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Congestion Management In Heart Failure

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Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

Duke Heart

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Disclosures

- Research Support:
  - NIH, Doris Duke, Alleviant, Gradient, Novo Nordisk, Reprieve, Sardacor, Tenax
- Consultant/Ownership Interest:
  - Abbott, Ajax, Alio Health, Alleviant, Artha, Audicor, AxonTherapies, Bayer, Bodyguide, Bodyport, Boston Scientific, Broadview, Cadence, Cardioflow, Cardionomics, Coridea, CVRx, Daxor, Deerfield Catalyst, Edwards LifeSciences, Echosens, EKO, Feldschuh Foundation, Fire1, FutureCardia, Galvani, Gradient, Hatteras, HemodynamiQ, Impulse Dynamics, Intershunt, Medtronic, Merck, NIMedical, NovoNordisk, NucleusRx, NXT Biomedical, Orchestra, Pharmacosmos, PreHealth, Presidio, Procyreon, ReCor, Rockley, SCPharma, Shifamed, Splendo, Summacor, SyMap, Verily, Vironix, Viscardia, Zoll.

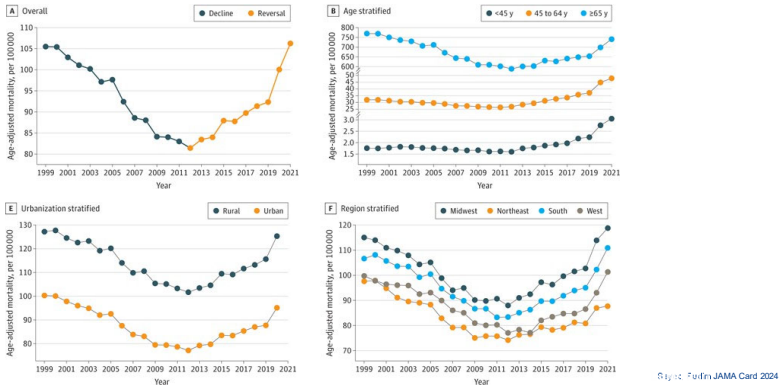
3

My Goals

- Not to bore you
- Challenge exiting concepts
- Open your mind to novel concepts in the management of congestion

4

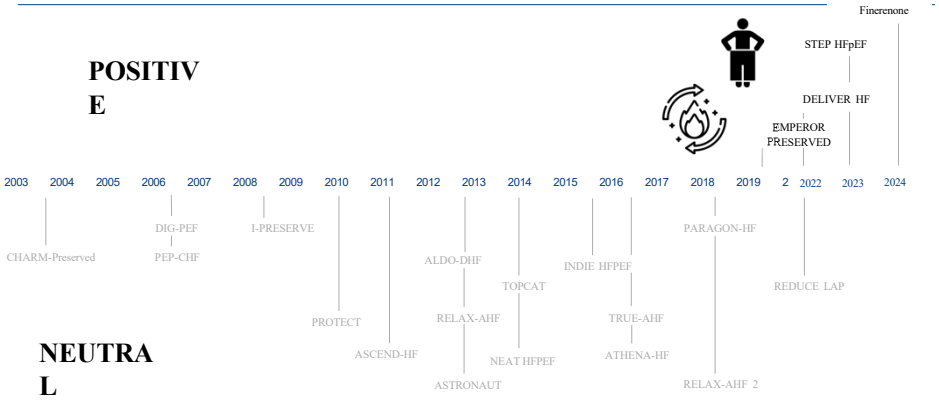
4 **Reversals in the Decline of Heart Failure Mortality in the US, 1999 to 2021**



Style: Fedin JAMA Card 2024

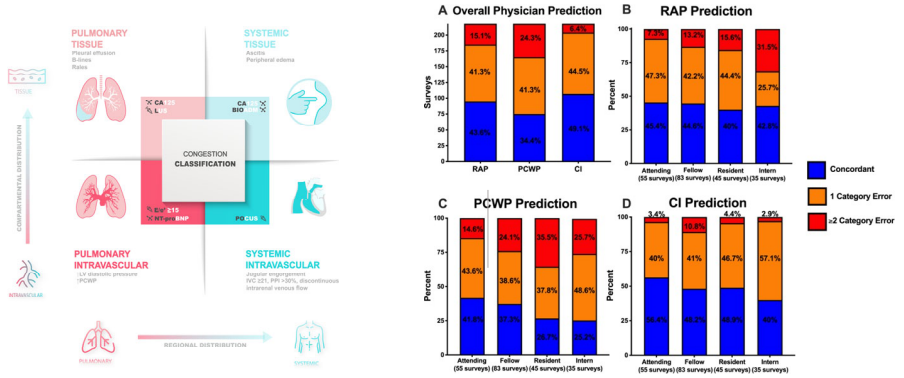
5

Unmet Need in HFpEF



6

How Do We Typically Assess Congestion?



Narang. JCF 2020, de la Espriella, Fudim, Rev Esp Cardiol 2023

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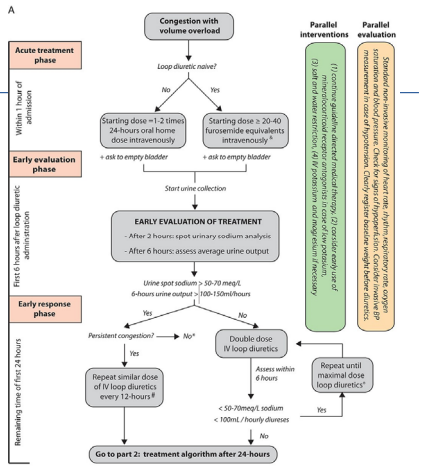
Decongestion in Clinical Practice

- Diuretics, Vasodilators, Ultrafiltration
- Strategy: Bolus diuretics vs IV Cont.



Felker et al. NEJM, 2011
Fudim et al. AHJ 2021
Mullens et al. EJHF 2019

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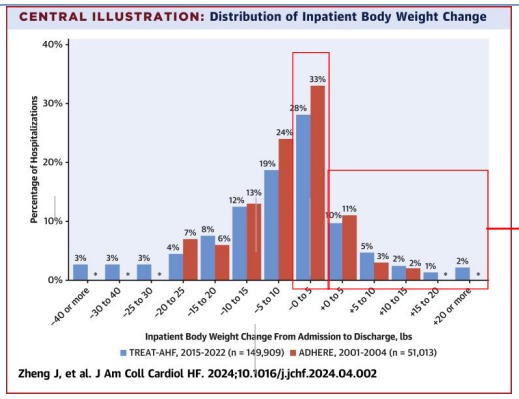
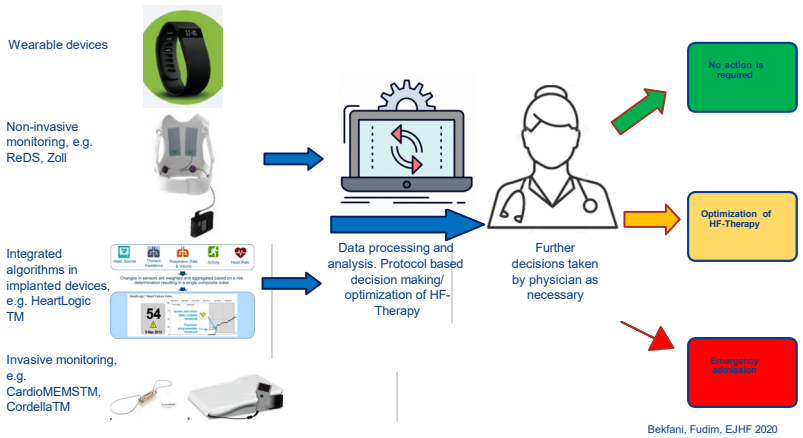
Decongestion is NOT all about diuresis



28% with insignificant weight loss

20% with weight gain

9



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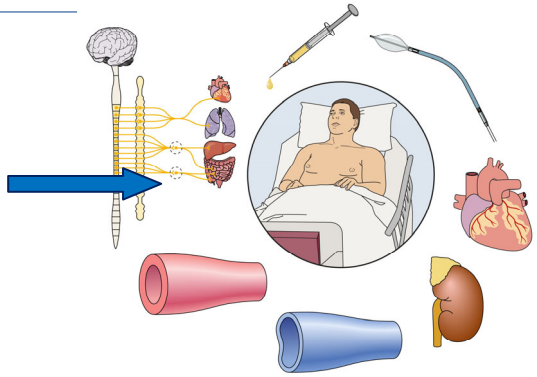
Innovation in Decongestion

Few advances in decongestive therapies

Innovation will require unconventional thinking



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Concept #1: Pressure Does Not Equal Volume

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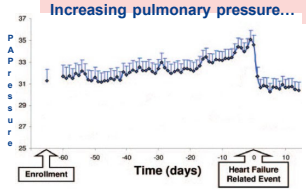
Challenging the Paradigm

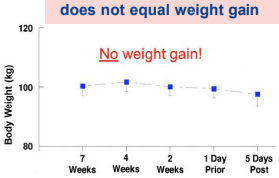
Chronic hemodynamic monitoring has demonstrated **increased pulmonary pressure without weight gain**

50% of patients had increase in pressure but no change in weight

Increasing pulmonary pressure…



does not equal weight gain



Chaudhry et al. Circulation. 2007
Zile et al. Circulation. 2008

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Process of Decompensation

- Experimental withdrawal of HF medications for 48 hours (diuretics and neurohormonal blockers), N=20

- Increase in symptoms
- NtproBNP n 99% increase 962 ng/L vs 1883 ng/L, p<0.001
- SBP n 16% increase 131 mmHg vs 152 mmHg, p<0.001
- LA volume n 21% increase 39 ml vs 50 ml, p<0.001
- Thoracic impedance n 10% decrease (volume increase), p<0.001

n **NO change in body weight : 79.6 kg (+/- 16.8) vs 80.1 kg (+/- 16.6)**

Dovancescu et al. EJHF 2017

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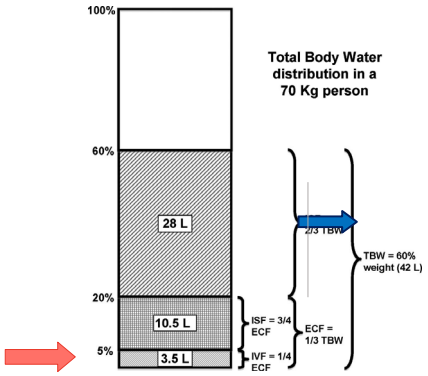
Volume Distribution in the Body



Intravascular Fluid

70% in Venous System

30% in Arterial System

60% in Splanchnic bed

□ **40% of total blood volume**

Veins □ 30 times more compliant

Fallick et al. Circ. HF. 2011
Gelman et al. Anesthesiology 2008
Fink et al. Hypertension 2009

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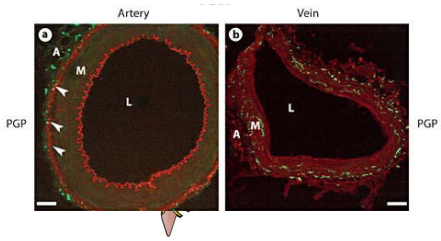
Splanchnic Compartment

- Splanchnic compartment is the main blood storage
- Up to 40% of total blood volume located in the splanchnic compartment
- Dense autonomic innervation
- Small increases in vasomotor tone 7 large fluid shifts



Fallick et al. Circ HF 2011
Fudim et al. JAHA 2017
Birch et al. J Vasc Res 2008

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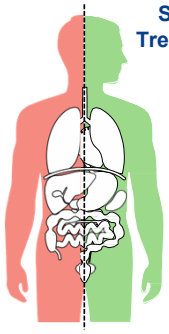
Volume Redistribution Concept: Splanchnic Nerve Modulation

Heart Failure

Congestion

Volume redistribution into thoracic compartment

↑ Sympathetic tone
↑ Splanchnic vascular tone
↓ Vascular compliance



Hypothesis: Splanchnic Nerve Block as Treatment in Acute Heart Failure

Decongestion

Volume redistribution into abdominal compartment

↓ Sympathetic tone
↓ Splanchnic vascular tone
↑ Vascular compliance

Fallick et al. Circ HF 2011
Fudim et al. JAHA 2017
Fudim et al. Circulation 2018

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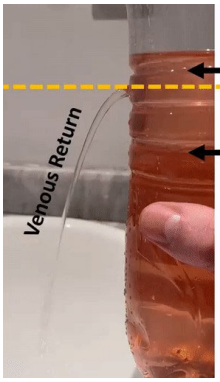
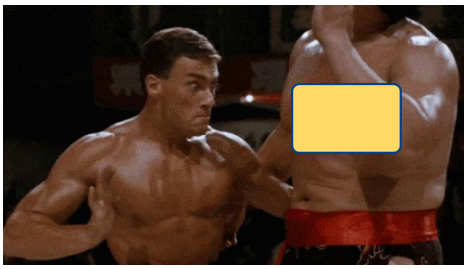
Volume Distribution - Stressed Blood Volume



Venoconstriction via Sympathetic tone increase



Argaiz, Twitter 2020
Jean Claude Van Damme, Blood Sport

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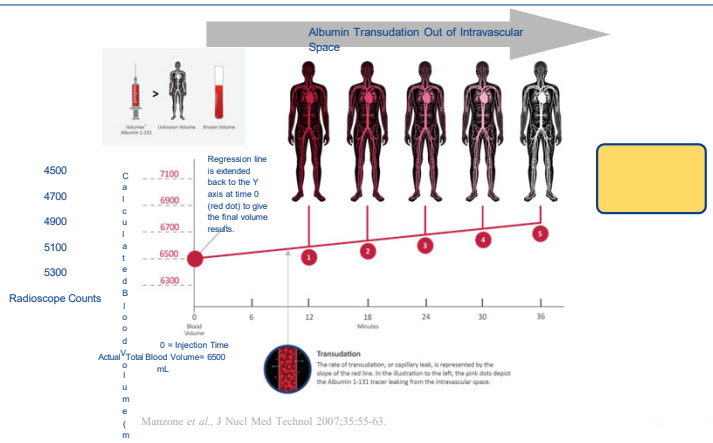
Pressure – Volume Phenotypes



Manzone *et al.*, J Nucl Med Technol 2007;35:55-63.

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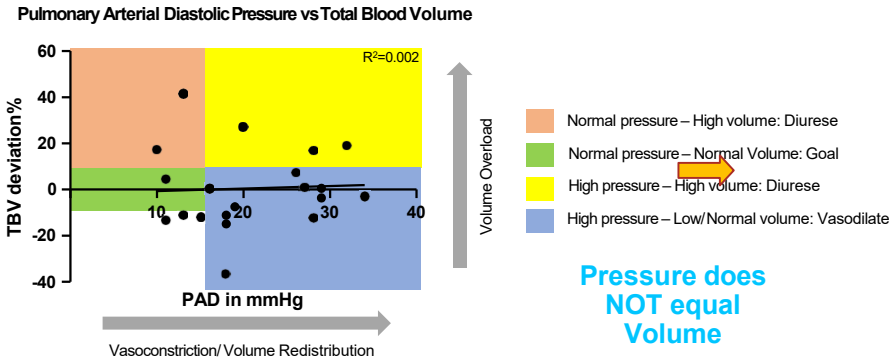
Mario Family Foundation Award



Pressure does NOT equal Volume

Yaranov, Fudim et al. JCF 2022

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Plasma and Red Cell Volume Phenotypes in Hospitalized HF Patients N=245

TABLE 2 Outcomes for Volume-Guided Subjects by Patient and Blood Volume Characteristics

			30-Day Readmissions		30-Day Mortality		365-Day Mortality	
	N = 245	% of N	Rate (%)	p Value	Rate (%)	p Value	Rate (%)	p Value
TBV								
Euvolemic or hypovolemic	154	63	11.7	<0.001	1.9	<0.001	5.2	<0.001
Hypervolemic	91	37	13.2	0.001	2.2	0.004	4.4	<0.001
RCV								
Anemic	151	62	11.9	<0.001	2.6	<0.001	6.6	<0.001
Normal RCV	66	27	13.6	0.009	1.5	0.009	3.0	<0.001
Polycythemic	28	11	10.7	0.055	0.0	0.067	0.0	<0.001
TBV and RCV								
Euvolemic or hypovolemic and anemic	122	50	12.3	<0.001	2.5	0.001	5.7	<0.001
Euvolemic or hypovolemic and normal RCV	29	12	10.3	0.037	0.0	0.069	3.4	<0.001
Euvolemic or hypovolemic and polycythemic	3	1	0.0	0.566	0.0	1.000	0.0	0.557
Hypervolemic and anemic	29	12	10.3	0.037	3.4	0.366	10.3	0.003
Hypervolemic and normal RCV	37	15	16.2	0.142	2.7	0.119	2.7	<0.001
Hypervolemic and polycythemic	25	10	12.0	0.115	0.0	0.105	0.0	<0.001
EF								
rEF (<40)	123	50	14.6	<0.001	3.3	0.004	5.7	<0.001
pEF (≥40)	122	50	9.8	<0.001	0.8	<0.001	4.1	<0.001

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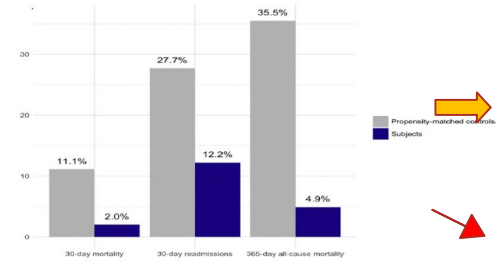
Heart Failure Outcomes With Volume-Guided Management

John E. Strobeck, MD, PhD,[a] Jonathan Feldschuh, AB,[b] Wayne L. Miller, MD, PhD[c]

FIGURE 1 Comparison Between Outcomes of Volume-Guided Patients and Propensity-Matched Control Patients



Data compare measured outcomes of 30-day mortality, 30-day readmissions, and 365-day all-cause mortality in volume-guided subjects and in non–volume-guided propensity-matched control subjects. All comparisons are statistically significant with p values <0.001.

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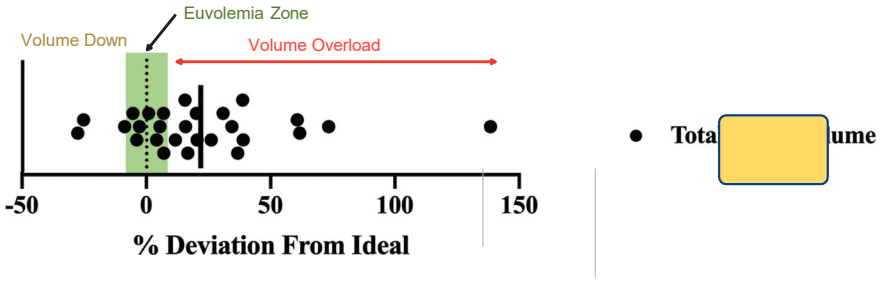
Admission Blood Volume Analysis



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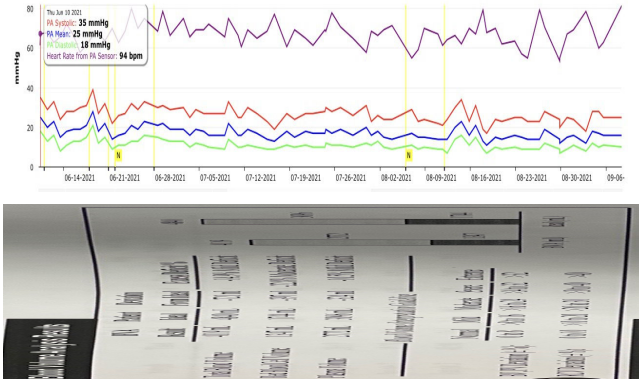
Pressure Does Not Equal Volume: Case 1. HCM



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Case 2: HFrEF – Young woman with chemo induced heart failure

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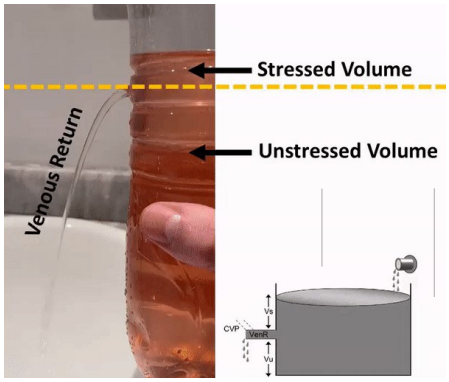
Volume Distribution - Stressed Blood Volume



Argaiz, Twitter 2020

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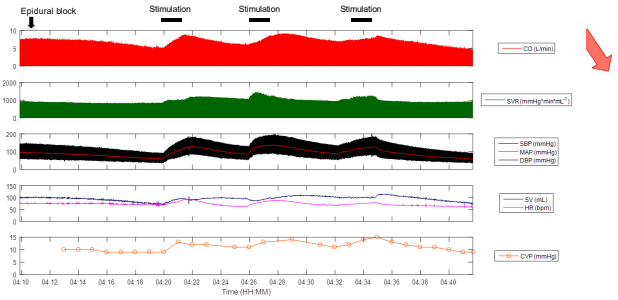
Splanchnic Nerve Stimulation - Humans



Fudim et al. J. Appl Phys 2017

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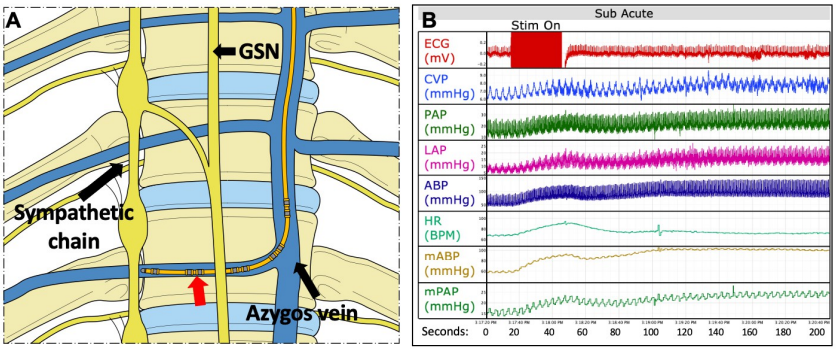
Splanchnic Nerve Stimulation in Heart Failure



Fudim, Reddy et al. JACC 2020

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Volume Redistribution Concept: Splanchnic Nerve Modulation

Heart Failure

Congestion

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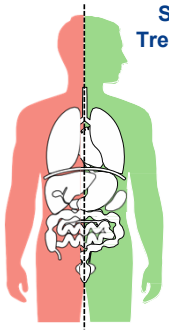
↑ Sympathetic tone
↑ Splanchnic vascular tone
↓ Vascular compliance



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Fallick et al. Circ HF 2011
Fudim et al. JAHA 2017
Fudim et al. Circulation 2018

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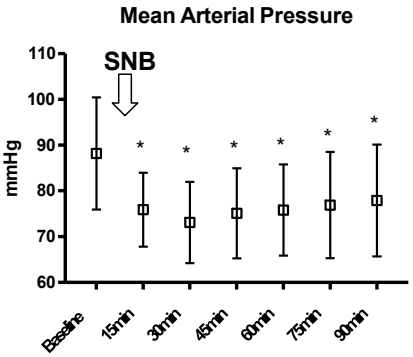
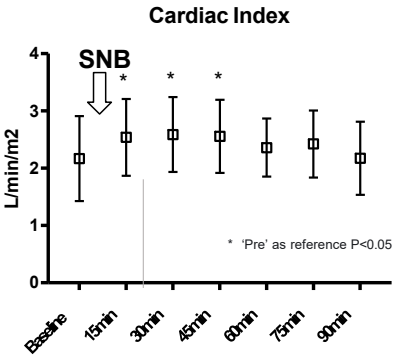
Results: Invasive Hemodynamics





Fudim et al. EHJ 2018

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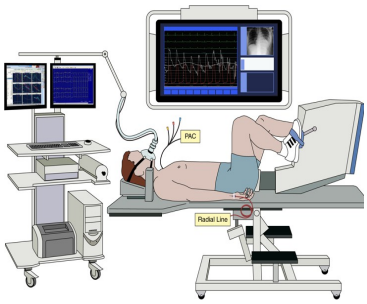
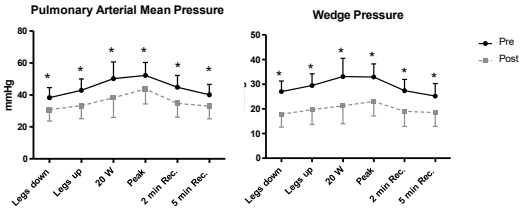
Splanchnic HF-2 (Chronic Heart Failure)

Translating Duke Health

* Pre as reference p <0.01 **N=17**





Fudim et al. JACC HF 2020

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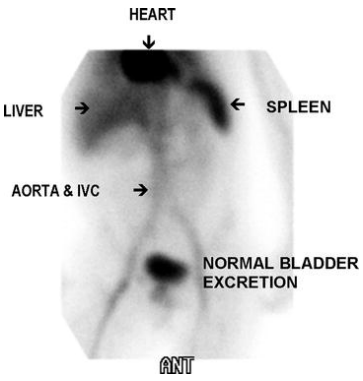
Splanchnic HF-3: Radionucleotide Plethysmography

NIH National Institutes of Health



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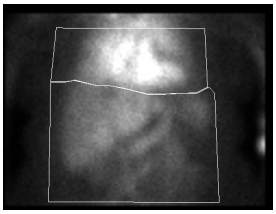
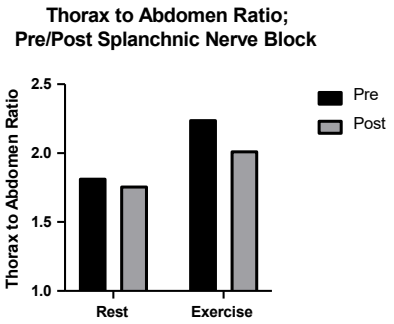
Splanchnic HF-3

Case 2





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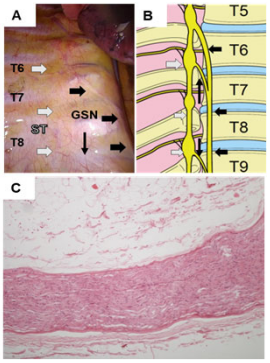
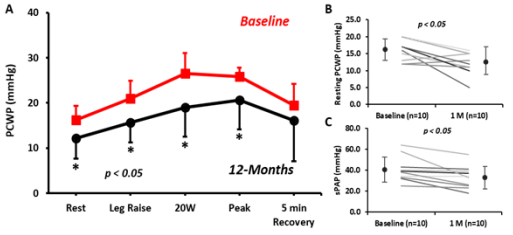
Long-term Splanchnic Nerve Blockade in HFpEF



N=10



Málek F. et al. EJHF 2021

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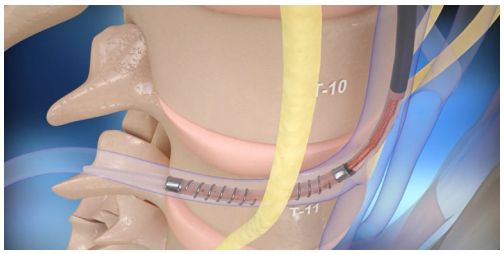
Catheter Based Approach



- Successful ablation achieved in all patients
- No device-related serious adverse events

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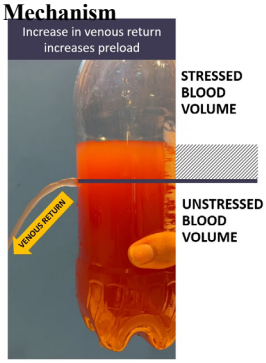
Responder Group

Target Mechanism



Responders

1. Preserved Cardiac Output with Exercise or Standing
2. Ability to Augment Heart Rate
3. Absence of Advanced Structural Disease

Fudim, JAMA Card 2024

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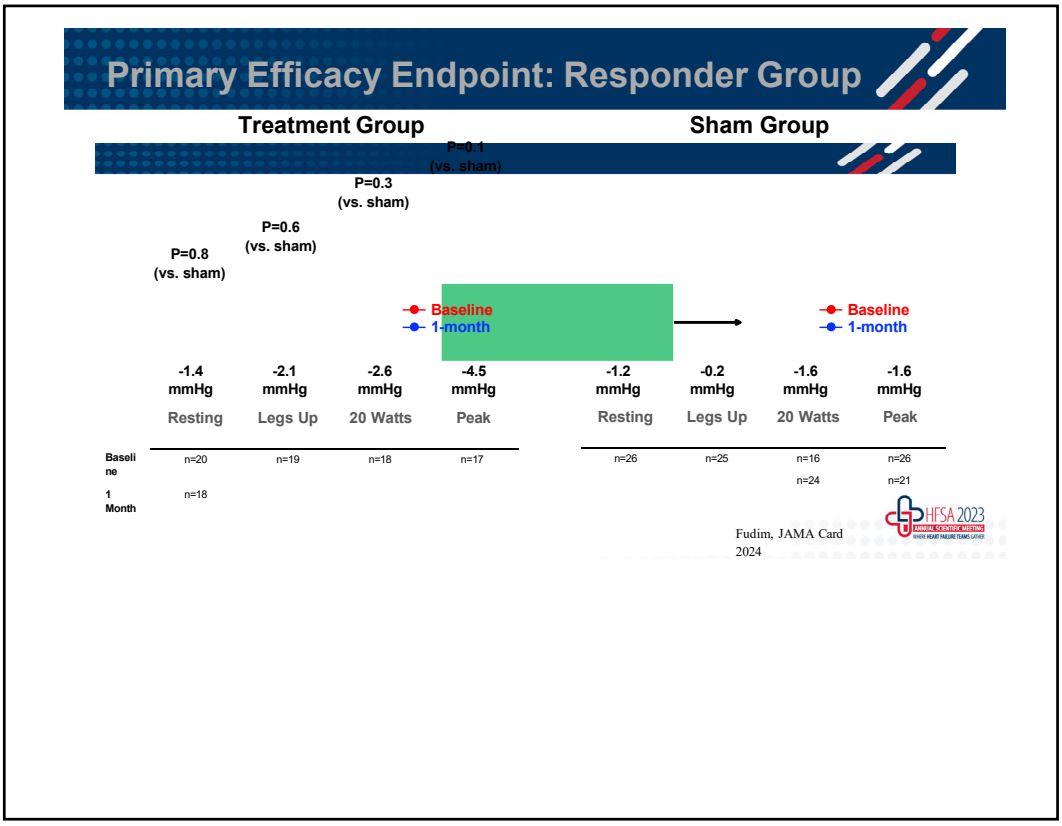
Primary Efficacy Endpoint: Responder Group
Treatment Group
Sham Group
P=0.1
(vs. sham)
P=0.3
(vs. sham)
P=0.6
(vs. sham)
P=0.8
(vs. sham)
Baseline
1-month
Baseline
1-month
-1.4 mmHg
Resting
-2.1 mmHg
Legs Up
-2.6 mmHg
20 Watts
-4.5 mmHg
Peak
-1.2 mmHg
Resting
-0.2 mmHg
Legs Up
-1.6 mmHg
20 Watts
-1.6 mmHg
Peak
Baseline
n=20
n=19
n=18
n=17
n=26
n=25
n=16
n=24
n=26
n=21
1 Month
n=18
Fudim, JAMA Card 2024
HFSA 2023

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Responder Patient Population Individual Outcomes
KCCQ Overall Summary Score
KCCQ OSS Paired Change from Baseline
+13 points p=0.02
+10 points p=0.1
6 Months
12 Months
Treatment
Sham
6 Minute Walk Test
6MWT Distance (m) Paired Change from Baseline
+36 meters p=0.08
+41 meters p=0.1
NTproBNP
NTproBNP (pg/ml) Paired Change from Baseline
-175 pg/ml p=0.1
-275 pg/ml p=0.04
Fudim, JAMA Card 2024
HFSA 2023

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Concept #2: Gravity Matters

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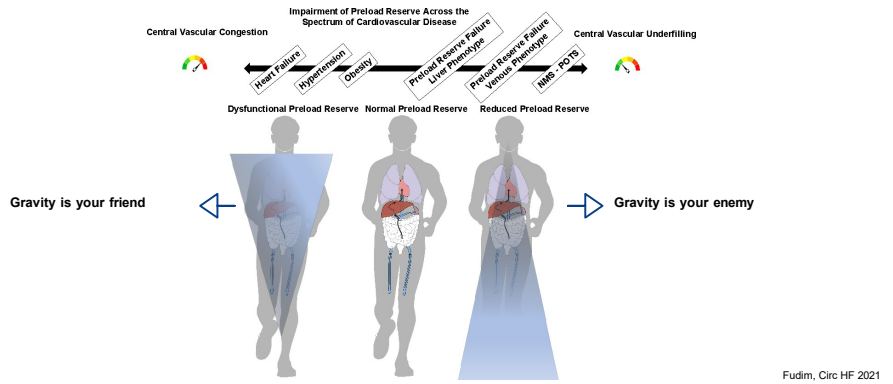
Preload Reserve



Fudim, Circ HF 2021

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Position Matters: Gravity Ain't a Joke

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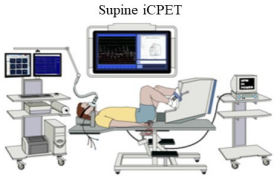
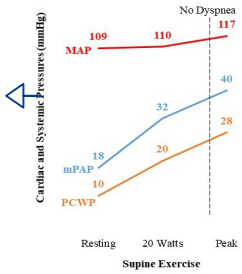
Supine iCPX





Rao, Fudim, Circ HF 2021

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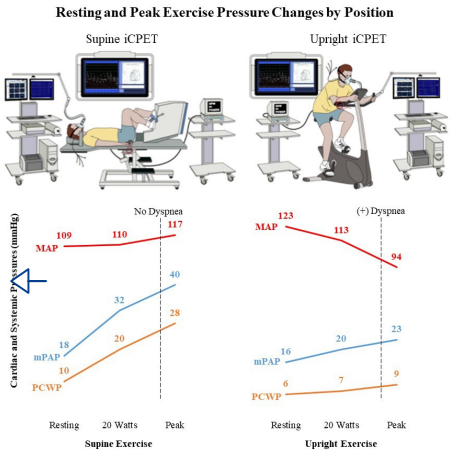

Rao, Fudim, Circ HF 2021

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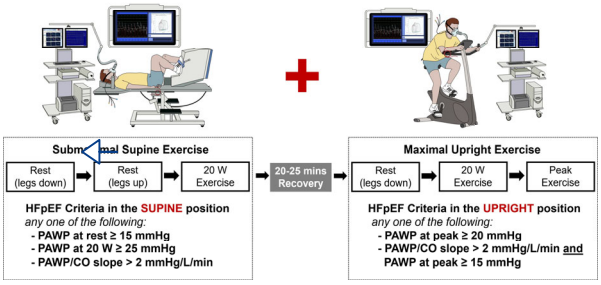
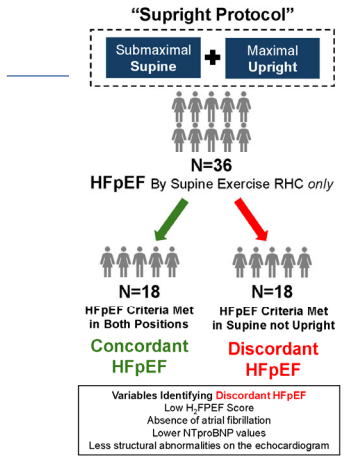
Supright Exercise Right Heart Catheterization



Fudim, Circ HF 2024- accepted

44



Clinical Implications

- Supine exercise RHC only could result in
  - Overdiagnosis of HFpEF
  - Under-recognition of preload failure
- Could explain prior failures of vasodilatory or preload reducing therapies in unselected HFpEF population
- Need to reconsider screening approaches for preload modulating therapies to avoid patients with discordant HFpEF

Fudim, Circ HF 2024- accepted

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Concept #3: It might not be the Kidney we should be after

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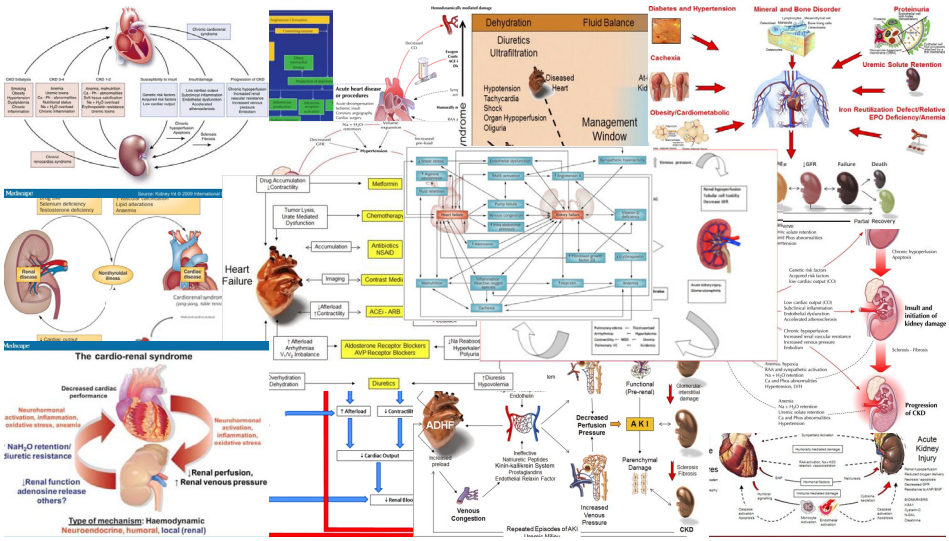

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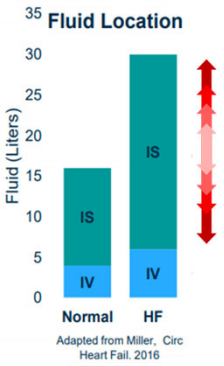
Heart Failure



- There are two main fluid reservoirs in the body
  - Intravascular Fluid Compartment (IV)
  - Interstitial Fluid Compartment (IS)
- In heart failure (HF) patients, the Interstitial Fluid compartment expands 3-4x more than the Intervascular Fluid compartment

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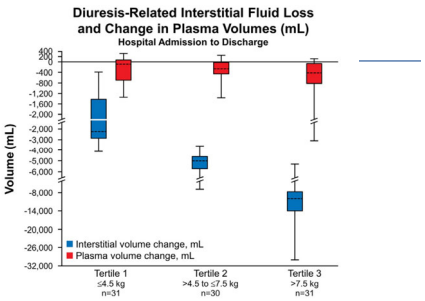

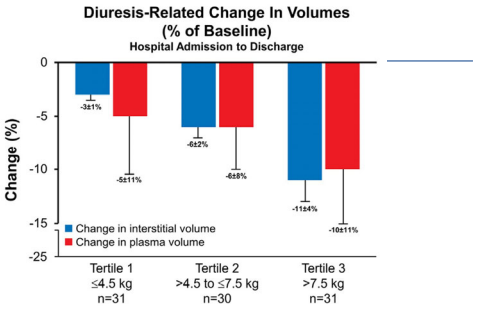

Miller, JCF 2021

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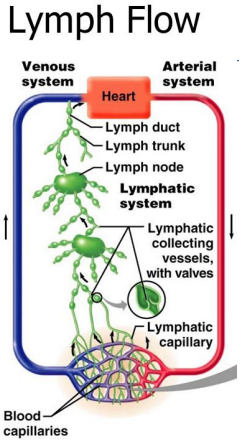
Lymph Fluid: What it is and how its drained

- 8L/day of transudate
- Only ~3L of lymph actually to move via the thoracic duct into venous system
- Proteins escaped from the blood or secreted tissues are transferred back to the blood via the lymphatics
- Lymph flow is facilitated via muscle pump, respiratory pump, valves and smooth muscle in the lymphatic walls



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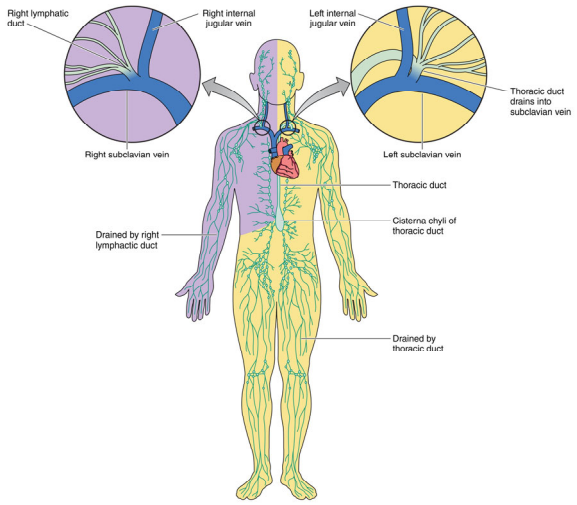
Anatomy



Fudim, JACC, 2021

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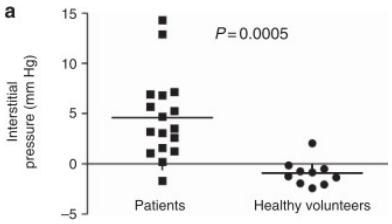
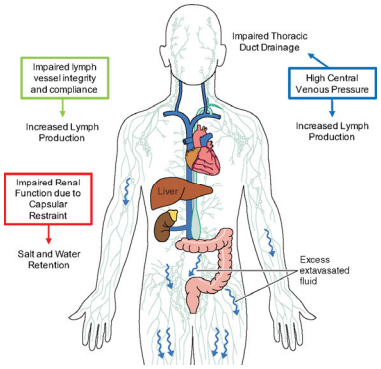
Interstitial Pressure in Health and Disease



Ebah, Kidney Intern. 2013

52

The Lymphatic System in Heart Failure



Fudim, JACC, 2021

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#1 Increased Lymph Production

- Higher venous pressures and arterial vasoconstriction lead to a net efflux of fluid out of the vessel.
- Increased interstitial volume → Increased lymph production

Compared to normal conditions: TD flow is approximately 8-fold higher in patients with heart failure (1 ml/min vs 8 ml/min)

The diameter of the thoracic duct is enlarged up to 6 times the normal diameter

The thoracic duct pressure is increased

Witte, Circulation, 1969

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#2 Obstruction to Outflow - Breaking Point

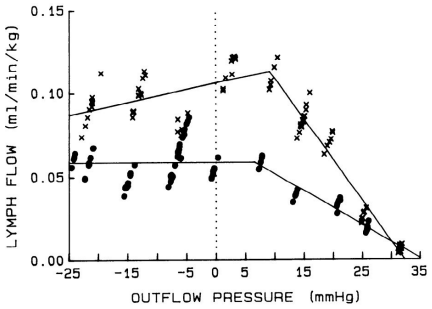
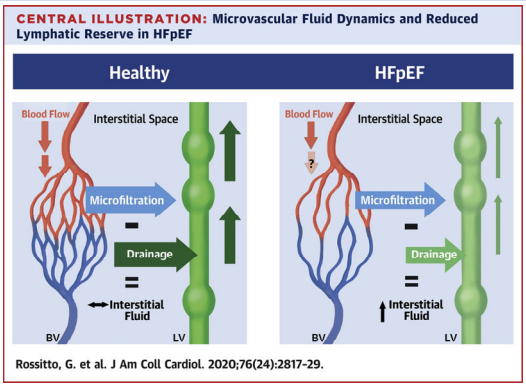


FIG. 1. Relationship between thoracic duct lymph flow rate and outflow pressure in 1 animal. Data are 1-min averages during steady-state conditions. ●, control conditions; ×, after fluid loading; ——, regression lines.

Brace , Amer J Physiology, 1990

55

#3 Heart Failure: A Lymphatic Compliance Problem



N=32

Controls vs HFpEF

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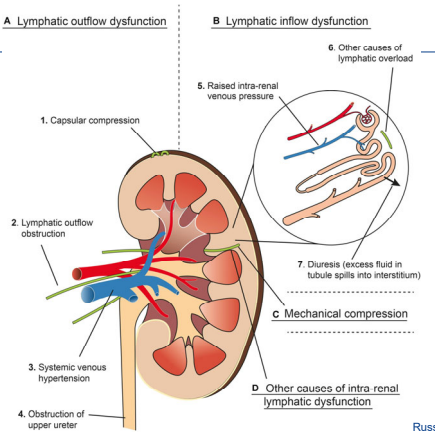
#4 Cardiorenal Syndrome



Russell, Front Physiol, 2019

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Vol. 269 No. 18 LYMPH DRAINAGE — DUMONT ET AL. 949

LYMPH DRAINAGE IN PATIENTS WITH CONGESTIVE HEART FAILURE*

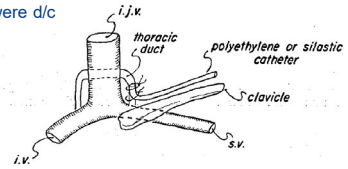
Comparison with Findings in Hepatic Cirrhosis

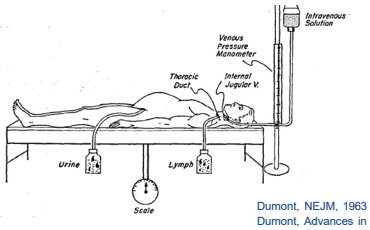
ALLAN E. DUMONT, M.D.,† ROY H. CLAUSS, M.D.,‡ GEORGE E. REED, M.D.,§ AND DAVID A. TICE, M.D.¶

NEW YORK CITY

N=5

All diuretics were d/c

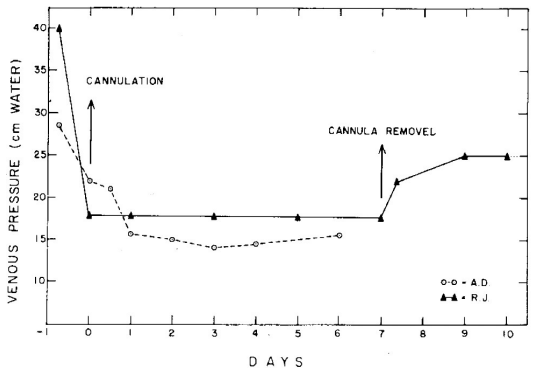


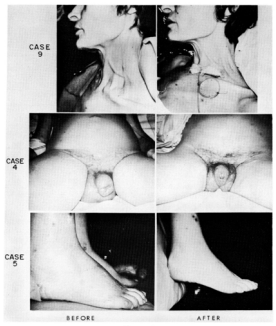


Dumont, NEJM, 1963
Dumont, Advances in IM, 1969

58

Changes in Venous Pressure in Two Cases after TD Cannulation





Dumont, NEJM, 1963
Dumont, Advances in IM, 1969

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Table 1. *Results of Thoracic-Duct Cannulation in 5 Patients with Congestive Heart Failure.*

Case No.	Venous Pressure		Opening Lymph Pressure	Opening Flow Rate	Total Lymph Output	Total Protein		Weight Loss		Duration of Cannulation
	Before operation	After operation				Serum	Lymph			
	cm. H_2O	*cm. H_2O*	*cm. H_2O*	*ml./min.*	*liters*	*gm./100 ml.*	*gm./100 ml.*	*kg.*	*lb.*	*days*
1	40	18	17	3.0	18.3	4.0	3.3	10.9	24	7
2	28	15	28	7.0	13.8	6.6	1.4	12.2	27	7
3	24	13	30	5.0	19.7	8.0	6.0	3.8	8½	7
4	26	16	80	11.0	44.4	5.4	1.7	24.9	55	8
5	27	15	30	9.0	12.0	6.6	2.6	10.9	24	3

Dumont, NEJM, 1963
Dumont, Advances in IM, 1969

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Clinical Summary of Acutely Drained Patients

	Baseline Information	Baseline RHC (mmHg)	Volume Removed	Thoracic Duct Pressure Change (Pre □ Post)
MAY-2022 Dr. Adrian Ebner & Dr. Ravi Srinivasa (UCLA) Dr. Jeff Chick (UW)	63M / BMI 32 NYHA II Ischemic HF LVEF 58% Hypertension Hyperlipidemia COPD	mRAP: 15 PAP: 28/1/7 PCWP: 11	**340ml over 3hrs** (110ml/hr)	**28□13mmHg (-15mmHg)**
	66M / BMI 35 NYHA III LVEF 30% Ischemic HF Hypertension	mRAP: 12 PAP: 50/16/33 PCWP: 15	**550ml over 3hrs** (180ml/hr)	**50□20mmHg (-30mmHg)**
	58F / BMI 40 NYHA III Non-Ischemic HF LVEF 32% Afib Hypertension Diuretics	mRAP: 7 PAP: 35/12/21 PCWP: 14	**230ml Over 3hrs** (80ml/hr)	**35□2mmHg (-32mmHg)**

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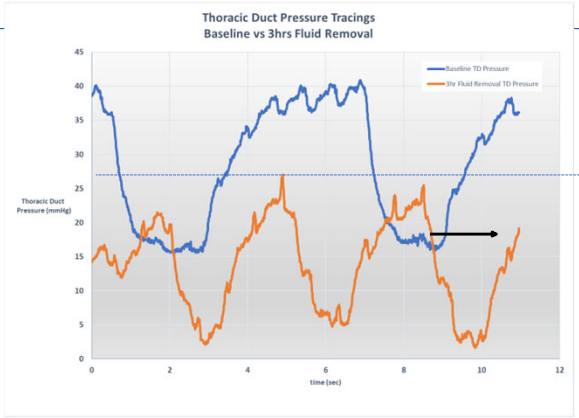
TD Pressure Change Graph: Version 3

(Raw Pressure Tracings Only)



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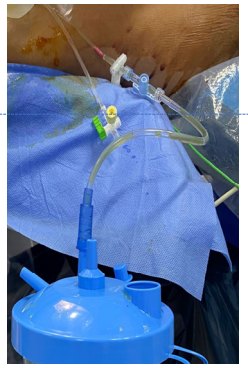
Lymph Removal

Pt 004: Retrograde Transvenous Access

Removed lymph at t=1hr (gravity induced)



NXT BIOMEDICAL

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Conclusions

- Congestion is a complex concept
- Pressure does not equal volume
- The redistribution of blood volume is a key driver of intra-cardiac pressure elevation
- The splanchnic nerve plays an important role in acute and chronic decompensation
- Gravity matters in our assessment of congestion
- Decongestion targets the interstitial space more so than intravasc. space

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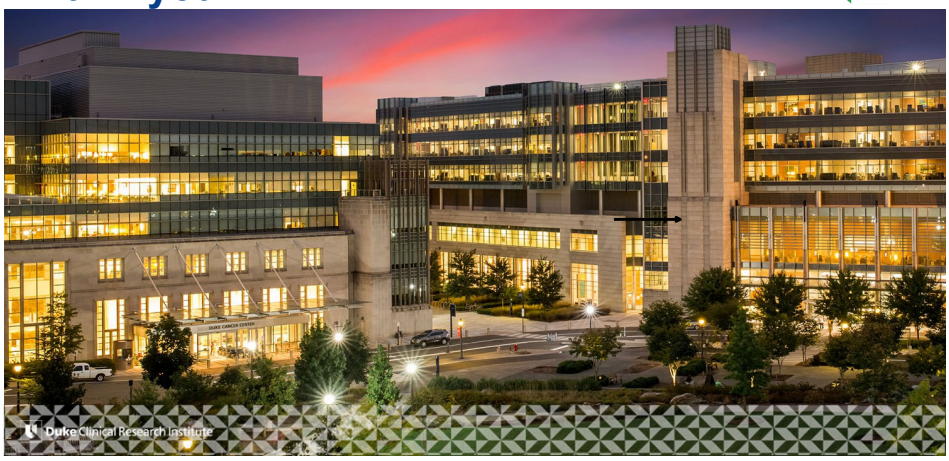
Thank you



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