialysate
(inlet/outlet)

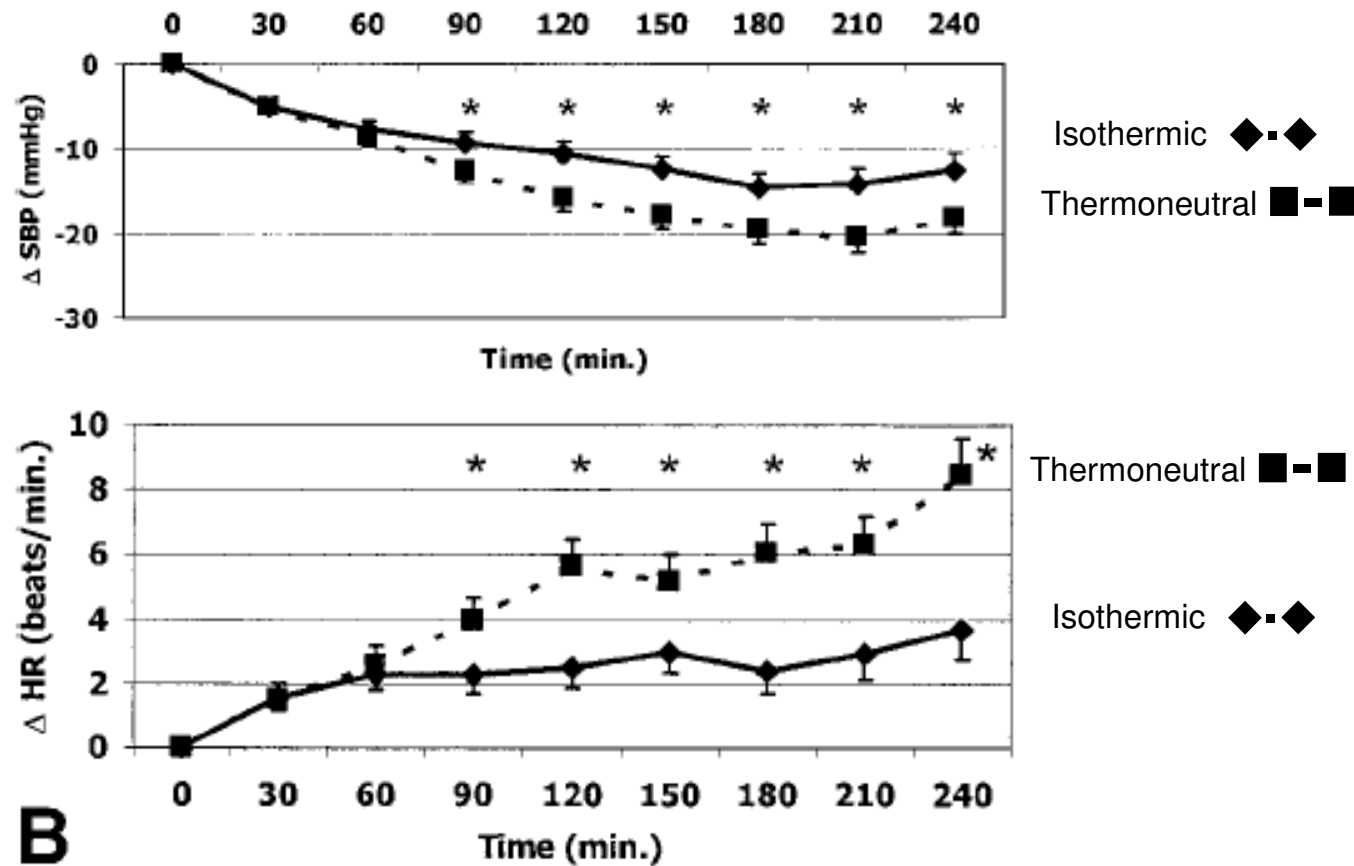
Thermal Balance Control



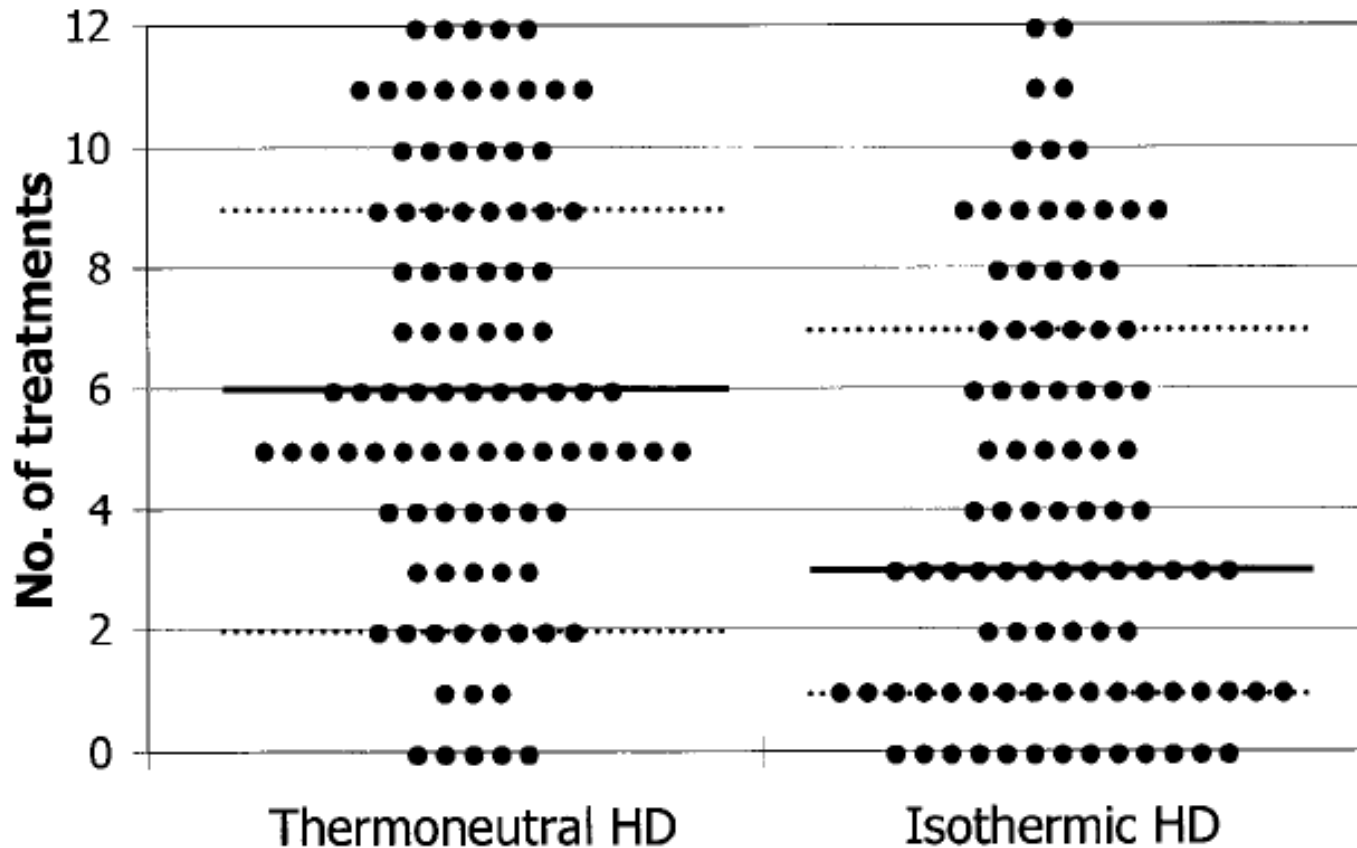
Thermoneutral balance leads HD patient to gain calories and to vasodilation



Changes in blood pressure (systolic) and heart rate according to thermal balance profile



Incidence of IDH Is Significantly Reduced During Isothermic HD

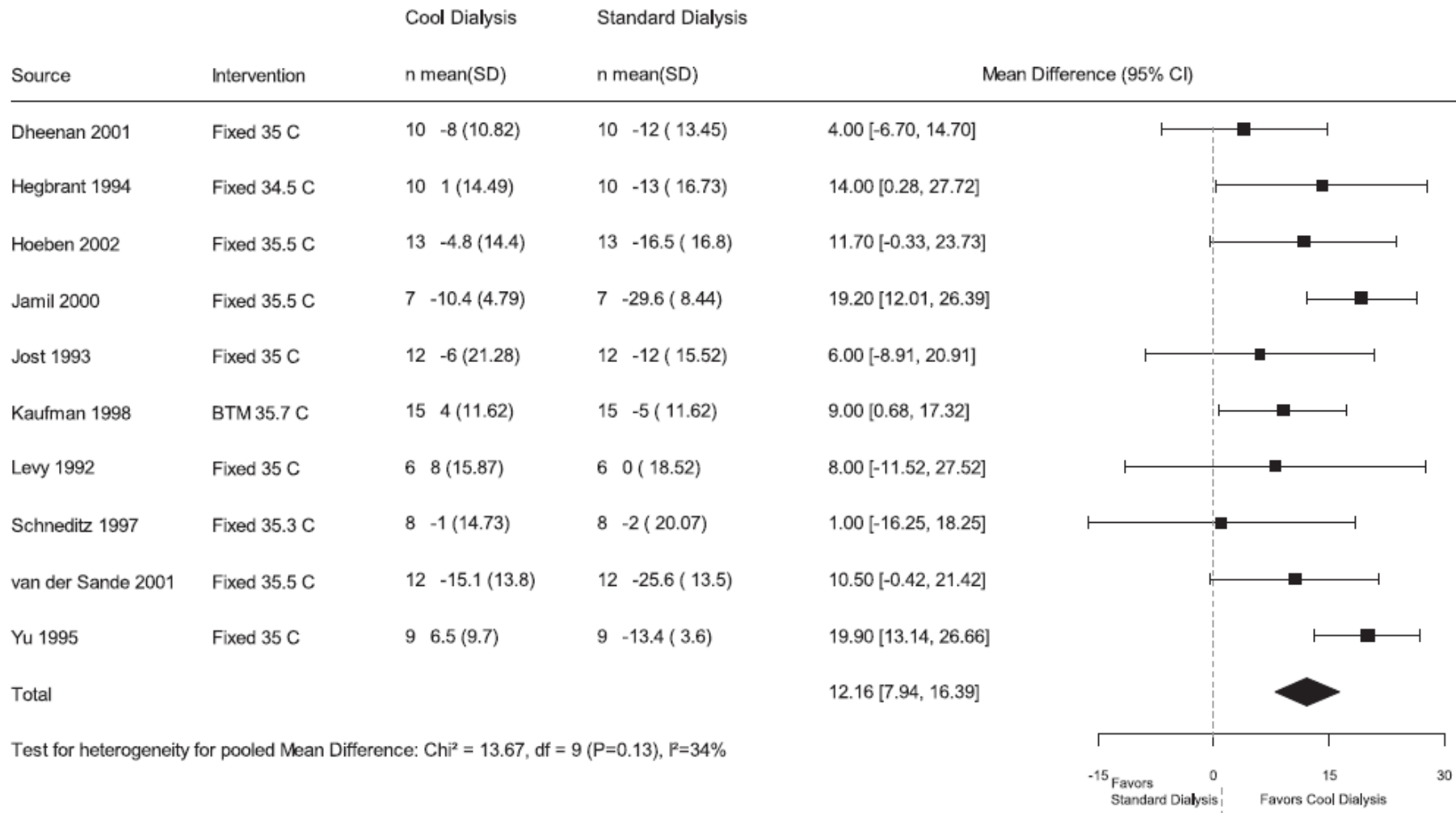


Preservation of Blood Pressure In HD Depends on Thermal Balance and Energy Mass Transfer

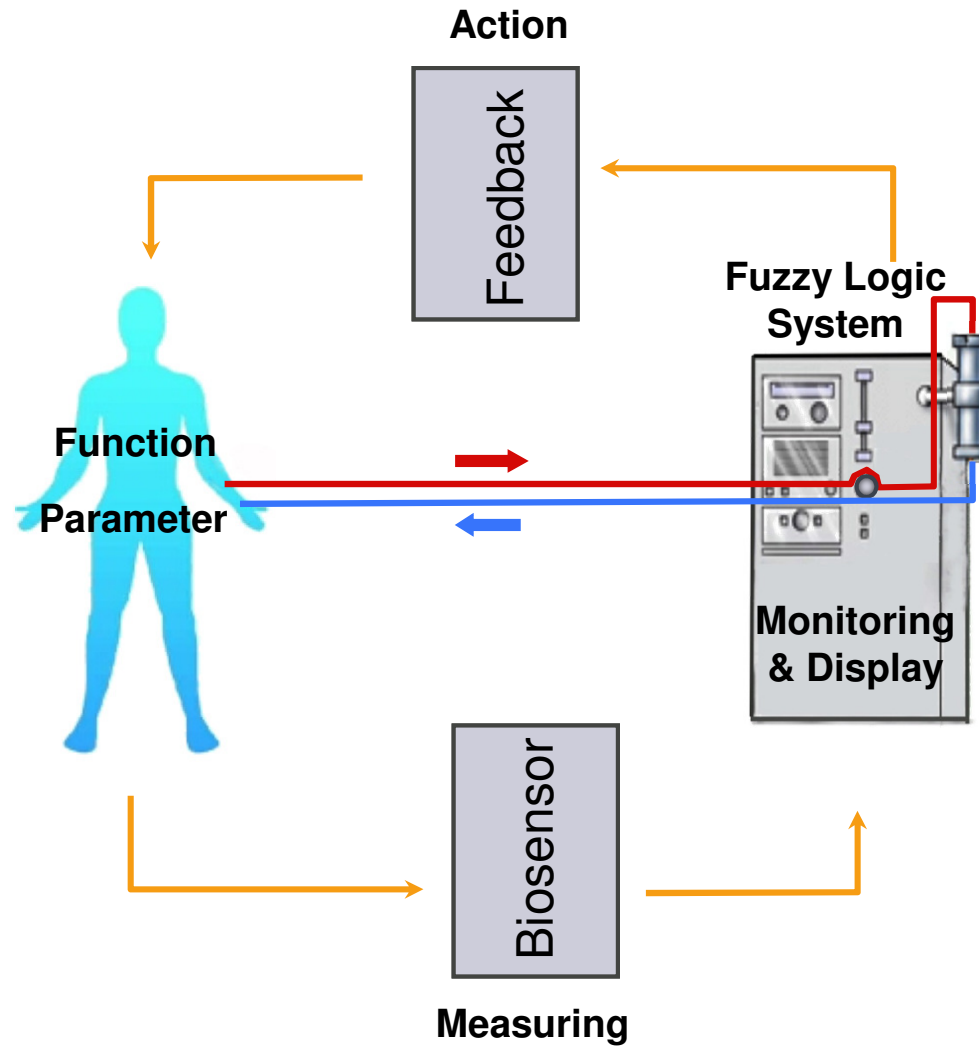
| | Treatment modality | Treatments with hypotension/all treatments (%) | T_{art} 0 min (°C) | ΔT_{av} (°C) | Min BV (%) | ET (W) |
|---------|--------------------|--|-----------------------------|-----------------------------|-------------------------|---------------------------|
| Study A | o-HDF | 1/25 (4%) | 36.4 ± 0.4 | 1.2 ± 0.3 ^c | 91.8 ± 3.1 | -16.6 ± 4.0 ^e |
| | HD | 10/25 ^a (40%) | 36.5 ± 0.5 | 0.4 ± 0.4 ^{c,b} | 94.0 ± 3.2 ^d | -5.4 ± 5.1 ^{b,e} |
| Study B | o-HDF | 1/25 (4%) | 36.5 ± 0.5 | 1.2 ± 0.3 ^c | 92.9 ± 4.0 | -15.9 ± 1.9 ^e |
| | Temp-HD | 1/25 ^f (4%) | 36.5 ± 0.3 | 1.1 ± 0.1 ^c | 93.5 ± 3.8 | -16.3 ± 4.2 ^e |

^a $P < 0.001$, vs o-HDF; ^b $P < 0.0001$, vs o-HDF; ^c $P < 0.0001$, vs beginning; ^d $P < 0.005$, vs o-HDF; ^e $P < 0.001$, vs beginning; ^f $P < 0.001$, vs HD.

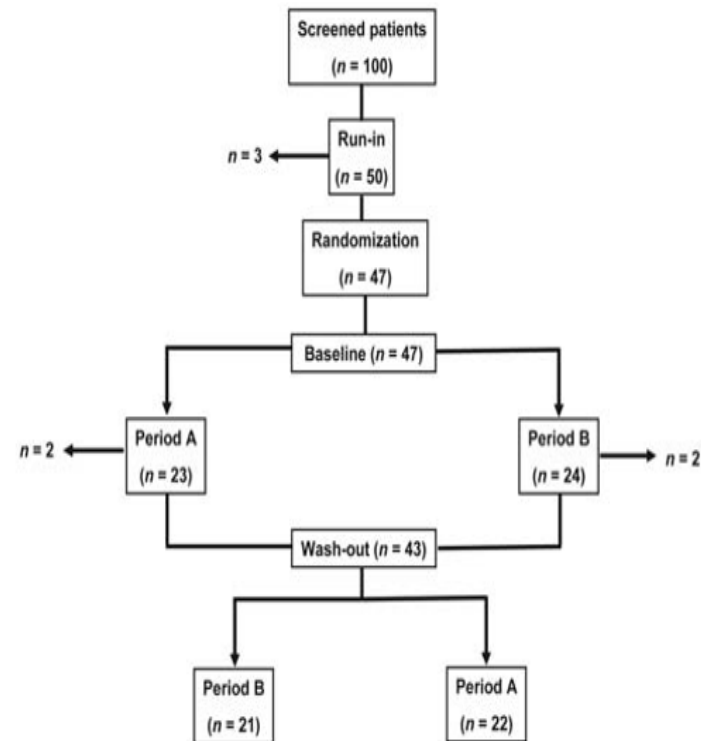
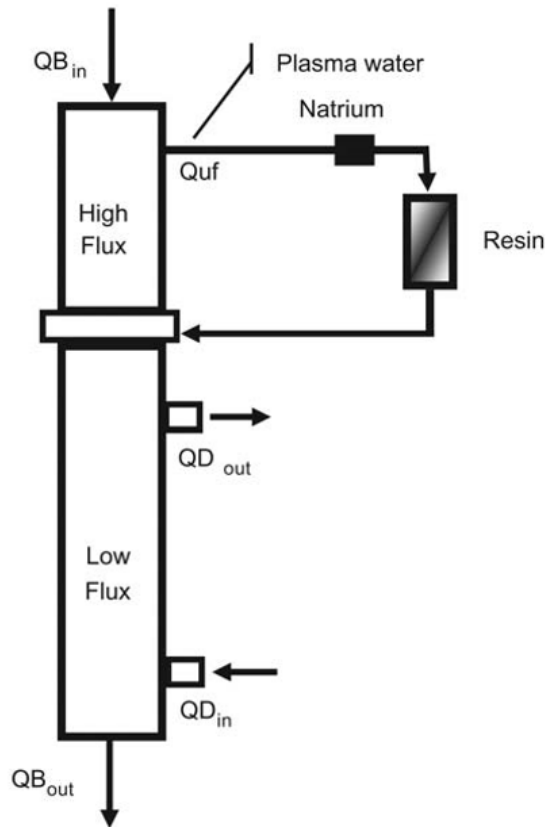
Low Temperature Dialysis Reduces Intra Dialytic Hypotension



Biofeedback systems are on the way



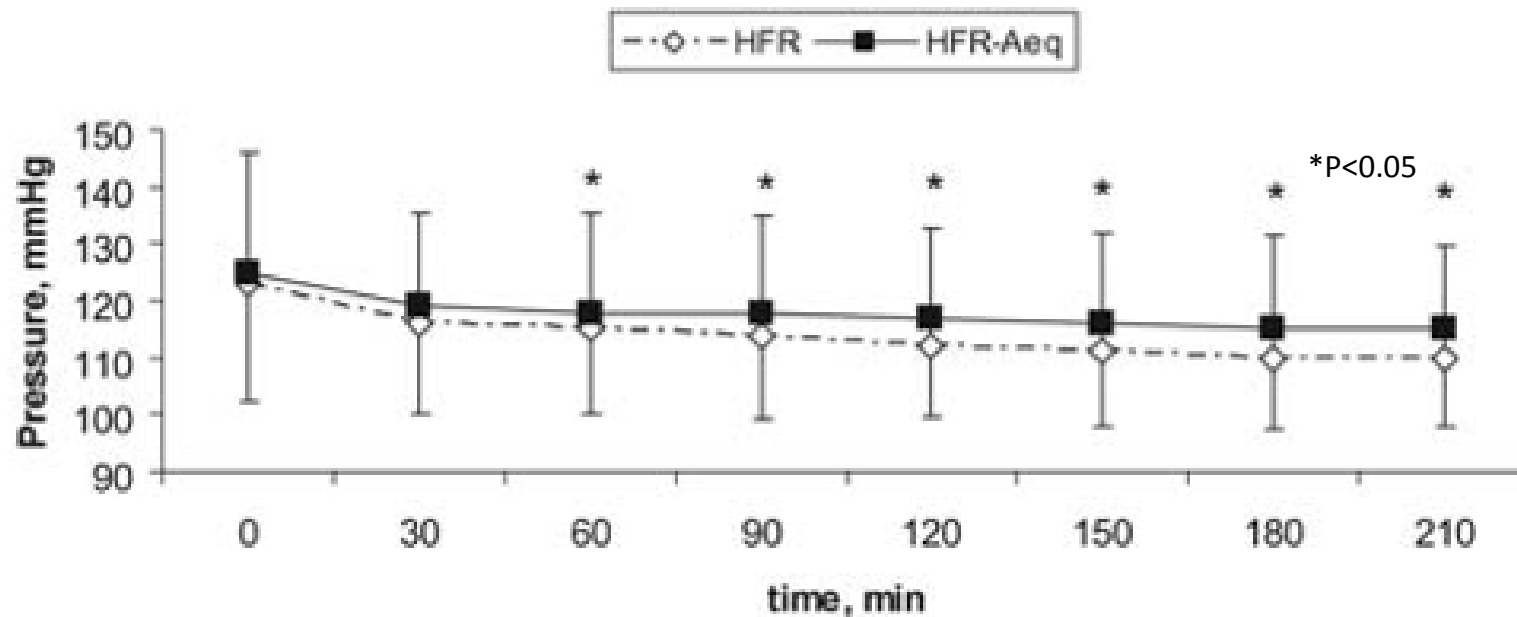
Effect of Plasma Sodium Biofeedback System on Intradialytic Cardiovascular Stability



RCT Cross-Over Study
Intern. multicenter 47 HD Pats

HFR : hemofiltration with endogenous reinfusion
HFR-Aeq : Aequilibrium, HFR plus Na controlled

Effect of Plasma Sodium Biofeedback System on Systolic Blood Pressure During Treatment



RCT Cross-Over Study
Intern. multicenter 47 HD Pats

HFR : hemofiltration with endogenous reinfusion
HFR-Aeq : Aequilibrium, HFR plus Na controlled

Plasma Sodium Biofeedback System Reduces Incidence of IDH

| All patients (<i>N</i> = 143) | HFR (%) | HFR-Aequilibrium (%) | Wilcoxon, <i>P</i> |
|--|---------|----------------------|--------------------|
| Primary end point Dialysis complicated by hypotension | 31 ± 4 | 23 ± 3 | 0.03 |
| Secondary end points | | | |
| Symptomatic hypotensions | 5 ± 1 | 3 ± 1 | 0.04 |
| Intradialytic symptoms | 9 ± 1 | 6 ± 2 | 0.01 |
| Nurse interventions | 22 ± 2 | 17 ± 3 | <0.01 |

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 - Means: diet, residual kidney function, hemodialysis, time
 - Stepwise approach
- 5. Take home message**

Take Home Message

- Restoring and controlling **sodium and fluid mass balance** are major targets of renal replacement adequacy
- **Sodium mass removal** relies on two components: **diffusive and convective**
- **Ultrafiltration** is a surrogate of sodium mass and fluid removal
- **Intradialytic hypotension** episodes have significantly reduced over time and are now recognized as a **risk factor for CV injury**
- Sodium and fluid control is a **trade-off** between risks of **EC fluid overload and depletion**
- **Dry weight probing** requires more sophisticated tools for assessment
- Prevention of intradialytic hypotension is **suitable, feasible and achievable**

Sodium and Fluid Mass Balance in HD Patient

Unstable Equilibrium

EC Fluid Overload

- Hypertension
- Left Ventricular Hypertrophy
- Lung edema
- Inflammation
- Malnutrition...



EC Fluid Depletion

- IDH
- Silent ischemic insults
- Cardiac stunning
- Gut ischemia
- Brain damage
- Liver damage...

