Cardiorenal Syndrome

ACOI 2019

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Disclosures

Nothing to declare

Case

65 yo woman admitted for ADHF – DOE and peripheral edema, PND and orthopnea

PE – edema, +JVD, rales, enlarged apex with Systolic Murmur of MR

Echo – moderate pulm HTN, moderate MR and EF 55%

Case

BP 122/ HR 88 RR 22

Admission labs – Creatinine 2.4 (1.5), Na 129, and Hg 9.5

Outpatient meds – lisinopril 20, metoprolol 50 and furosemide 40 2X day

What is her diagnosis?

How to manage volume?

ADHF - Background

#1 admission diagnosis in patients > 65 yo

Inpatient mortality – 4%

30 day readmission rate - 27%

Renal Disease in patients with ADHF

ADHERE – 105,000 - 30% with GFR < 45 ml/min

The worse the heart failure the worse the average GFR

Lower GFRs are associated with worse outcomes (inpatient and outpatient)

CKD has high incidence for CV disease and CHF is more common

Cardiorenal Syndromes

Definition – Negative effects of heart or kidney dysfunction on the other organ

CRS 1 - rapid worsening of cardiac function leading to AKI

CRS 2 – chronic cardiac dysfunction leads to CKD

CRS 3 – AKI leads to cardiac dysfunction

CRS 4 – CKD and cardiovascular disease

CRS 5 – Systemic illness affecting heart and kidney

AKI in ADHF

- AKI (creatinine elevation >0.2)in all patients has been shown (not always) to predict poor outcomes
- Admission and discharge GFR are best outcome predictors in ADHF
- Rarely due to over diuresis in 1st 72 hrs, elevated CVP and IAP are predictive of AKI and often present in the patient with AKI

AKI ADHF

AKI – uses KDIGO definition – abrupt and sustained elevation of creatinine by 0.3

Associated with worse outcomes

WRF – worsening renal function – 0.3 elevation in creatinine at time of DC.

outcomes mixed. Some studies have shown improved prognosis (? More decongestion)

AKI CRS 1

3 Phenotypes

1. AKI that gets better with diuresis
2. AKI ATN from “flash” pulmonary edema
3. GFR stable then worse with diuresis (always thought to be due to over diuresis but 75% still with high RAP)

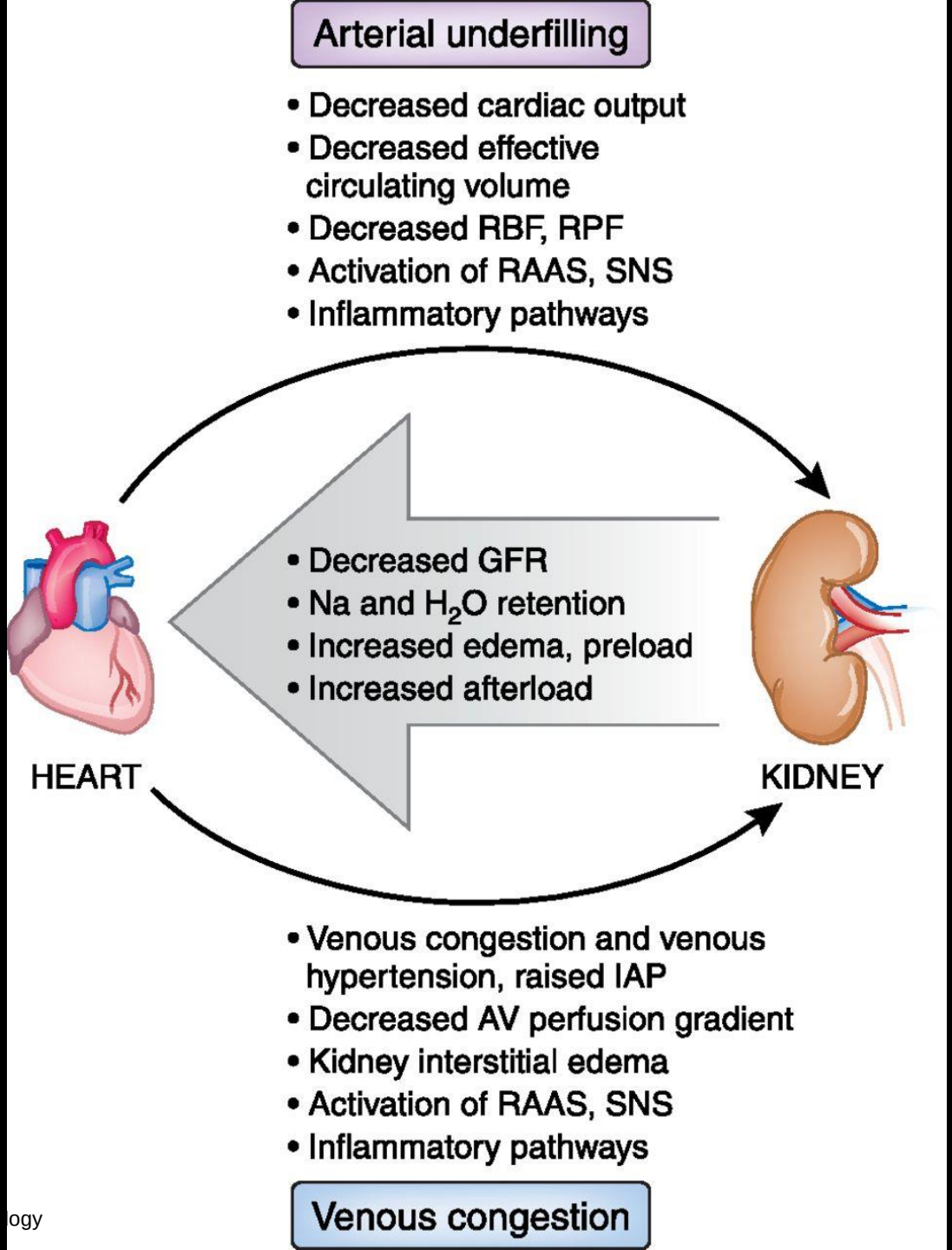
Pathophysiology of CRS

Low flow state - poor CO leads to renal hypoperfusion and worsening GFR. Therapies directed at improving flow have not lead to improved outcomes

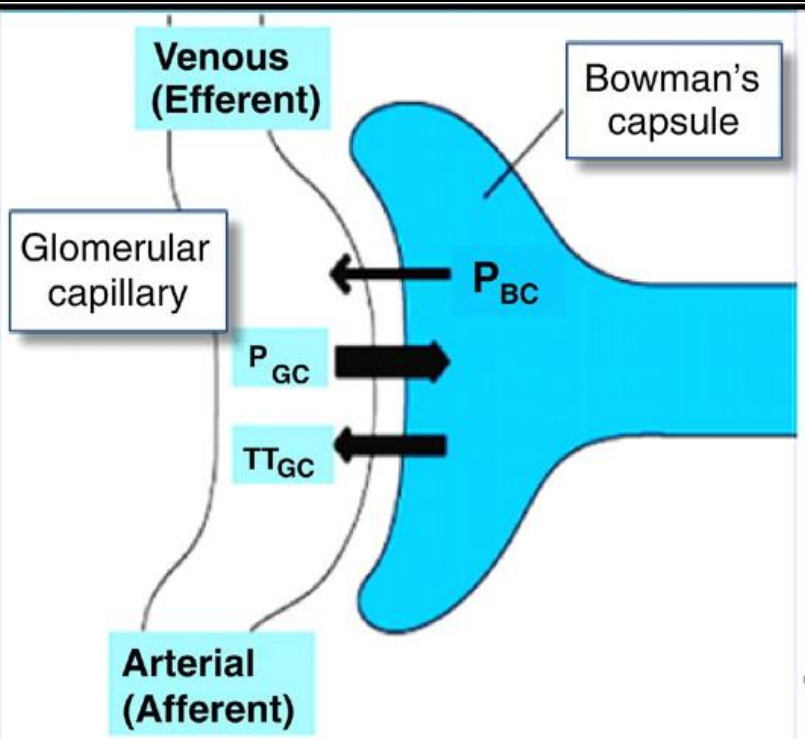
ESCAPE – use of PA catheters to diagnose and aid in therapy of ADHF. No correlation between CO and GFR. RAP was the strongest predictor of outcomes and GFR (venous congestion). This is a back flow disease. Happens as frequently in ADHFpEF

Intra-abdominal hypertension

Pulmonary HTN

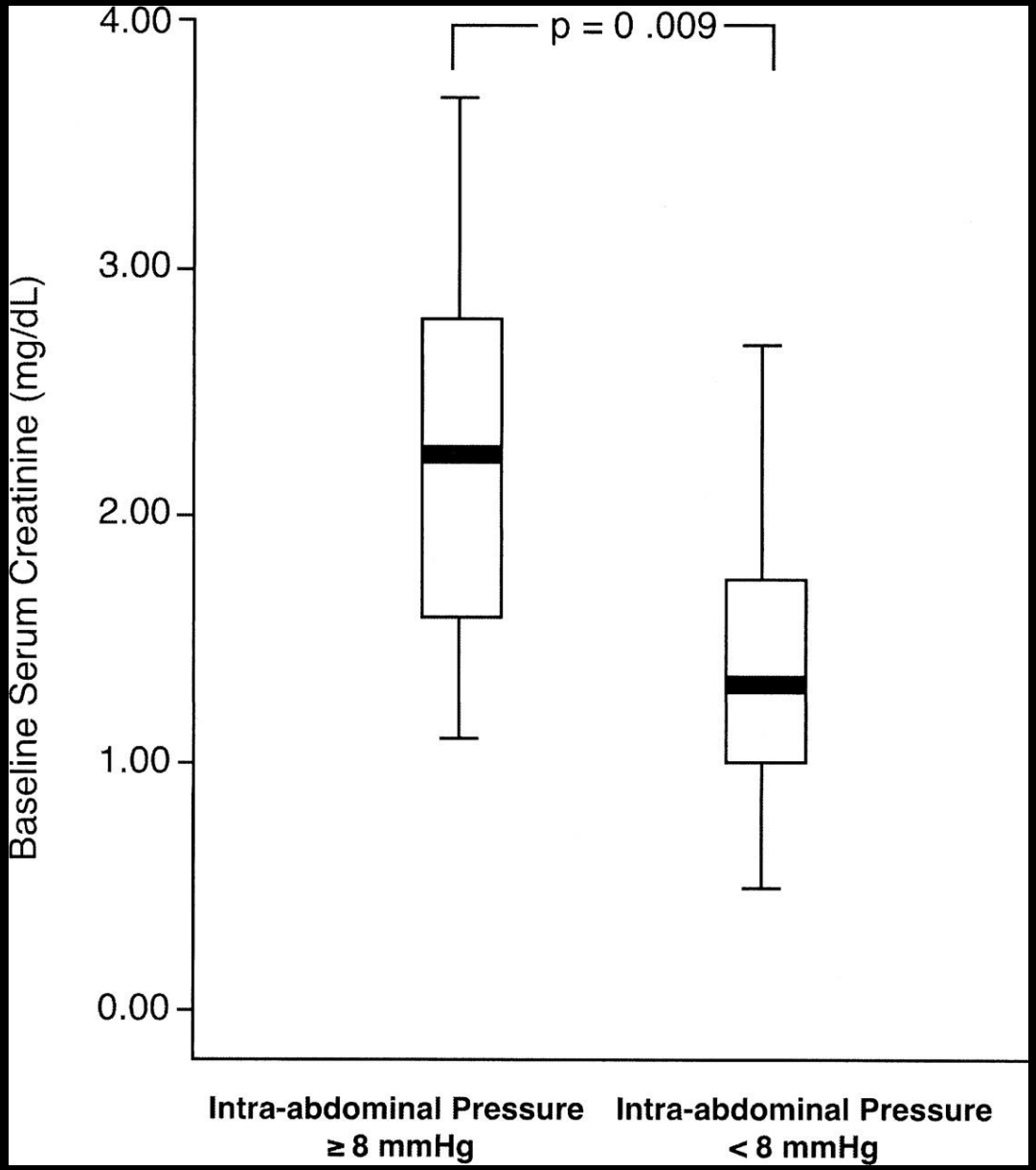

Arterial underfilling
• Decreased cardiac output
• Decreased effective circulating volume
• Decreased RBF, RPF
• Activation of RAAS, SNS
• Inflammatory pathways
• Decreased GFR
• Na and H_2O retention
• Increased edema, preload
• Increased afterload
HEART
KIDNEY
• Venous congestion and venous hypertension, raised IAP
• Decreased AV perfusion gradient
• Kidney interstitial edema
• Activation of RAAS, SNS
• Inflammatory pathways
Venous congestion

Impact of Venous Congestion on Glomerular Net Filtration Pressure

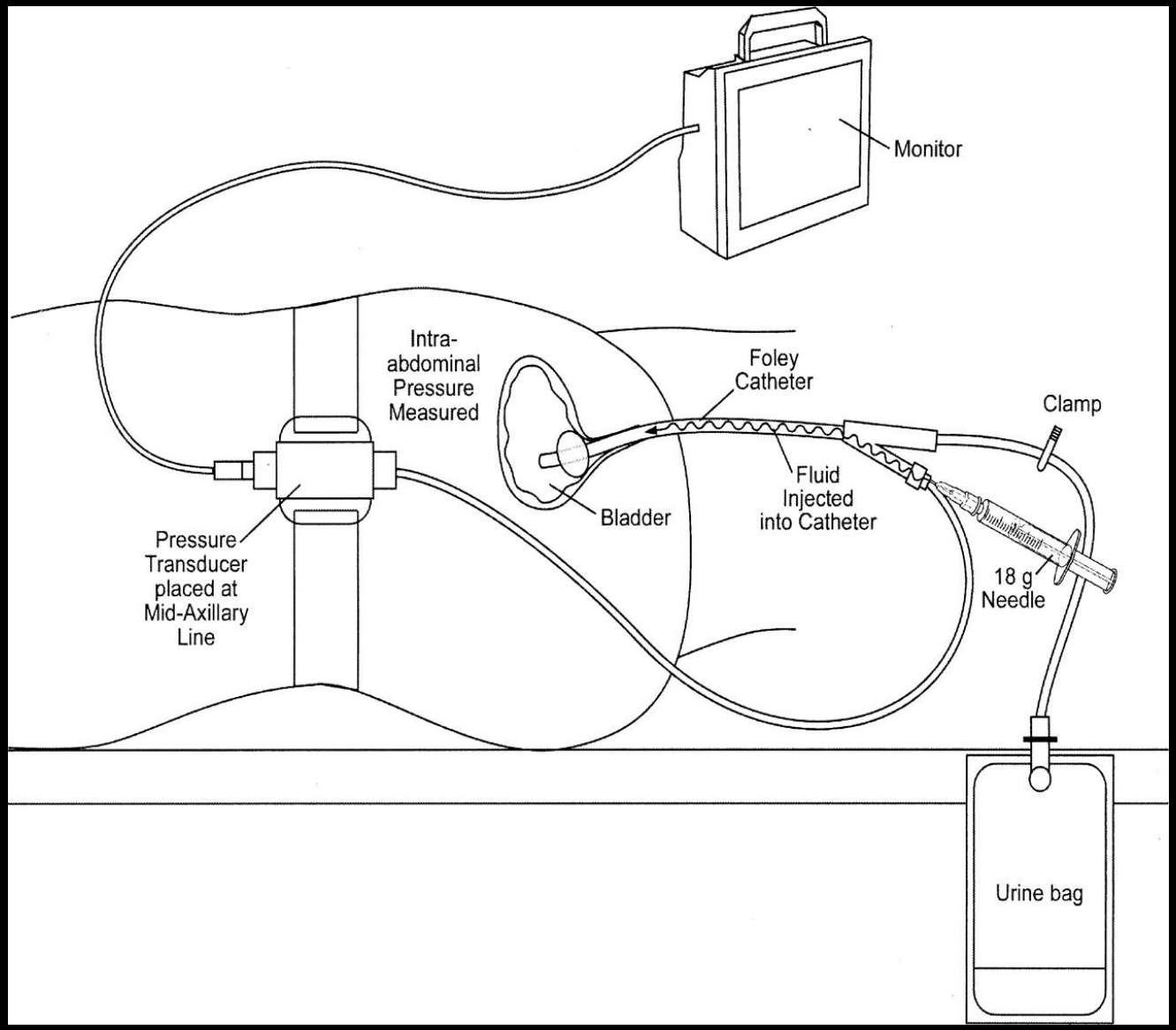


Forces	Normal: Afferent end of glomerular capillary (mmHg)	Normal: Efferent end of glomerular capillary (mmHg)	↑ RA pressure: Afferent end of glomerular capillary (mmHg)	↑ RA pressure: Efferent end of glomerular capillary (mmHg)
1. Favoring Filtration				
Glomerular-capillary hydrostatic pressure, P_{GC}	**60**	**58**	**55**	**63**
2. Opposing Filtration				
a. Hydrostatic pressure in Bowman's capsule, P_{BC}	**15**	**15**	**15**	**15**
b. Oncotic pressure in glomerular capillaries, π_{GC}	**21**	**33**	**21**	**33**
Net filtration pressure (1-2)	**24**	**10**	**19**	**15**
Filtration pressure:	*14 mmHg*		*4 mmHg*	

Baseline Serum Creatinine Level and IAP



Transvesical Method for Measuring Intra-Abdominal Pressure



Mullens, W. et al. J Am Coll Cardiol 2008;51:300-306

Intra Abdominal Hypertension

- Mullens intervention trial – refractory ADHF patients (9) with elevated IAP received paracentesis or ultrafiltration which resulted in a decrease in IAP 13 to 7.
- Creatinine improved from 3.4 to 2.4 and there was no change in hemodynamics

ADHF – Goals of Therapy

1. Adequate decongestion
2. Improved patient outcomes
3. Decreased hospital readmissions
4. No significant complications

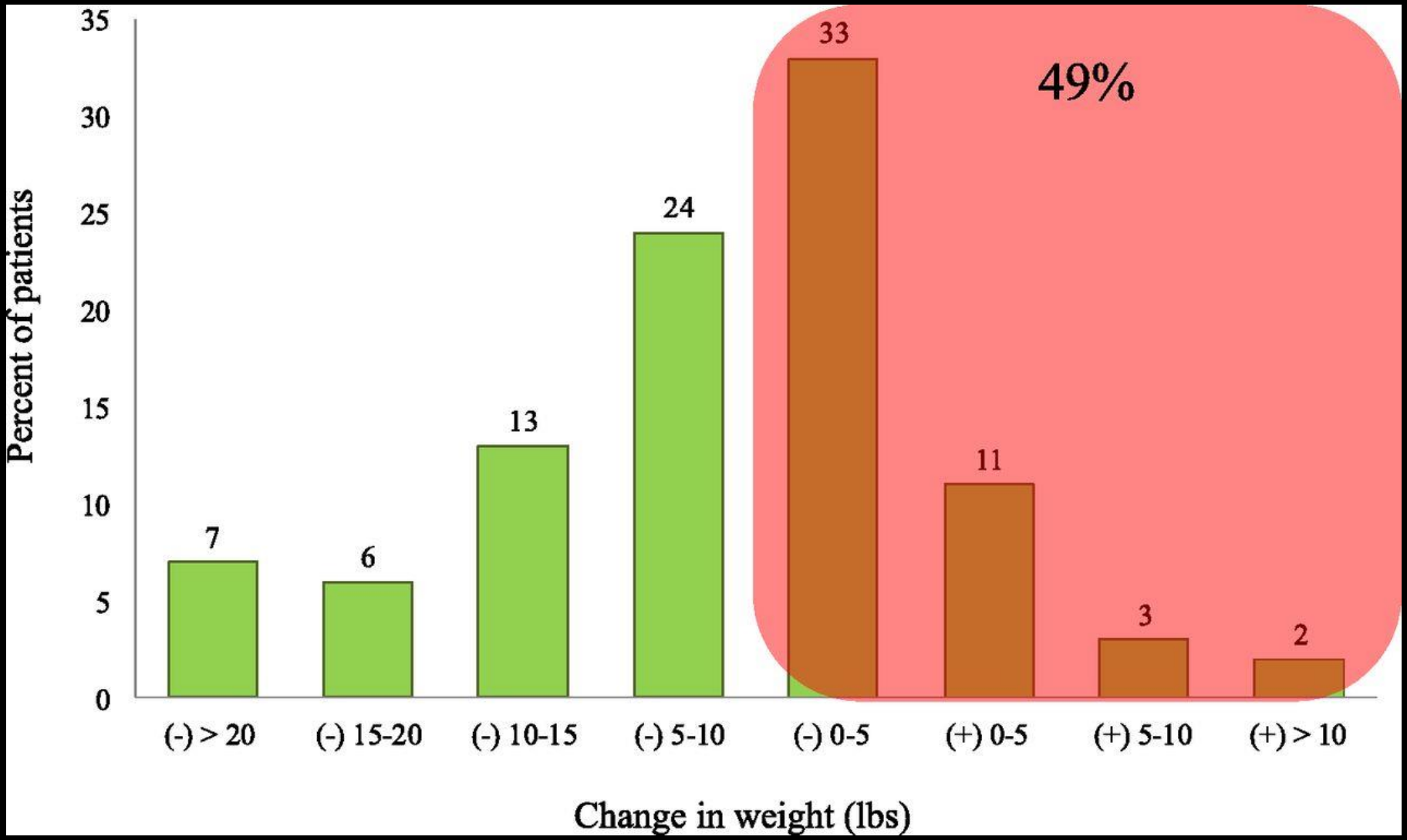
Decongestion

Patients admitted for ADHF are often inadequately decongested

European registry data

If therapies are compared, they should have similar degrees of decongestion

Patients admitted for ADHF are often inadequately decongested


35
30
25
20
15
10
5
0
Percent of patients
7
6
13
24
33
11
3
2
49%
(-) > 20
(-) 15-20
(-) 10-15
(-) 5-10
(-) 0-5
(+) 0-5
(+) 5-10
(+) > 10
Change in weight (lbs)

DOSE Trial

308 patients with ADHF RCT comparing low dose (outpt dose) vs. high dose (2.5X outpt dose) q12 bolus furosemide

Bolus was compared to continuous infusion

High dose better for relief of symptoms and decongestion

Bolus and continuous equal

STANDARD DIURETIC DOSE 2.5X OUTPATIENT

Secondary End Points for Each Treatment Comparison.

Table 2. Secondary End Points for Each Treatment Comparison.*

End Point	Bolus Every 12 Hr (N=156)	Continuous Infusion (N=152)	P Value	Low Dose (N=151)	High Dose (N=157)	P Value
AUC for dyspnea at 72 hr	4456±1468	4699±1573	0.36	4478±1550	4668±1496	0.04
Freedom from congestion at 72 hr — no./total no. (%)	22/153 (14)	22/144 (15)	0.78	16/143 (11)	28/154 (18)	0.09
Change in weight at 72 hr — lb	−6.8±7.8	−8.1±10.3	0.20	−6.1±9.5	−8.7±8.5	0.01
Net fluid loss at 72 hr — ml	4237±3208	4249±3104	0.89	3575±2635	4899±3479	0.001
Change in NT-proBNP at 72 hr — pg/ml	−1316±4364	−1773±3828	0.44	−1194±4094	−1882±4105	0.06
Worsening or persistent heart failure — no./total no. (%)	38/154 (25)	34/145 (23)	0.78	38/145 (26)	34/154 (22)	0.40
Treatment failure — no./total no. (%)†	59/155 (38)	57/147 (39)	0.88	54/147 (37)	62/155 (40)	0.56
Increase in creatinine of >0.3 mg/dl within 72 hr — no./total no. (%)	27/155 (17)	28/146 (19)	0.64	20/147 (14)	35/154 (23)	0.04
Length of stay in hospital — days			0.97			0.55
Median	5	5		6	5	
Interquartile range	3–9	3–8		4–9	3–8	
Alive and out of hospital — days			0.36			0.42
Median	51	51		50	52	
Interquartile range	42–55	38–55		39–54	42–56	

* Plus–minus values are means ±SD. To convert pounds to kilograms, divide by 2.2. AUC denotes area under the curve, and NT-proBNP N-terminal pro-brain natriuretic peptide.

† Treatment failure was defined as the development of any one of the following during the 72 hours after randomization: increase in serum creatinine level of more than 0.3 mg per deciliter (26.5 μmol per liter), worsening or persistent heart failure, clinical evidence of excessive diuresis requiring intervention (e.g., administration of intravenous fluids), or death.

Felker GM et al. N Engl J Med 2011;364:797-805.

AT RANDOMIZATION – STEPPED PHARMACOLOGIC CARE ARM

UO > 5 L/day → Reduce current diuretic regimen *if desired*
UO 3-5 L/day → Continue current diuretic regimen
UO < 3 L/day → See table

	Current Dose		Suggested Dose	
	loop (/day)	thiazide	loop (/day)	thiazide
A	≤ 80	+ or -	40 mg iv bolus+ 5 mg/hr	0
B	81-160	+ or -	80 mg iv bolus+ 10 mg/hr	5 mg metazolone QD
C	161-240	+ or -	80 mg iv bolus+ 20 mg/hr	5 mg metazolone BID
D	> 240	+ or -	80 mg iv bolus+ 30 mg/hr	5 mg metazolone BID

AT 24 Hrs - STEPPED PHARMACOLOGIC CARE ARM

Persistent Volume Overload Present
UO > 5 L/day → Reduce current diuretic regimen *if desired*
UO 3-5 L/day → Continue current diuretic regimen
UO < 3 L/day → Advance to next step on table

AT 48 Hrs - STEPPED PHARMACOLOGIC CARE ARM

Persistent Volume Overload Present
UO > 5 L/day → Reduce current diuretic regimen *if desired*
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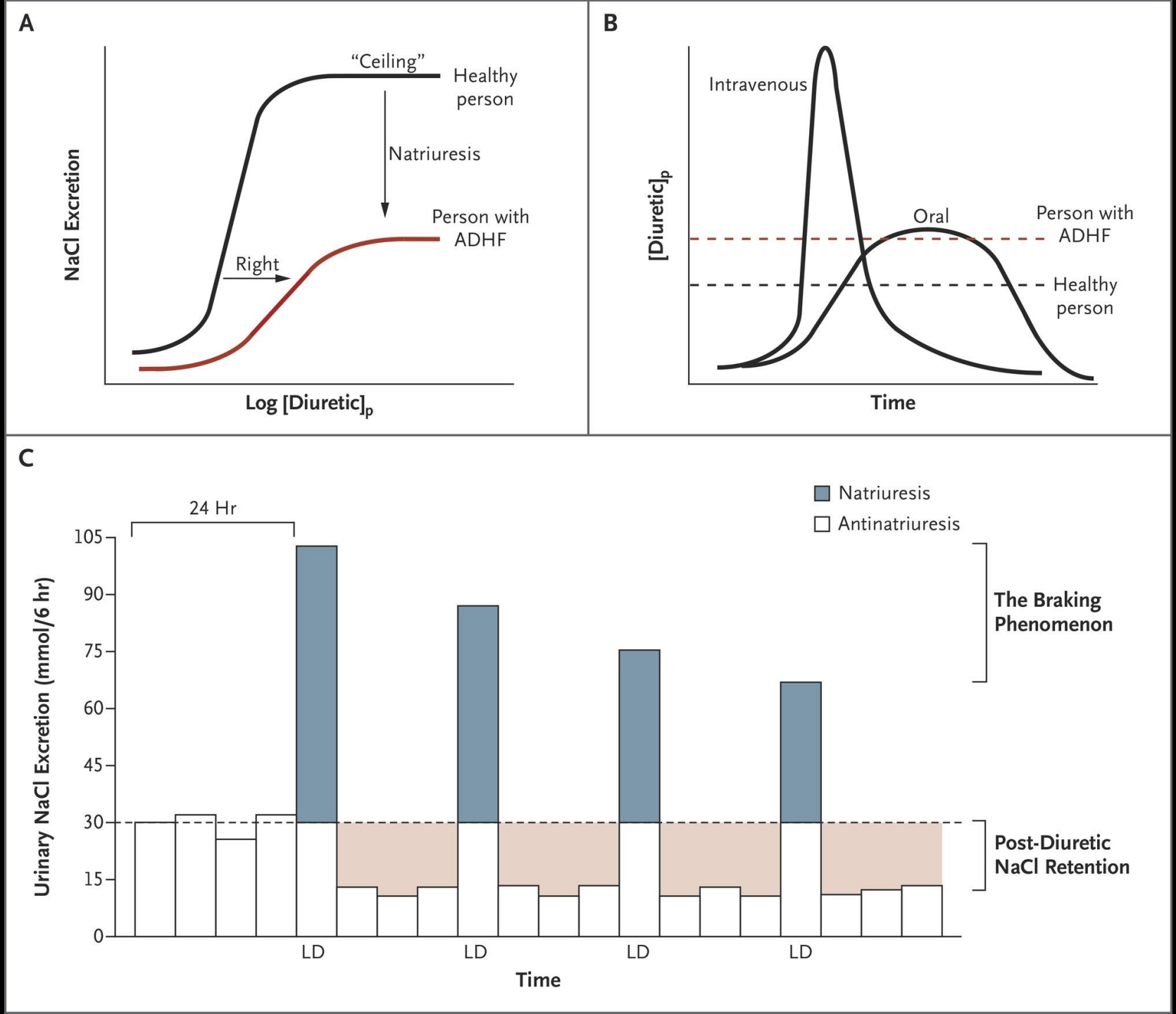
Dopamine or dobutamine at 2 ug/kg/hr if SBP < 110 mmHg and EF<40% or RV systolic dysfunction. Nitroglycerin or Nesiritide if SBP > 120 (any EF) and Severe Symptoms


A
"Ceiling"
Healthy person
Natriuresis
Person with ADHF
Right
NaCl Excretion
Log [Diuretic]p
B
Intravenous
Oral
Person with ADHF
Healthy person
[Diuretic]p
Time
C
24 Hr
Natriuresis
Antinatriuresis
105
90
75
60
45
30
15
0
Urinary NaCl Excretion (mmol/6 hr)
LD
LD
LD
LD
Time
The Braking Phenomenon
Post-Diuretic NaCl Retention

Diuretics in ADHF

- Diuretic dose should be 2.5X outpatient dose
- Titration should occur at least 2X day to achieve a urine output of 100-250 mL/hr
- Continuous infusion = bolus
- This should occur until adequate decongestion occurs
- This dosing strategy should be compared to other therapies - ULTRAFILTRATION

Diuretics in ADHF

Diuretic resistance = UO < 3000 ml/d on maximum diuretics (furosemide 240 IV q 6h)

Options – UF, HD, thiazides, vaptans, inotropes, paracentesis

Why Ultrafiltration(UF)

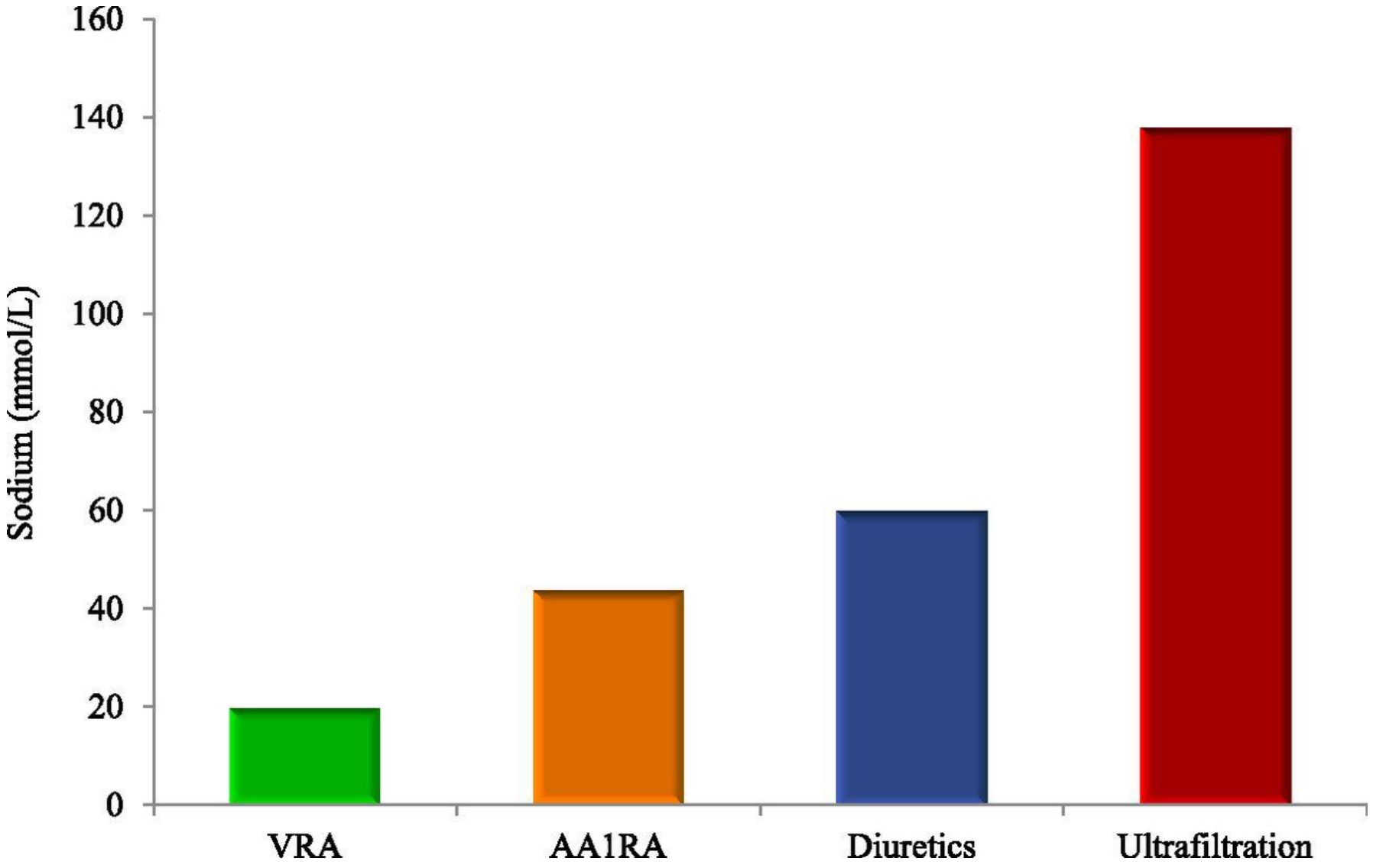
- Usual care does not improve outcomes in ADHF
- UF Theoretical advantages
  - Isotonic fluid removal (more Na removed)
  - Better decongestion
  - Decreased risk of electrolyte abnormalities
  - Inpatient or outpatient
  - Will lead to sustained hemodynamic and neuro-humoral changes

Why Ultrafiltration(UF)

UF theoretical disadvantages

- High cost
- Need for venous access (may be peripheral)
- Anticoagulation
- Availability
- Outcomes

Comparison of sodium removal with various treatment options.



The New England
Journal of Medicine

Volume 291 OCTOBER 10, 1974 Number 15

TREATMENT OF SEVERE FLUID OVERLOAD BY ULTRAFILTRATION

MARC ELIOT SILVERSTEIN, M.D., CHERYL A. FORD, B.S., MICHAEL J. LYSAGHT, M.S., AND LEE W. HENDERSON, M.D.

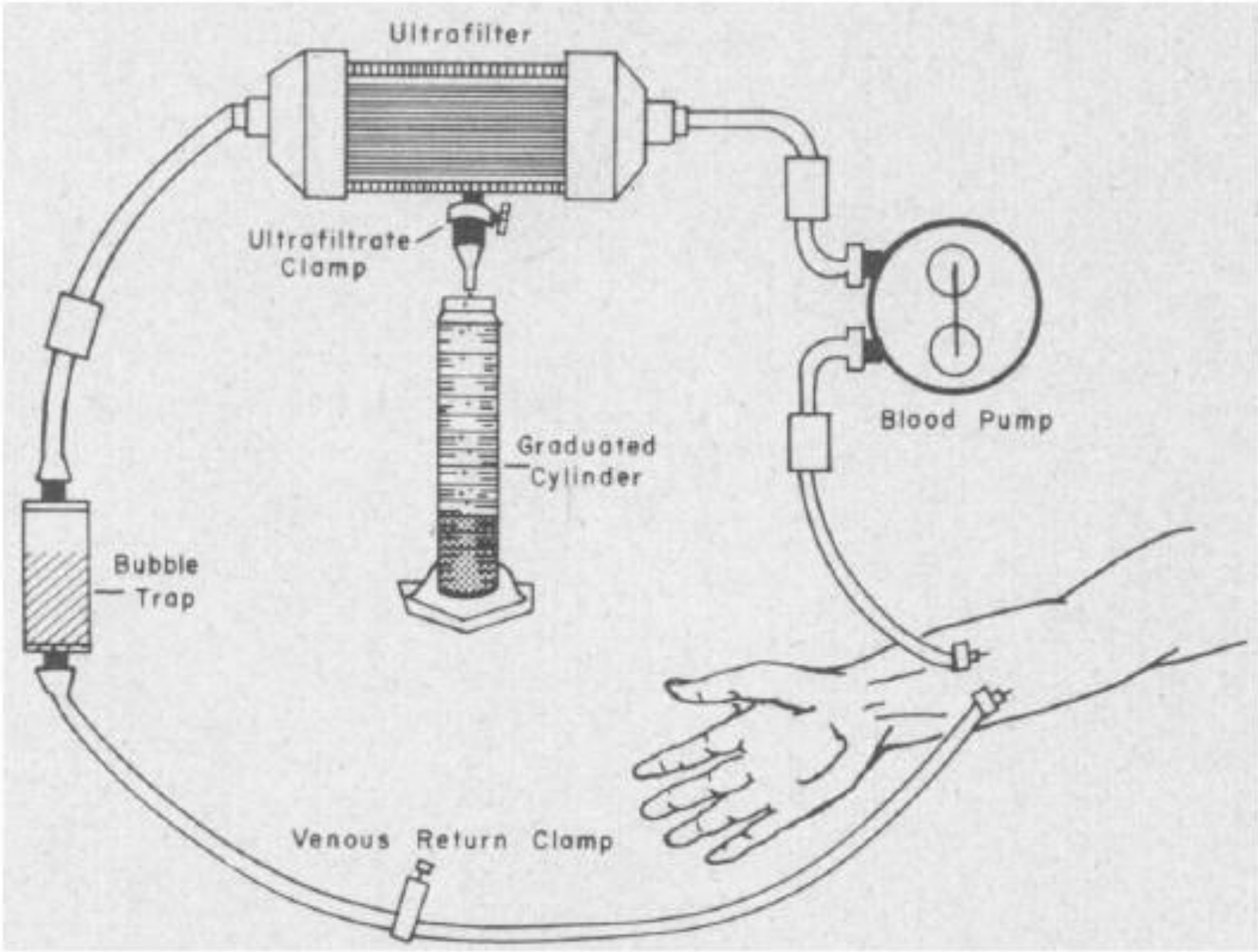


Figure 6. Extracorporeal Circuit for Use of the Ultrafilter in Clinical Setting Other than Extracorporeal Hemodialysis.

ADHF – Role for Ultrafiltration

Clinical Trials

- RAPID – CHF
- UNLOAD
- CARRESS – HF
- AVOID - HF

CARRESS – HF

RCT 188 patients ADHF and worsening renal function – UF vs. defined medical care

Exclusion – creatinine > 3.5

Weight loss at 96 hrs same in both groups

GFR declined in UF group

Because of GFR decrease and adverse events study stopped short of goal of 200 patients

RATE OF CLINICAL DECONGESTION 10% (96 hrs)

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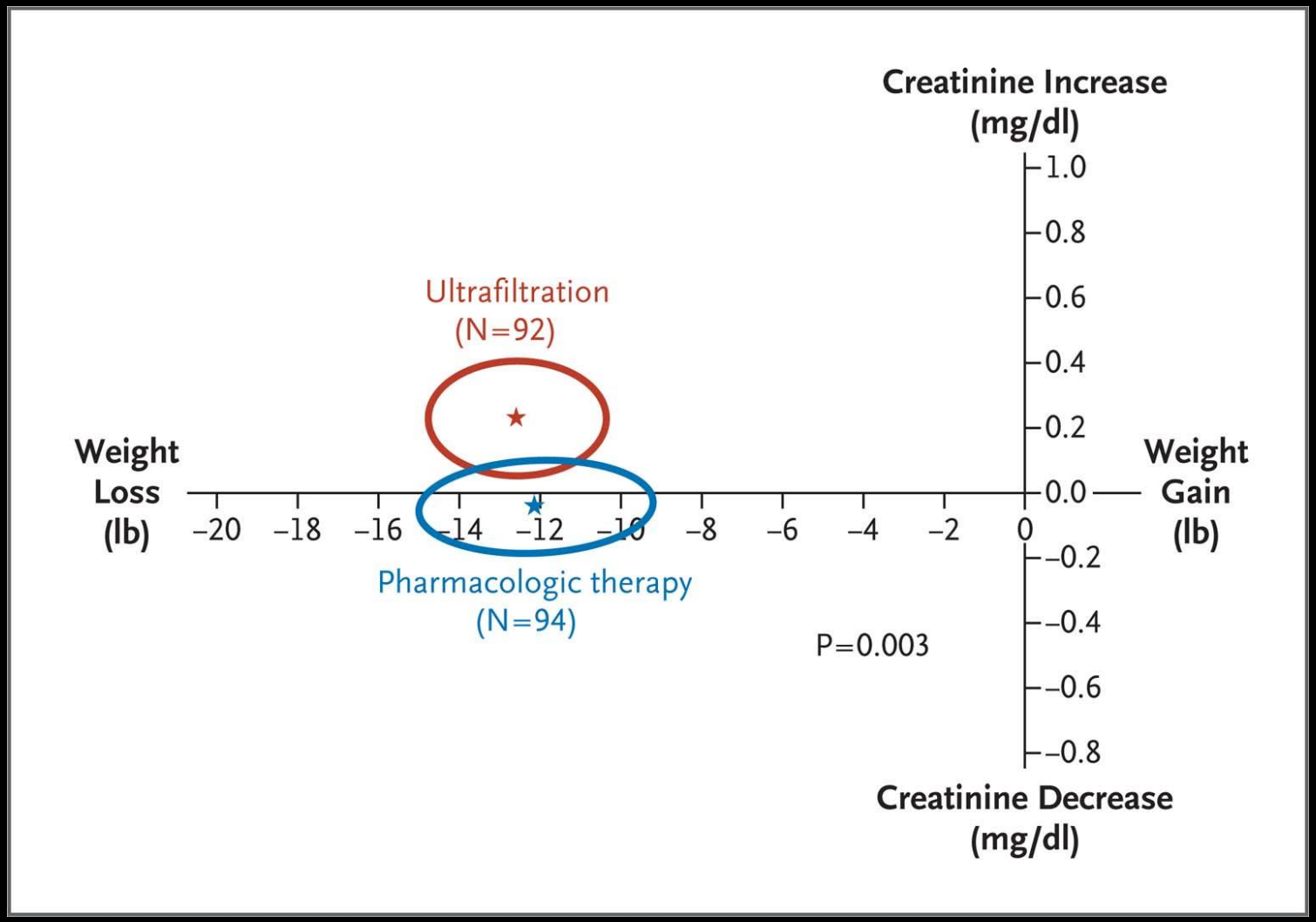
Changes in Serum Creatinine and Weight at 96 Hours (Bivariate Response).



Bart BA et al. N Engl J Med 2012;367:2296-2304

UF Recommendations

Canada, US and European guidelines

- UF **may** be considered as an alternative treatment for ADHF in diuretic resistant patients
- Definition of diuretic resistance unclear (< 3000 mL urine output day on titrated loop diuretics?)
- UF should be one component of protocolized guideline treatment of ADHF

Table 1 Clinical assessment of acute heart failure syndromes, adapted and modified [3]

		Congestion	
		−	+
Adequate perfusion	+	Dry and warm	Wet and warm Orthopnea, rales Abnormal valsalva ↑Jugular venous pressure Abdominojugular reflux Hepatomegaly
	−	Dry and cold ↓Pulse pressure Cool extremities Altered mentation Worsening renal function	Wet and cold Hepatomegaly Ascites Edema

ADHF – Treatment (warm and wet)

- 2.5X home diuretics total for 24 hrs and give IV q6. Reassess in 6-12 hours
- If UO adequate – continue. If not – double diuretics. Reassess in 6-12 hours
- If UO adequate – continue. If not – continuous loop diuretic. Reassess in 6-12 hours
- If UO adequate – continue. If not –DIURETIC RESISTANT
- UO adequacy 150 ml/hr or 3000 ml/day

ADHF -Treatment (cold and wet)

If SBP < 90, add pressors, mechanical support and inotropes

Use diuretic protocol

ADHF – Treatment (diuretic resistant)

- Measure IAP
  - If > 8mm, do abdominal US.
  - If US shows ascites, tap to IAP of < 8
  - If no ascites, consider alternative treatments
  - If < 8, consider for alternative treatments
- Alternative treatment – ultrafiltration, dialysis, inotropes, combination diuretics, vasodilators, and ADH antagonists (if hyponatremic)

Case

65 yo woman admitted for ADHF – DOE and peripheral edema, PND and orthopnea

PE – edema, +JVD, rales, enlarged apex with Systolic Murmur of MR

Echo – moderate pulm HTN, moderate MR and EF 55%

Case

BP 122/ HR 88 RR 22

Admission labs – Creatinine 2.4 (1.5), Na 129, and Hg 9.5

Outpatient meds – lisinopril 20, metoprolol 50 and furosemide 40 2X day

Case

What is her diagnosis? CHF

How to manage volume? Stepped diuretics starting at 40-60 IV q 6H

ACE/ARB/Nephrilysin inhibitors are continued unless MAP < 65

CRS Additional Therapy

LVAD

Cardiac Resynchronization Therapy

Palliative Care

LVAD and CRS - INTERMACS

Pre-op GFR is not a contraindication to LVAD

Postop AKI 2-3X more likely to die if RRT

Improvement in GFR

- 70% of patients improve in first month
- If transplanted – same outcomes as cohort
- If destination – long term GFR improvement tends to be minimal (<3 ml/min)

LVAD ESRD die within 1 month

Cardiac Resynchronization Therapy

- Improvements across all levels of GFR (although worse than patients without CKD)
- Stage 3 CKD – improvement of GFR
- Outcomes based on observational and post hoc analysis

Palliative Care

- Patients with CRS 1 and 2 have a poor prognosis and it is appropriate to consider palliative care in this group
- Integration of patient priorities and preferences into a treatment plan

Case CRS

62 yo woman with ESRD of < 1 year duration due to DM II.

She has had access problems and 4 weeks ago had revision of her L brachial graft

Admitted after syncope 3 hrs post dialysis when her daughter could not find a pulse and did CPR at home

Syncope occurred when she was up and walking

Case CRS

PMH – DM II, Obesity (BMI 32), HTN, mild OSA

PSH = graft X 2, TVC

Lifelong non smoker

Meds usual renal. No antihpertensives

Case CRS

Admitted to telemetry – no further events. DCed

1 week later had a similar event. Woke up quickly and was admitted again

Echo – EF 50% . LVH. Decreased RV fx with paradoxical septal movement, pulmonary HTN

Cath – minimal coronary disease

RRT with repeat event. Monitor 3rd degree HB

No orthostasis documented. + DOE

Case CRS

Pacer maker placed. Ready for DC after HD and RRT again with syncope. Pacer interrogated and working well

R Heart cath

RA mean 12 PCWP 20

RV 100/5 PVR 6.5

PA 102/40 mean 60 CI 4.2

V/Q negative PFTs mild obstruction

Table 1: Classification Pulmonary Hypertension

Group 1	Pulmonary Arterial Hypertension
Group 2	PH from left-sided heart disease
Group 3	PH from chronic hypoxic lung disease
Group 4	PH from chronic blood clots
Group 5	Unclear multifactorial mechanisms (sarcoidosis, hematological disorders, etc)

Case CRS

Duplex of L arm graft – flow 1300 ml/min

She continued to have syncope and near syncope mostly upright and exertional and mostly post dialysis (not happy)

R heart cath with occlusion of graft

RV pre 104/6 RV post 55/4

PA pre 108/40 PA post 60/30

CI pre 4.2 CI post 2.3

Case CRS

Graft banded

Duplex – blood flow 550 ml/min

Home with no further events for 1 month

CRS 4 – CKD leading to heart dx

Pulmonary HTN in ESRD

- Common – 10-50% unselected patients and somewhat based on diagnostic technique (80% in ESRD patient with unexplained dyspnea R heart cath)
- Risk higher in HD than PD
- Predicts poorer outcomes in dialysis and transplantation

Pulmonary HTN in ESRD

Likely due to increased venous return, increased pulmonary flow and stiff L ventricle due to LVH

Vascular access reinforces above and can lead to progressive pulmonary HTN

Pulmonary HTN in ESRD

Diagnosis

R heart cath is gold standard

Occlusion of vascular access with R heart cath – response is variable (decrease mean PAP by 20%, decrease CI, decrease HR, increase MAP

Echocardiogram

Pulmonary HTN in ESRD

Clinical:

DOE, unexplained dyspnea, exertional CP, exertional syncope

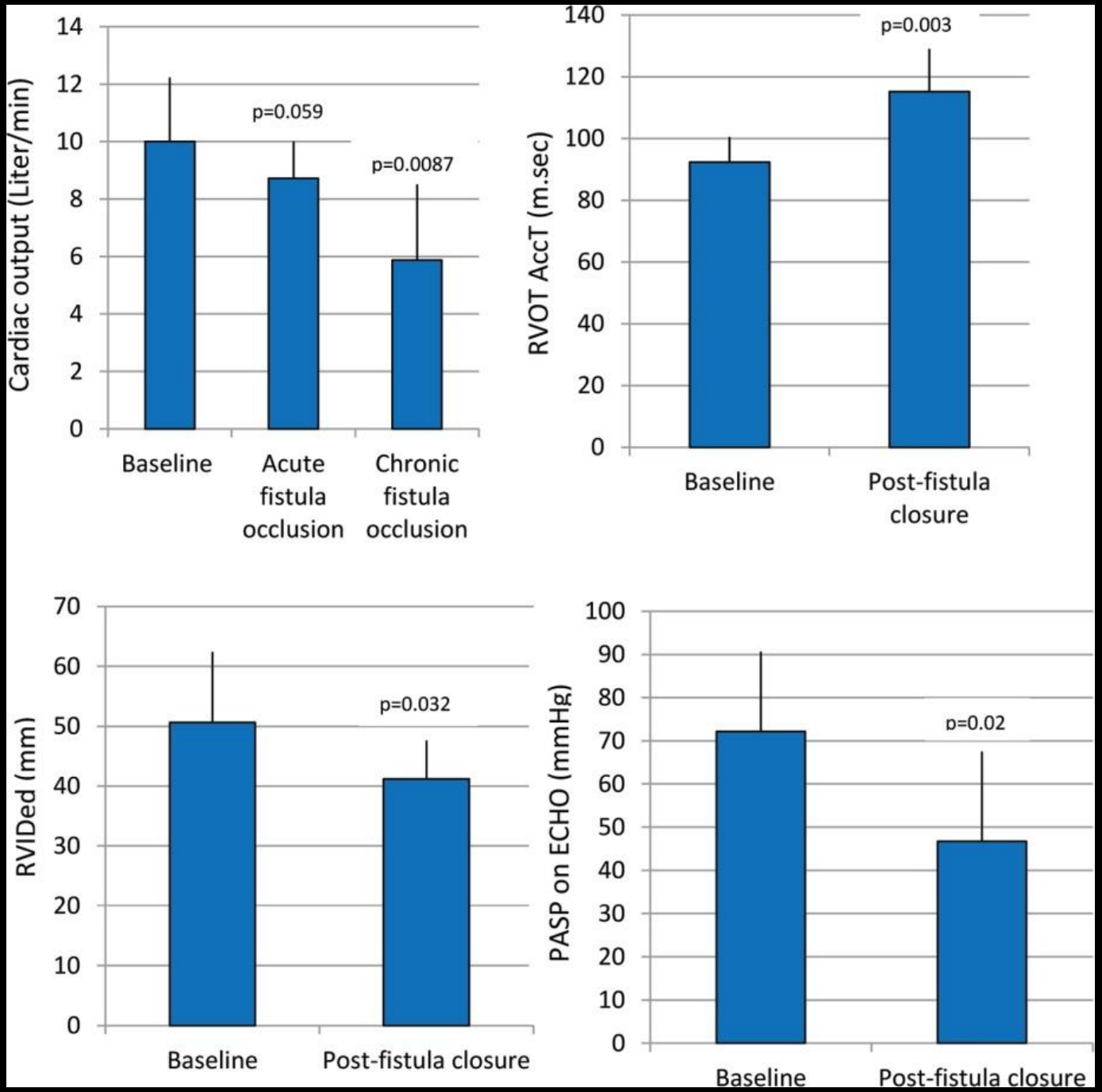
Inability to achieve dry weight due to hypotension

Pulmonary HTN in ESRD

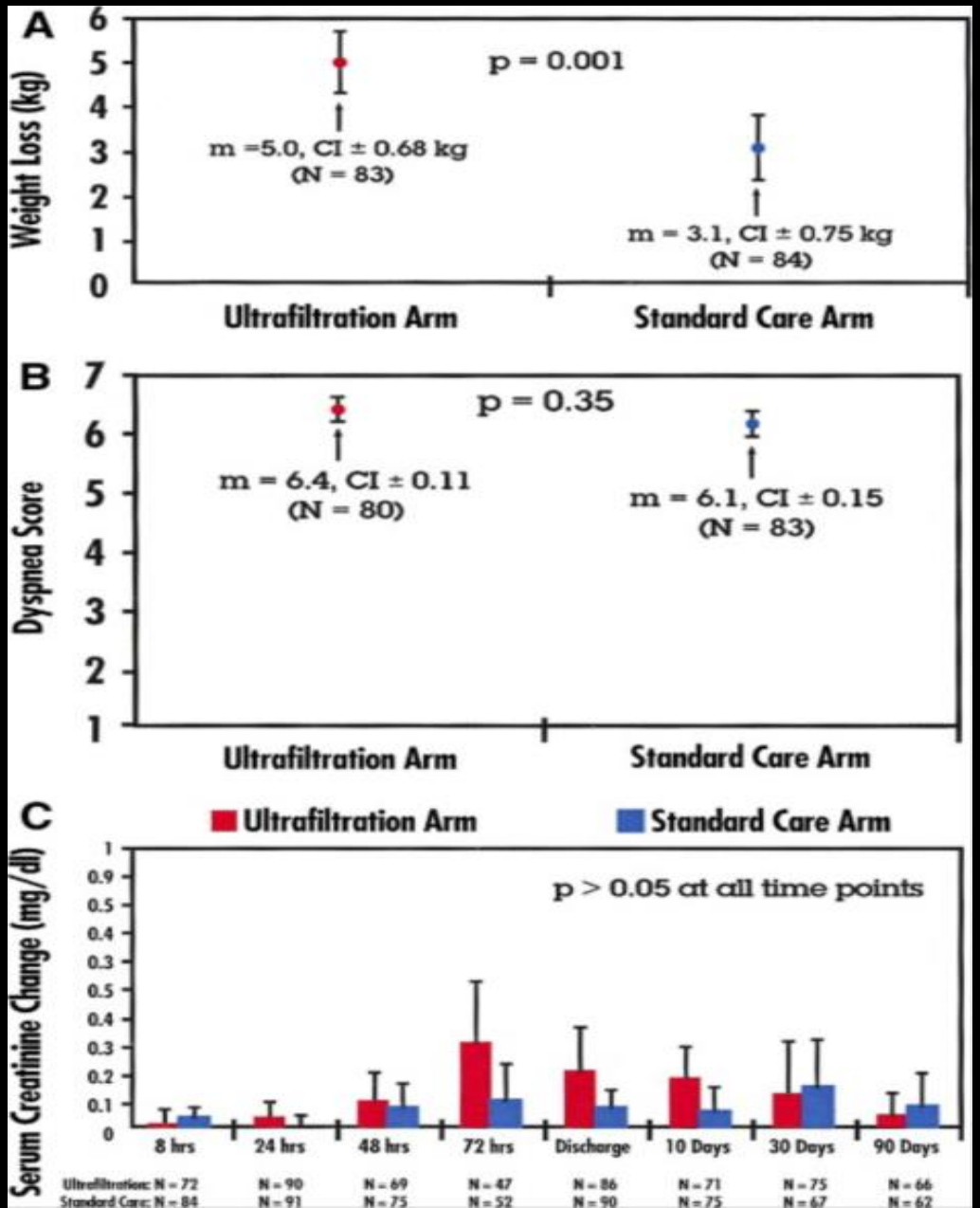
- Treatment
  - Dialysis modality – PD VS HD. HHD frequent dialysis
  - Control volume
  - Proximal VS distal access
  - Banding of access
  - TVC as last resort
  - Transplant - kidney

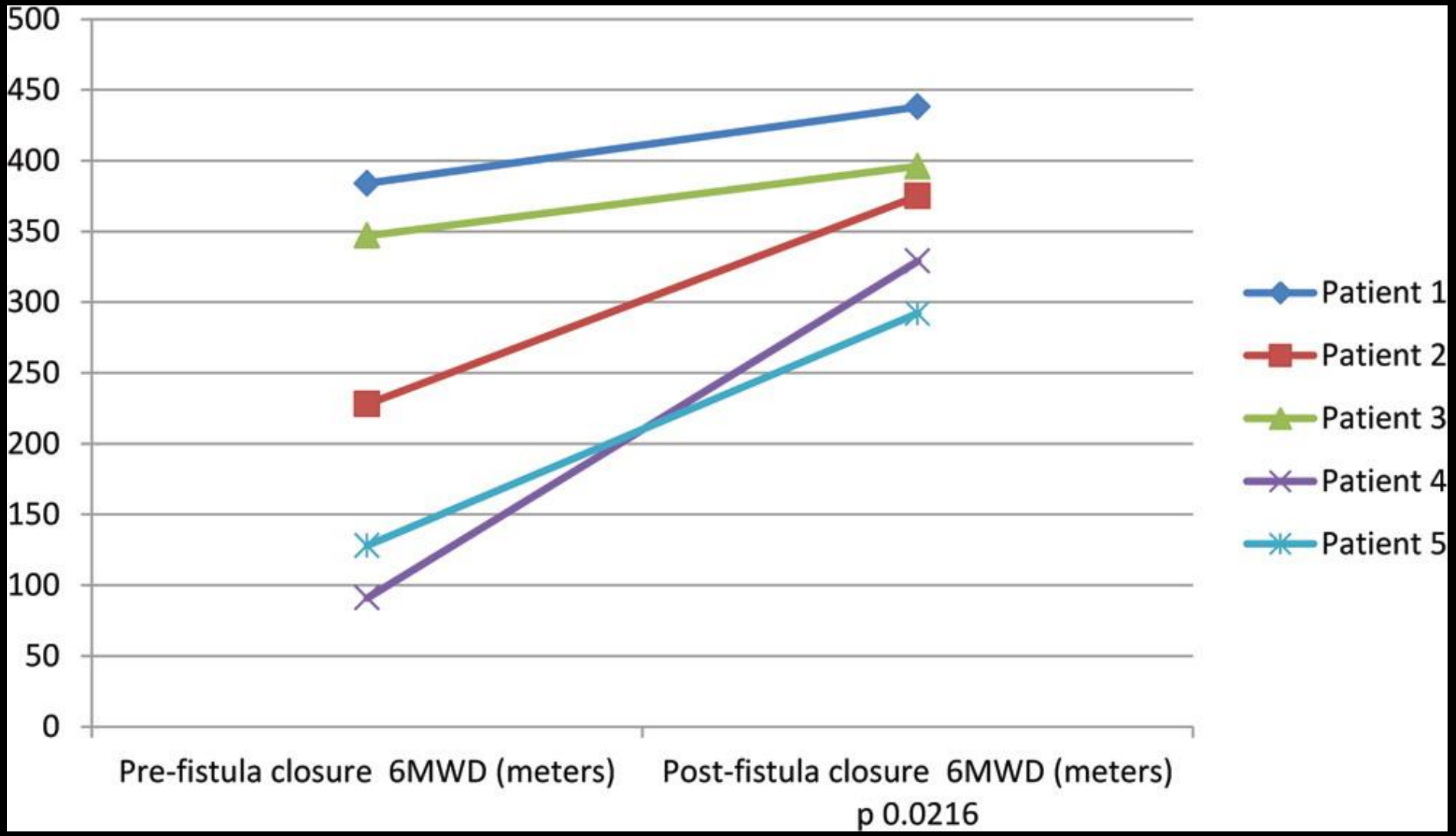
Pulmonary HTN in ESRD

- Common in ESRD
- Classic patient – HD patient with vascular access with flow > 1000 ml/m with unexplained DOE
- Results in poor outcomes in dialysis and transplant patients
- Dx – R heart cath, access occlusion
- Tx – dialysis modality, access management in select patients, volume control


Cardiac output (Liter/min)
14
12
10
8
6
4
2
0
p=0.059
p=0.0087
Baseline
Acute fistula occlusion
Chronic fistula occlusion
RVOT AccT (m.sec)
140
120
100
80
60
40
20
0
p=0.003
Baseline
Post-fistula closure
RVIDed (mm)
70
60
50
40
30
20
10
0
p=0.032
Baseline
Post-fistula closure
PASP on ECHO (mmHg)
100
90
80
70
60
50
40
30
20
10
0
p=0.02
Baseline
Post-fistula closure

Unload Trial




500
450
400
350
300
250
200
150
100
50
0
Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Pre-fistula closure 6MWD (meters)
Post-fistula closure 6MWD (meters)
p 0.0216