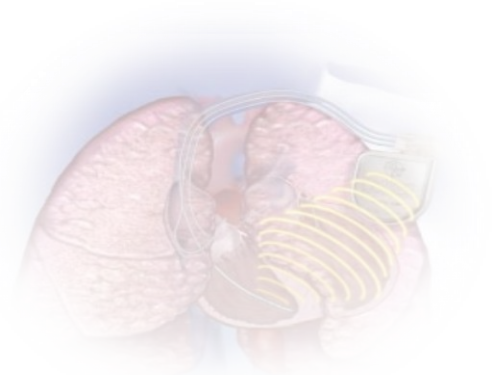
DIURÉTIQUES
&
OAP CARDIOGÉNIQUE
NON

Pr Souheil Elatrous

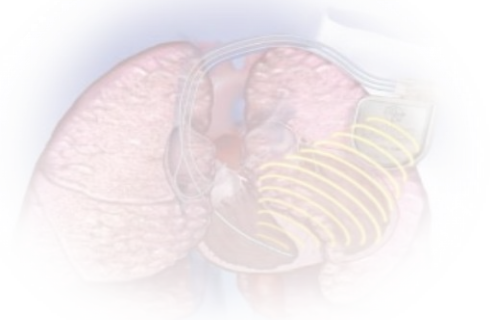
E.P.S. Taher Sfar Mahdia

Old theories result in old therapies



Éléments importants à considérer

- Les errances du passé
  - Insuffisance cardiaque aigue = Dysfonction systolique
  - Insuffisance cardiaque aigue = Hypervolémie
- Œdème pulmonaire plutôt les œdèmes pulmonaires



Insuffisance cardiaque aigue

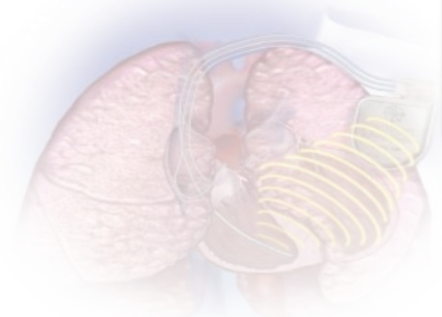
Les errances du passé

Insuffisance cardiaque aigue

1

=

Toujours et obligatoirement due à une dysfonction cardiaque systolique



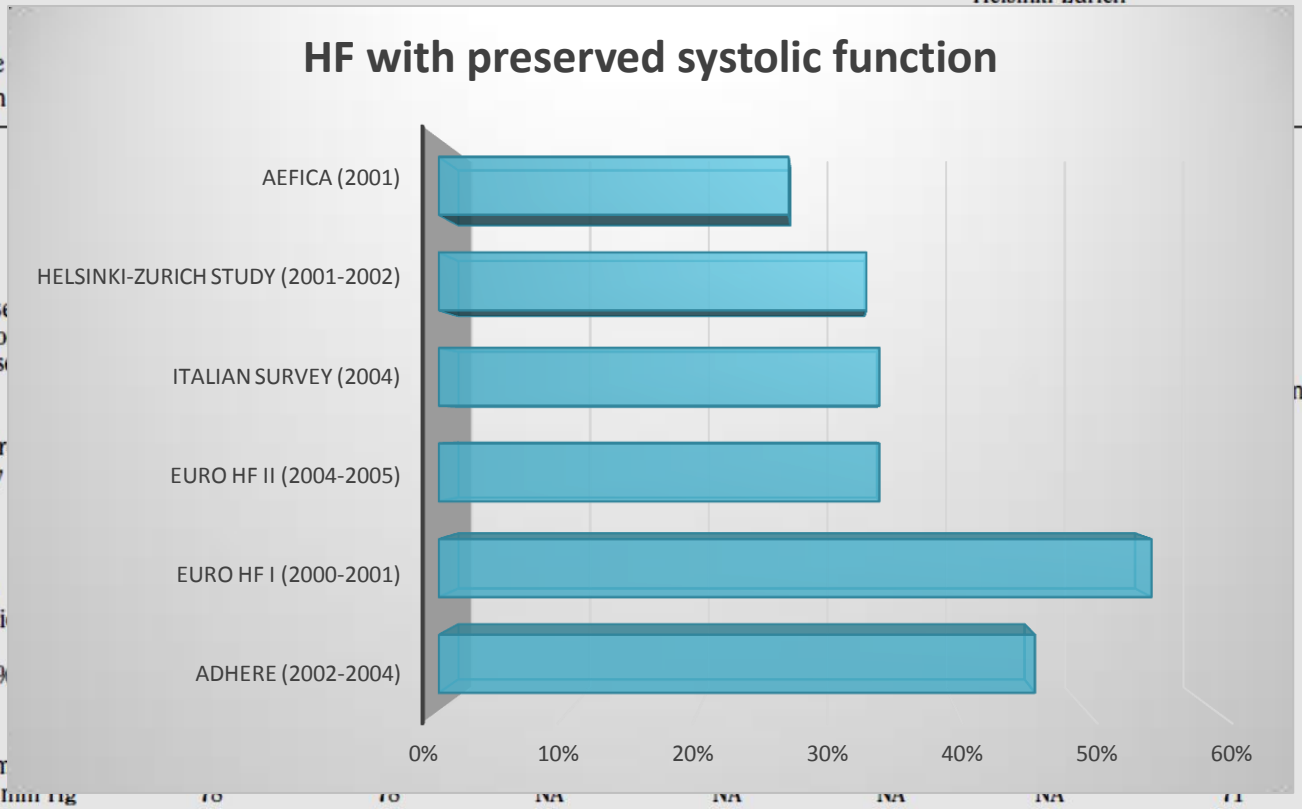
Acute heart failure in the intensive care unit: Epidemiology

Owais Dar, MB ChB, MRCP; Martin R. Cowie, MD, MSc, FRCP

CCM 2008; 36:S3-S8

Table 2. Characteristics of acute heart failure patients enrolled in the key surveys

Clinical Profile / Presentation	Helsinki-Zurich							New York Study (11) 1999–2001 (n = 619)
Age, yrs (mean, SD)								72 (14)
Gender, % male								28
History, %								
Prior evidence of heart failure								
Coronary artery dise								43
Myocardial infarctio								NA
Cardiac valvular dis								NA
AF								23
Hypertension								78
Chronic renal failur								Approx 50
Chronic respiratory disease								24
Diabetes mellitus								46
Presenting features								
Dyspnea at rest, %								11
Dyspnea with exerti								75
Rales, %								NA
Peripheral edema, %								NA
Mean systolic BP, mm Hg								160
Systolic BP >140 m								NA
Mean diastolic BP, mm Hg	78	78	NA	NA	NA	NA	71	84
Heart rate, beats/min	89	75	95	97	NA	90	NA	NA
Cardiogenic shock, %	3%	<1%	3.9	7.7	NA	4.2	29	NA
HF with preserved systolic function, %	46 (EF >40%)	55 (EF ≥40%)	34 (EF ≥45%)	34% (EF >40%)	NA	33 (EF ≥50%)	27 (EF >45%)	Entry criterion: EF ≥50%



THE PATHOGENESIS OF ACUTE PULMONARY EDEMA ASSOCIATED WITH HYPERTENSION

N Engl J Med 2001;344:17-22.

During Acute Pulmonary Edema

Blood pressure, 240/144 mm Hg

Insuffisance cardiaque aigue

Les errances du passé

OAP

2 = Hyper volémie

les œdèmes aigus du poumon (OAP) survenaient chez des patients ayant une défaillance cardiaque au long cours, la dénomination **insuffisance cardiaque «congestive»** des Anglo-Saxons a laissé penser que les patients, présentant un OAP, étaient toujours **hypervolémiques**.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Transition From Chronic Compensated to Acute Decompensated Heart Failure: Pathophysiological Insights Obtained From Continuous Monitoring of Intracardiac Pressures

Michael R. Zile, Tom D. Bennett, Martin St. John Sutton, Yong K. Cho, Philip B. Adamson, Mark F. Aaron, Juan M. Aranda, Jr, William T. Abraham, Frank W. Smart, Lynne Warner Stevenson, Fred J. Kueffer and Robert C. Bourge

American Heart Association

Circulation. 2008;118:1433-1441

- 274 patients; 204 FE < 50% et 70 FE > 50%
- 163 ont un HFRE (Heart failure related event : hospitalisation, ED visit, urgent clinic visit requiring IV therapy) lié a une hypervolémie
  - Dysfonction diastolique : 41 HFRE / 22 patients
  - Dysfonction systolique : 122 HFRE/ 68 patients
- 111 patients : **40% ont un HFRE sans hypervolémie**

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Patterns of Weight Change Preceding Hospitalization for Heart Failure

Sarwat I. Chaudhry, Yongfei Wang, John Concato, Thomas M. Gill and Harlan M. Krumholz

Circulation. 2007;116:1549-1554

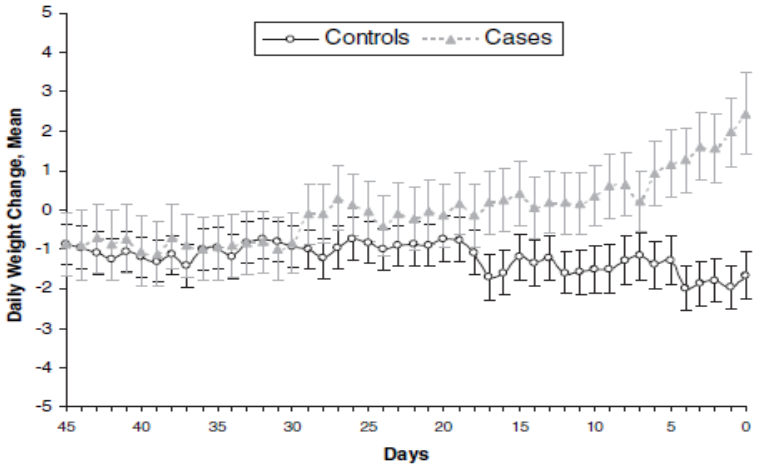


TABLE 2. Conditional Logistic Regression Models of Heart Failure Hospitalization (n=240)

Weight Gain, lbs	Case Patients, n (%)	Control Patients, n (%)	Matched Unadjusted OR (95% CI)	Matched Adjusted OR (95% CI)	Adjusted *P*
≤2	65 (54)	92 (77)	Reference group	. . .	. . .
>2 up to 5	21 (18)	16 (13)	2.40 (1.05–5.45)	2.77 (1.13–6.80)	0.026
>5 up to 10	17 (14)	8 (7)	3.81 (1.35–10.77)	4.46 (1.45–13.75)	0.009
>10	17 (14)	4 (3)	5.65 (1.81–17.65)	7.65 (2.22–26.39)	0.001

Weight gain is during 1 week preceding hospitalization of case patients. Results were adjusted for comorbid conditions and the medications shown in Table 1.

< 1 kg

Circulation
Heart Failure

American Heart Association®

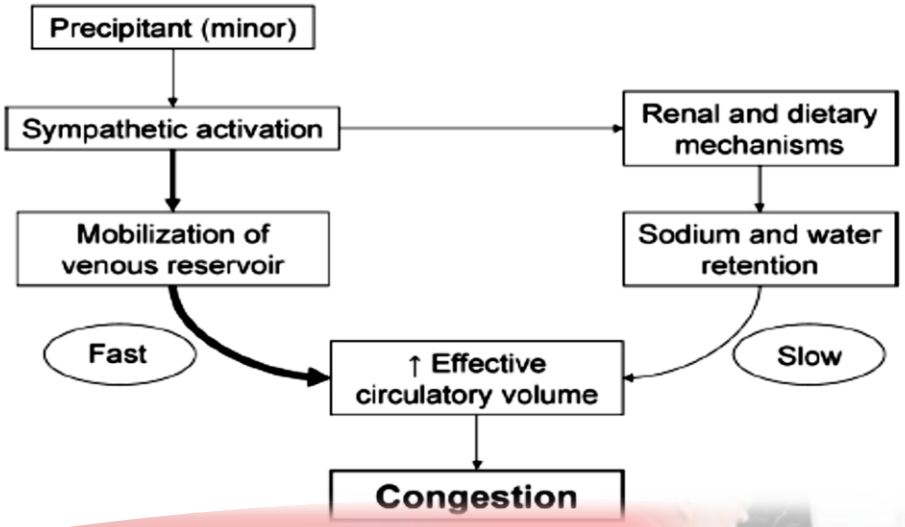
Sympathetically Mediated Changes in Capacitance: Redistribution of the Venous Reservoir as a Cause of Decompensation

Catherine Fallick, Paul A. Sobotka and Mark E. Dunlap

Circ Heart Fail. 2011;4:669-675

Congestion,
is caused by
fluid redistribution rather than by
fluid accumulation

Fast and slow mechanisms of circulatory congestion



Blood volume prior to and following treatment of acute cardiogenic pulmonary edema.

J Figueras and M H Weil

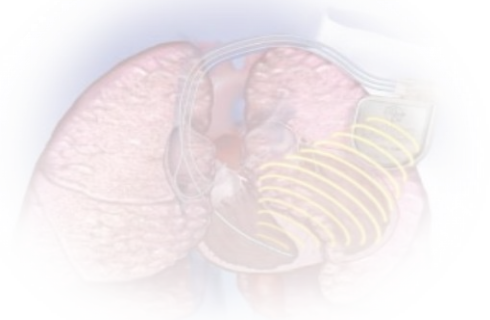
Circulation. 1978;57:349-355

TABLE 2. *Initial Plasma and Total Blood Volumes (mean ± SEM)*

	No.	Plasma vol. (ml/kg)	Total blood vol. (ml/kg)	Hct. %
Normal subjects (group 1)	13	44.6 ± 1.4	73.3 ± 2.3	42.9 ± 0.9
Acute pulmonary edema	21	36.6 ± 1.7*	60.6 ± 2.6*	45.1 ± 1.7

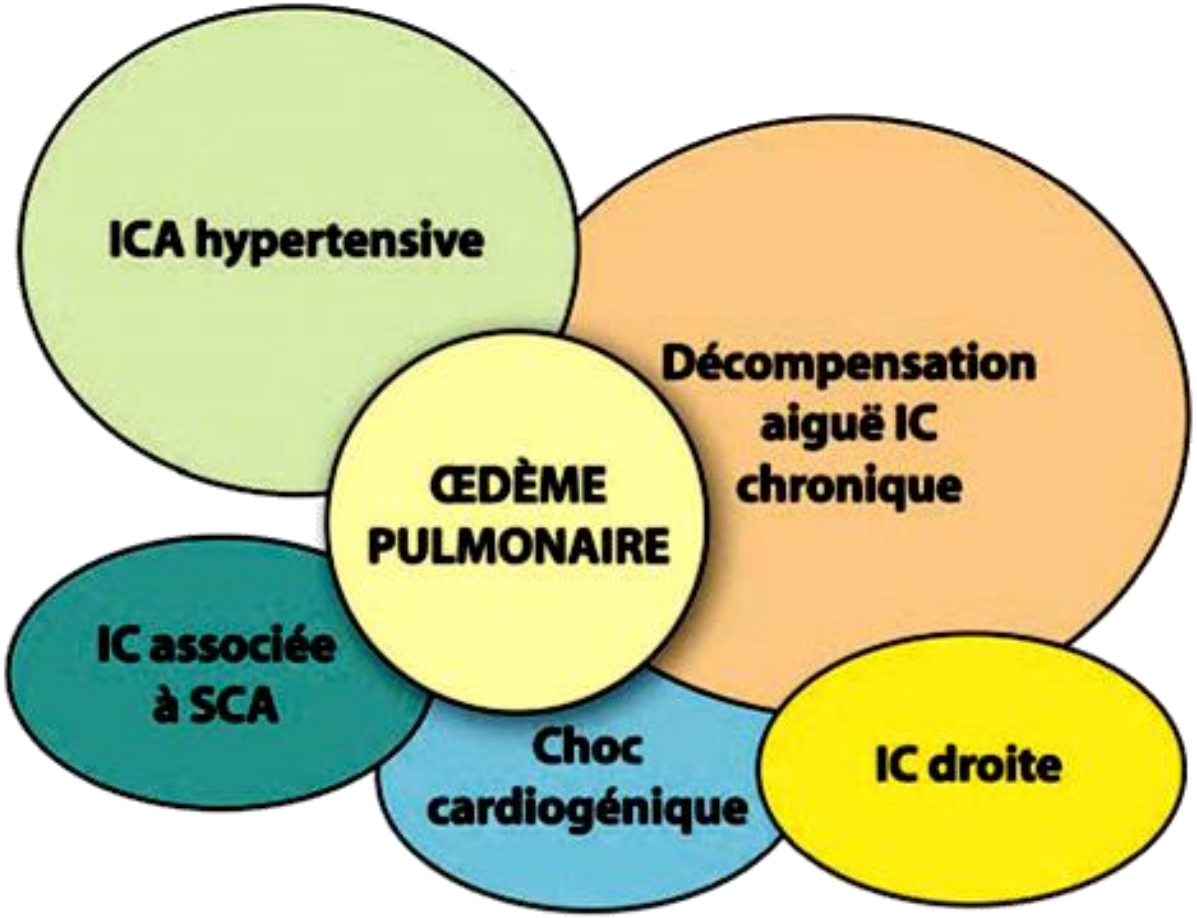
*P <0.005, control vs PE.

- La congestion pulmonaire n’est pas toujours associée à une hypervolémie
- Plus de 50% ne sont pas associés a une surcharge volémique



Insuffisances cardiaques aigues

3



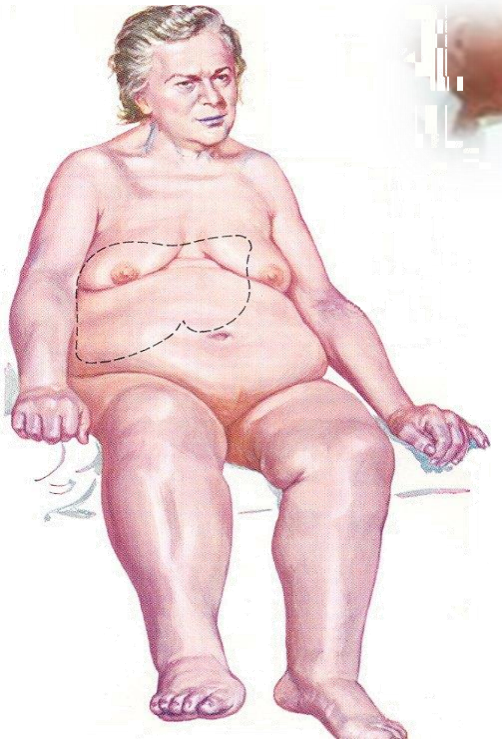
Practical recommendations for prehospital and early in-hospital management of patients presenting with acute heart failure syndromes

Mebazaa A CCM 2008

Table 1. Clinical scenarios in acute heart failure syndrome

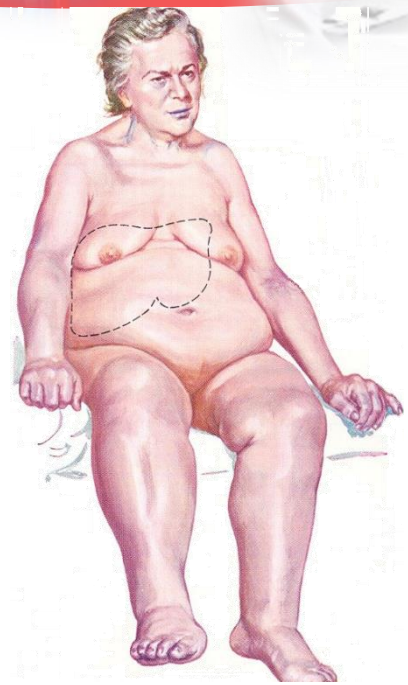
Clinical Scenario	Characteristics
CS1	SBP >140 mm Hg
	Symptoms develop abruptly
	Predominantly diffuse pulmonary edema
	Minimal systemic edema (patient may be euvolemic or hypovolemic)
	Acute elevation of filling pressure often with preserved LVEF
	Vascular pathophysiology
CS2	SBP 100–140 mm Hg
	Symptoms develop gradually, together with a gradual increase in body weight
	Predominantly systemic edema
	Minimal pulmonary edema
	Chronic elevation of filling pressure, including increased venous pressure and elevated pulmonary arterial pressure
	Manifestations of organ dysfunction (renal impairment, liver dysfunction, anemia, hypoalbuminemia)
CS3	SBP <100 mm Hg
	Rapid or gradual onset of symptoms
	Predominantly signs of hypoperfusion
	Minimal systemic and pulmonary edema
	Elevation of filling pressure
	Two subsets:
	Clear hypoperfusion or cardiogenic shock
	No hypoperfusion/cardiogenic shock
CS4	Symptoms and signs of acute heart failure
	Evidence of ACS
	Isolated elevation of cardiac troponin is inadequate for CS4 classification
CS5	Rapid or gradual onset
	No pulmonary edema
	Right ventricular dysfunction
	Signs of systemic venous congestion

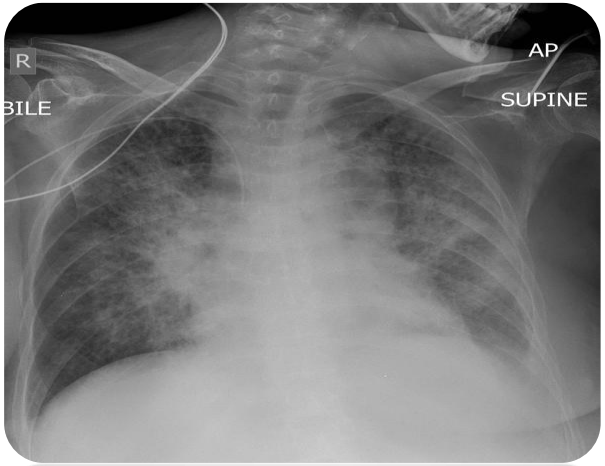
SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; ACS, acute coronary syndrome.

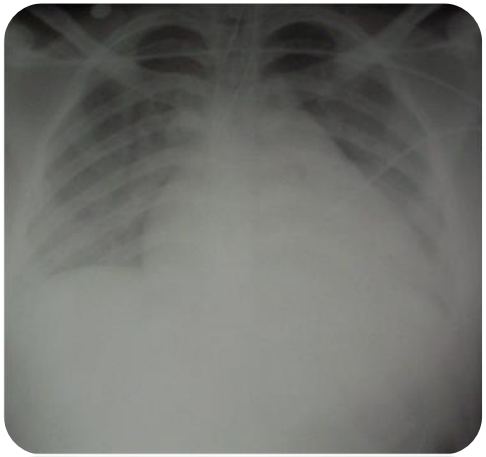


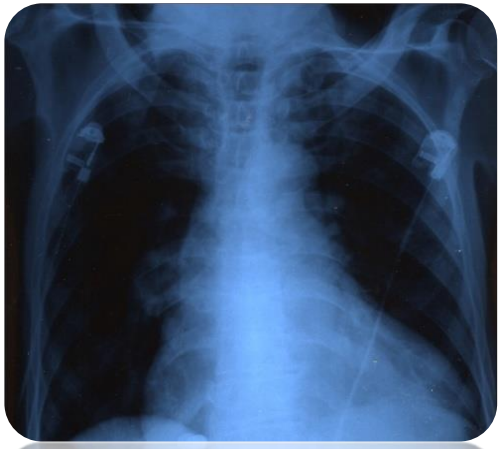
- ***Scénario 1: PAS >140 mmHg***
  - Symptômes se développent brutalement
  - Œdème pulmonaire prédominant
  - Peu ou pas d'œdème périphérique
  - Augmentation des pressions de remplissage et fonction VG préservée
  - Pathologie vasculaire

- ***Scénario 2: PAS 100-140 mmHg***
  - Symptômes d'installation progressive
  - Œdème systémique prédominant
  - Œdème pulmonaire minime
  - Augmentation des pressions de remplissage
  - Dysfonction d'organes (rénale, hépatiques, anémie
  - hypoalbuminémie




R
AP
SUPINE





Présentation clinique

Scénarios	Fréquence	Profils cliniques	Physiopathologie
1. PAS > 140 mmHg	~50%	• Apparition brutale • Œdème pulmonaire diffus	• HTA d'origine vasculaire • ↓ compliance VG • FEVG souvent préservée
2. PAS 100-140 mmHg	~40%	• Apparition progressive • Œdèmes systémiques prédominants	• Rétention hydrosodée progressive • Insuffisance cardiaque chronique
3. PAS < 100 mmHg	< 10%	• Apparition brutale ou progressive • Congestion souvent peu marquée • Détecter hypoperfusion	• IC chronique avancée • ↓ souvent sévère de la FEVG • Bas débit cardiaque
4. Syndrome coronarien aigu	~20%	• Apparition brutale • DRS/signes ECG d'ischémie • Elévation significative troponine	• Ischémie myocardique • Altération de la fonction systolique et diastolique du VG
5. Insuffisance ventriculaire droite isolée	~3%	• Apparition brutale ou progressive • Signes de congestion veineuse systémique • Symptômes gastro-intestinaux	• Dysfonction ventriculaire droite • Hypertension artérielle pulmonaire • Bas débit cardiaque

Intensive Care Med (2011) 37:619–626
DOI 10.1007/s00134-010-2113-0

ORIGINAL

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J. T. Parissis
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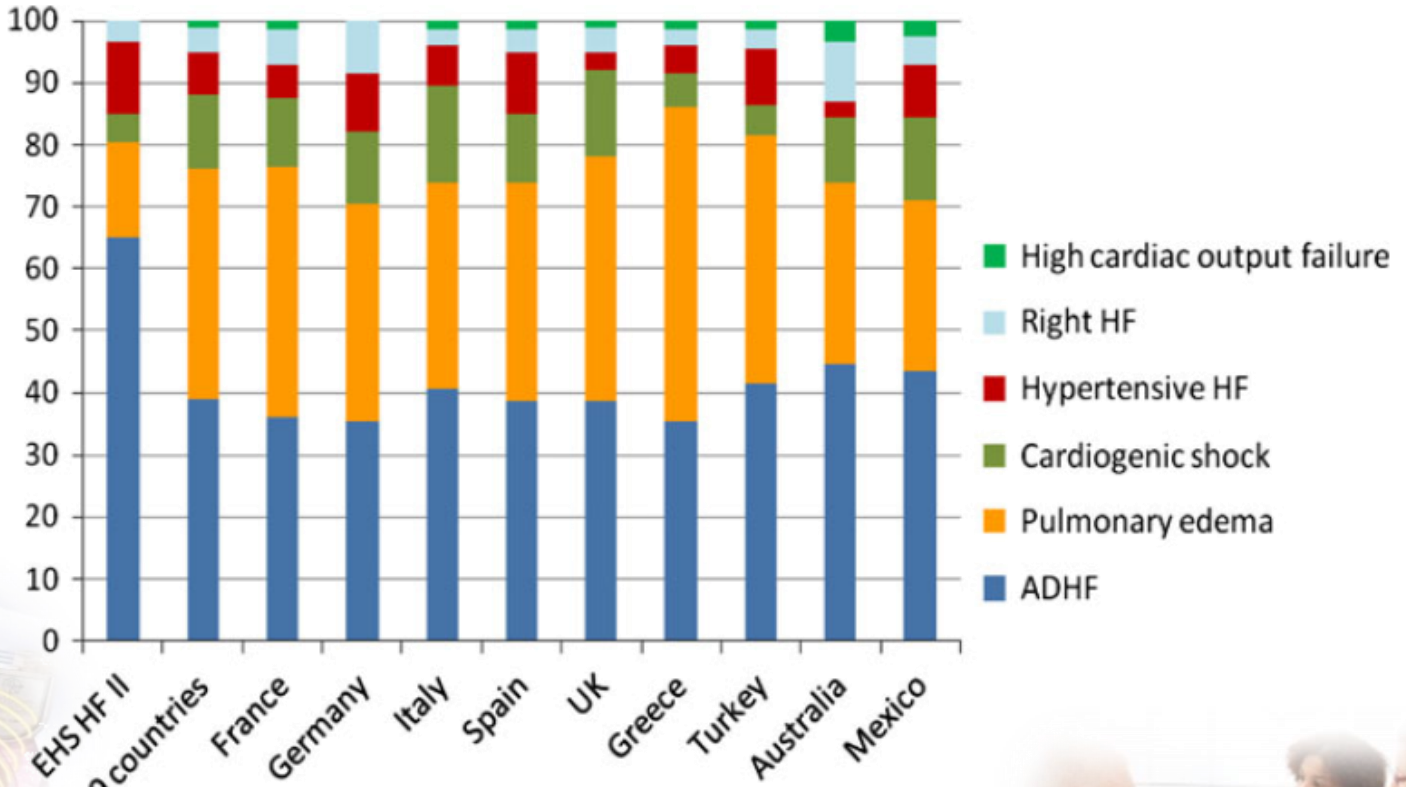
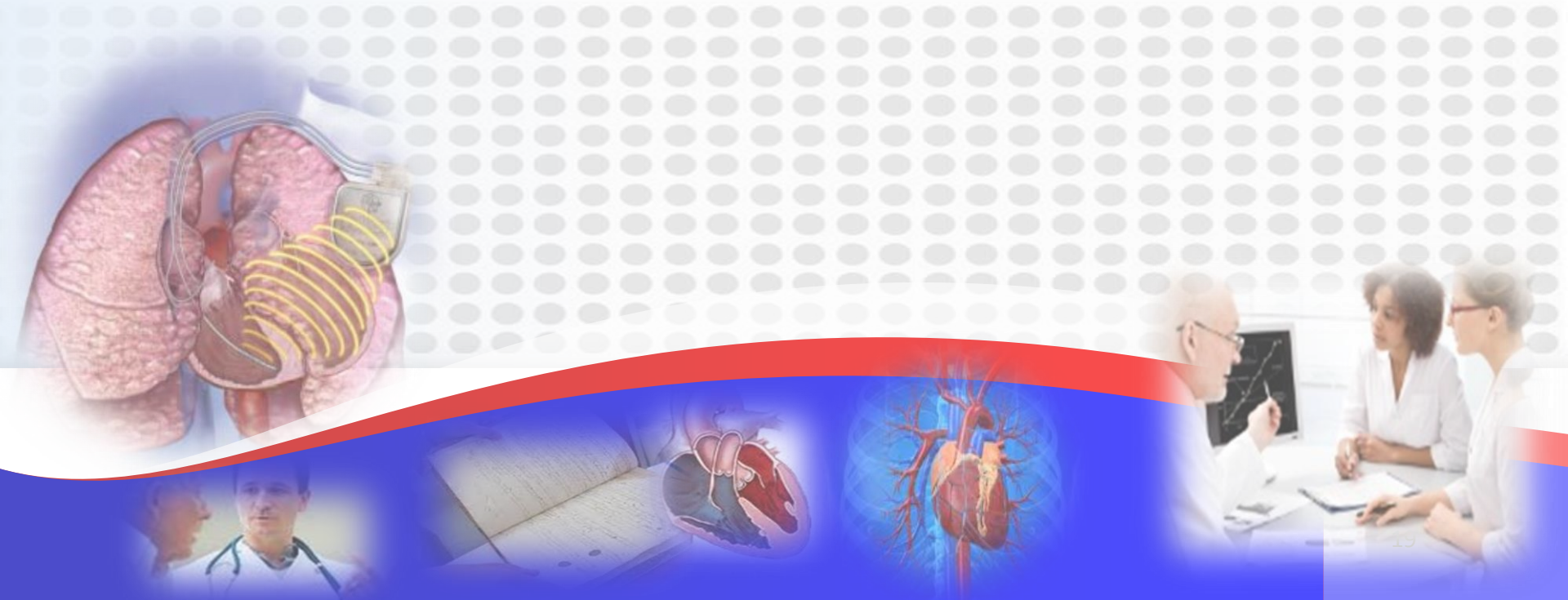
Clinical presentation, management and outcomes in the Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF)



Diurétiques

- Utilisation importante
- Peu de données issues d'essais thérapeutiques randomisés



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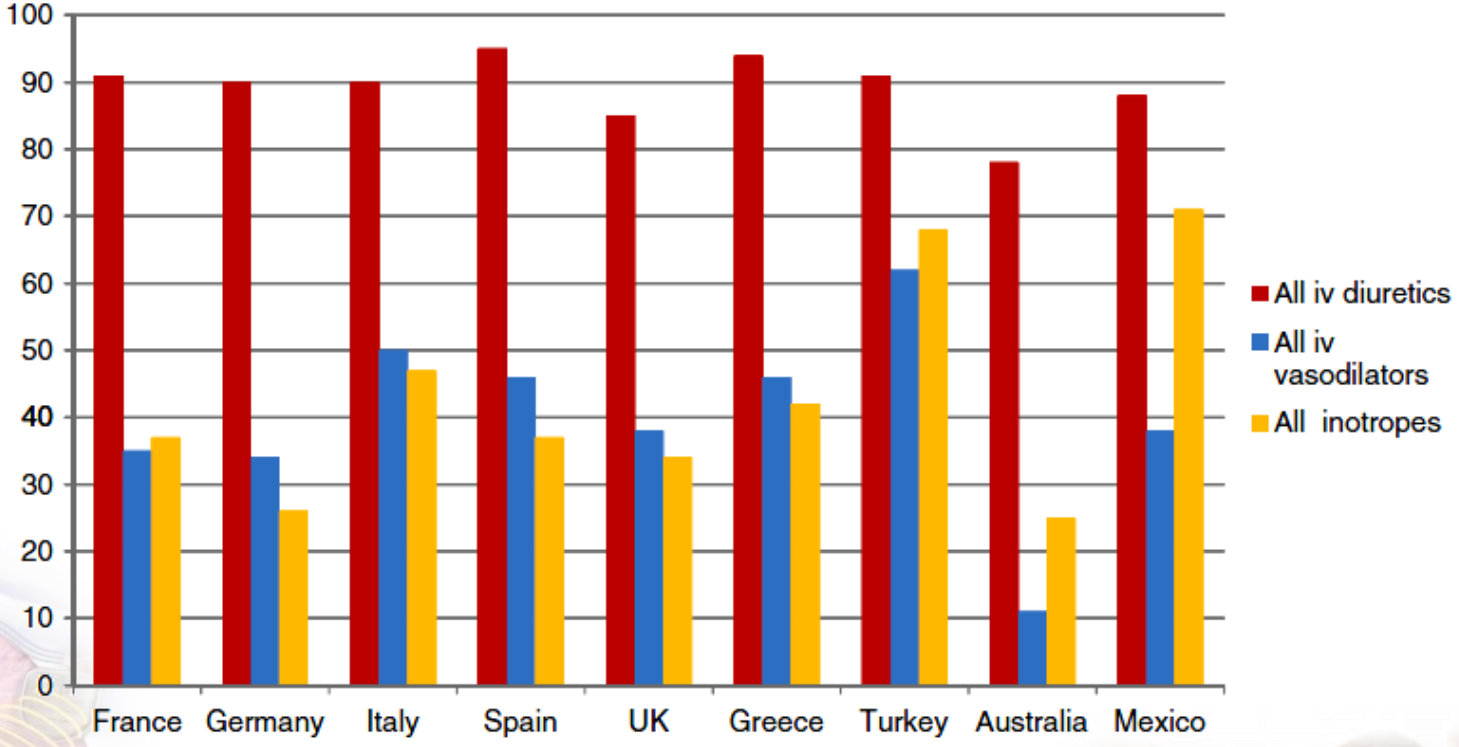


Non aux diurétiques dans tous les cas

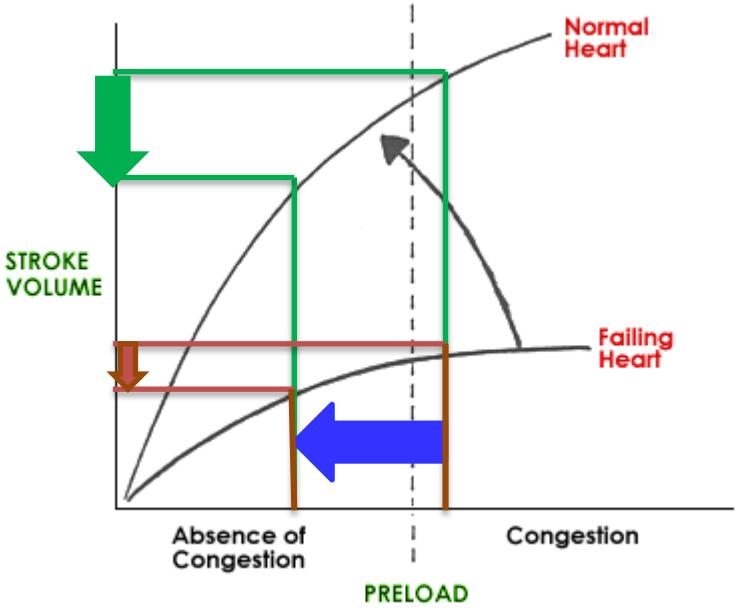
Les arguments scientifiques

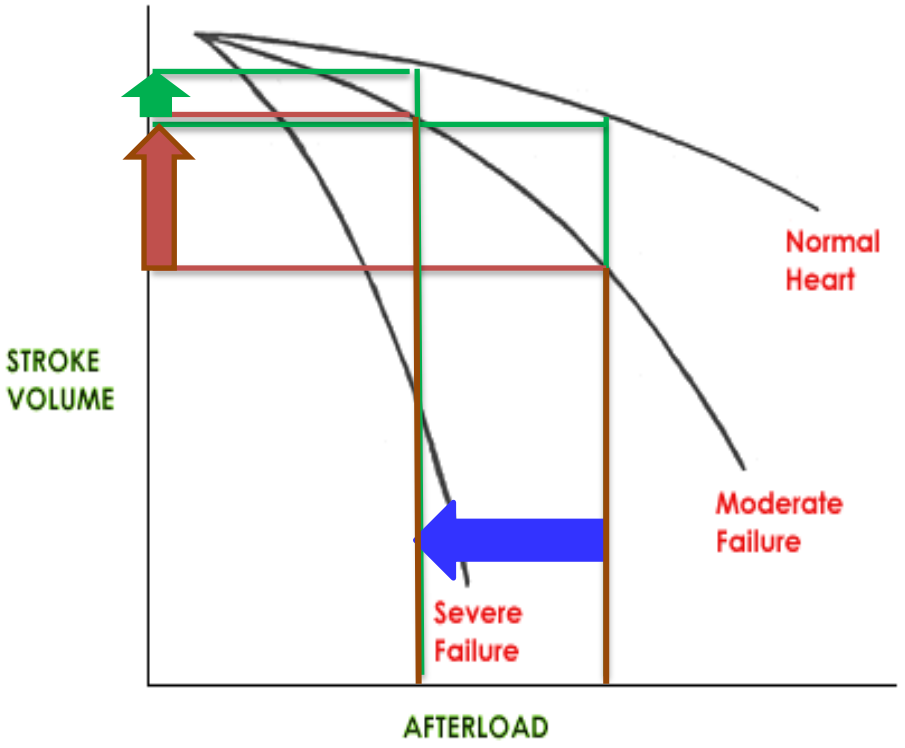
1. Effets hémodynamiques et neuroendocrines
2. Diurétiques de l'anse et congestion pulmonaire
3. Résistance
4. Effets indésirables
5. Mortalité

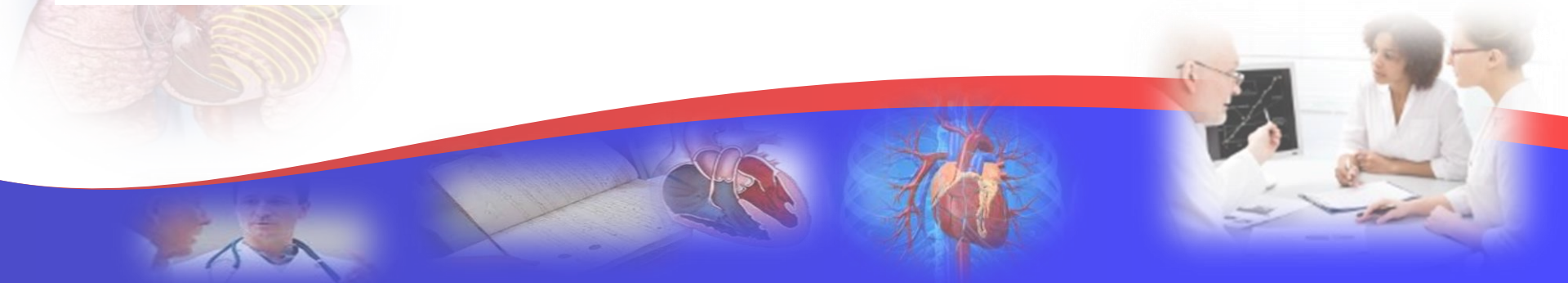
Non aux diurétiques dans tous les cas

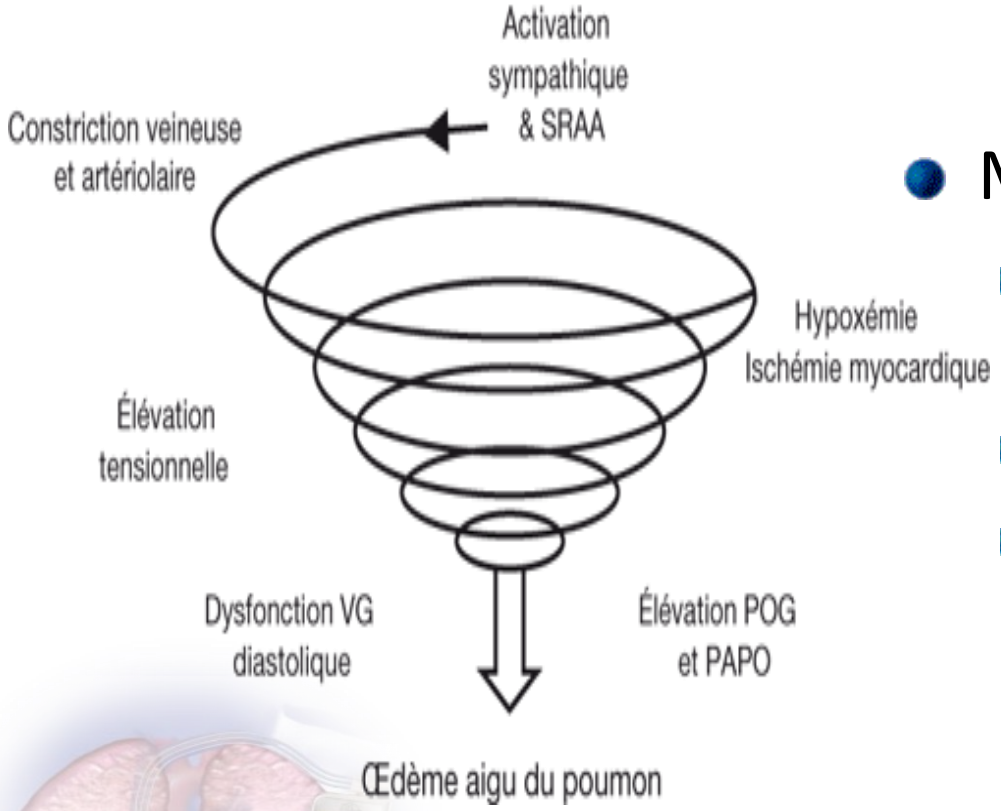
Les arguments scientifiques

1. **Effets hémodynamiques et neuroendocrines**
2. **Diurétiques de l'anse et congestion pulmonaire**
3. **Résistance**
4. **Effets indésirables**
5. **Mortalité**


Normal
Heart
STROKE
VOLUME
Failing
Heart
Absence of
Congestion
Congestion
PRELOAD


Normal
Heart
STROKE
VOLUME
Moderate
Failure
Severe
Failure
AFTERLOAD



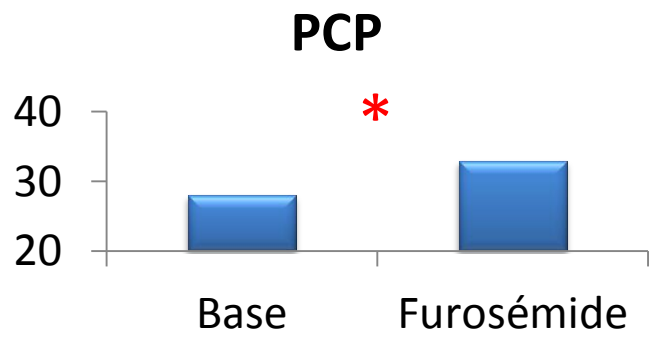


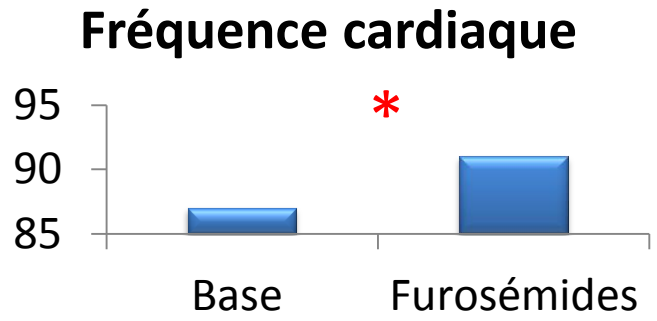
- Modèle neuro-hormonal
  - Norépinephrine, rénine, angiotensine, aldostérone
  - Effets vasoconstricteurs
  - Augmentation du volume intravasculaire

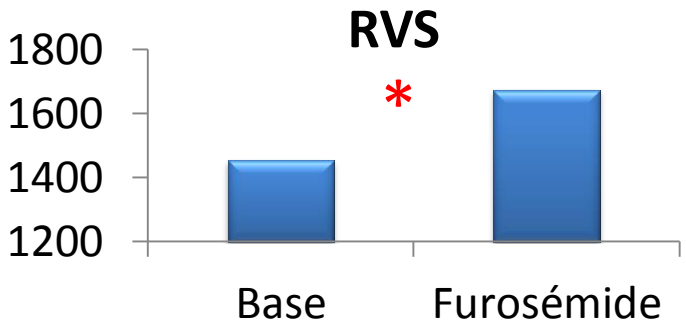
Acute Vasoconstrictor Response to Intravenous Furosemide in Patients with Chronic Congestive Heart Failure: Activation of the Neurohumoral Axis

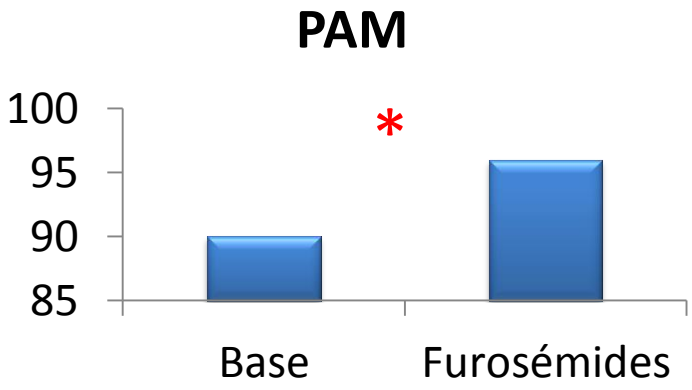
Francis GS Ann Intern Med 1985

- 15 patients insuffisance cardiaque sévère
- 1.3 ± 0.6 (SD) mg/kg Furosémide → 20 min

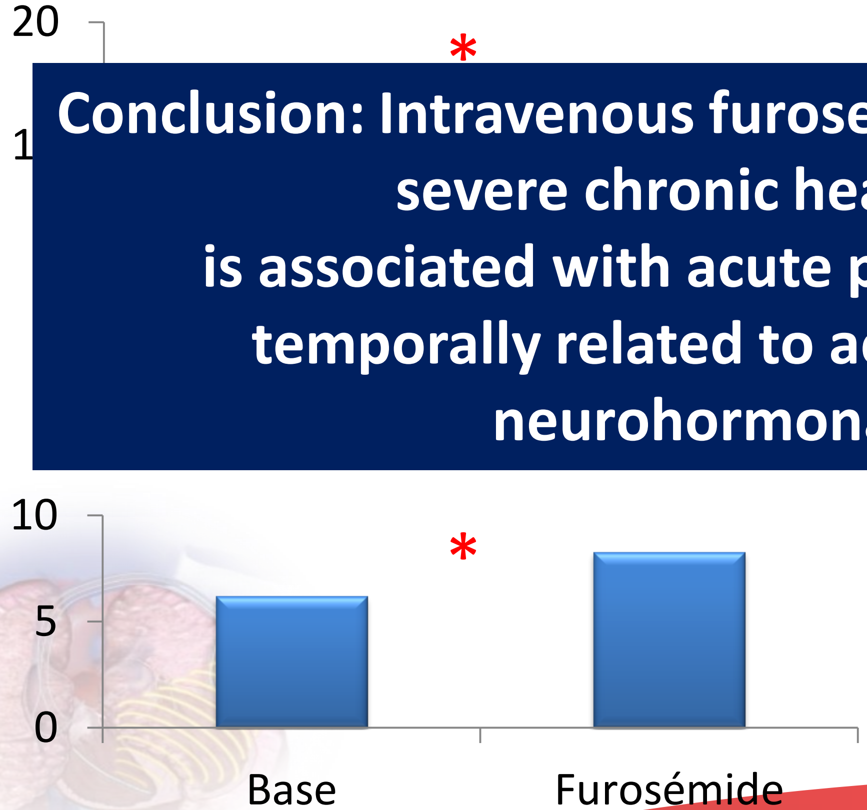




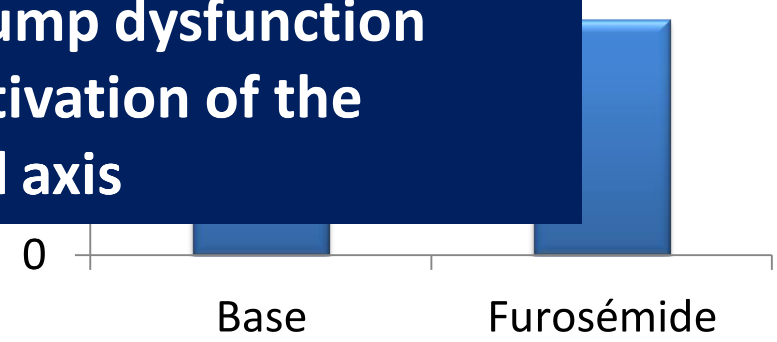




Acute Vasoconstrictor Response to Intravenous Furosemide in Patients with Chronic Congestive Heart Failure: Activation of the Neurohumoral Axis



Conclusion: Intravenous furosemide, in patients with severe chronic heart failure is associated with acute pump dysfunction temporally related to activation of the neurohormonal axis



GARY S. FRANCIS, *Ann Intern Med*. 1 July 1985;103(1):1-6

Comparison of Neuroendocrine Activation in Patients With Left Ventricular Dysfunction With and Without Congestive Heart Failure

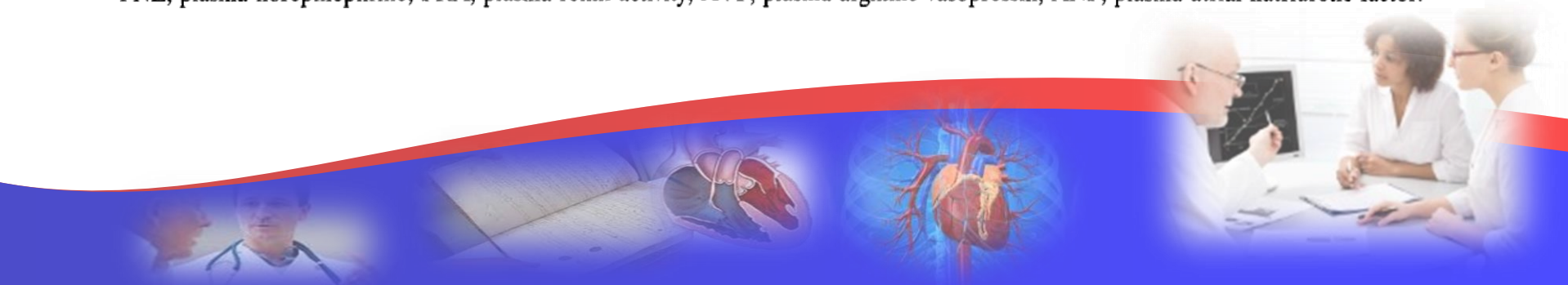
A Substudy of the Studies of Left Ventricular Dysfunction (SOLVD)

Gary S. Francis, Circulation 1990;82:1724-1729

TABLE 3. Plasma Neuroendocrine Levels in Prevention Patients, Treatment Patients, and Control Subjects

Neurohumoral measurement	Median and interquartile ranges				
		Prevention patients		Treatment patients	
	Control	No diuretics	On diuretics	No diuretics	On diuretics
PNE (pg/ml)	316.5 (242–450) (n=54)	422.0 (309–548) (n=121)	416.5 (341–625.8) (n=30)	473.0 (330–553) (n=9)	507.5 (366–669.5) (n=72)
PRA (ng/ml/hr)	0.6 (0.3–0.9) (n=56)	0.7 (0.3–1.5) (n=121)	1.0 (0.5–2.4) (n=30)	0.7 (0.4–1.6) (n=9)	1.7 (0.5–4.3) (n=71)
AVP (pg/ml)	1.8 (1.4–2.3) (n=54)	2.3 (1.7–3.0) (n=117)	2.2 (1.7–2.8) (n=30)	2.9 (2.1–3.5) (n=9)	3.0 (2.3–4.5) (n=71)
ANF (pg/ml)	48.3 (30.6–64.8) (n=54)	102.8 (68.5–133.3) (n=117)	103.9 (73.6–180.2) (n=30)	105.5 (65.1–209.1) (n=9)	148.0 (96.7–202.3) (n=71)

PNE, plasma norepinephrine; PRA, plasma renin activity; AVP, plasma arginine vasopressin; ANF, plasma atrial natriuretic factor.



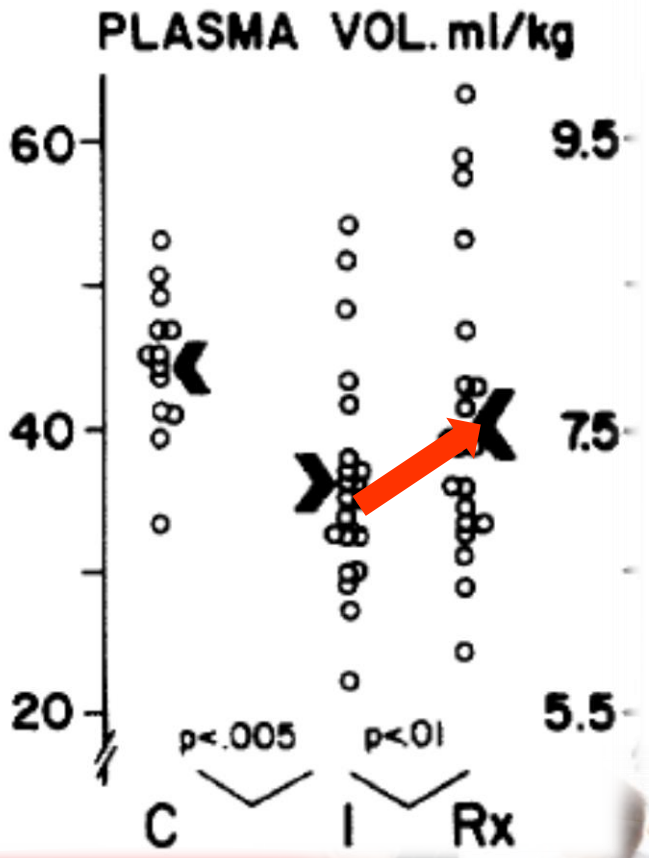
Blood volume prior to and following treatment of acute cardiogenic pulmonary edema.

J Figueras and M H Weil

Circulation. 1978;57:349-355

TABLE 6. *Changes in Plasma Volume, Hematocrit (Hct), Total Protein (TP), Colloid Osmotic Pressure (COP), and Net Fluid Loss after an Average Interval of 21.3 ± 2.1 Hours of Treatment in 10 Patients with Acute Pulmonary Edema* (mean ± SEM)

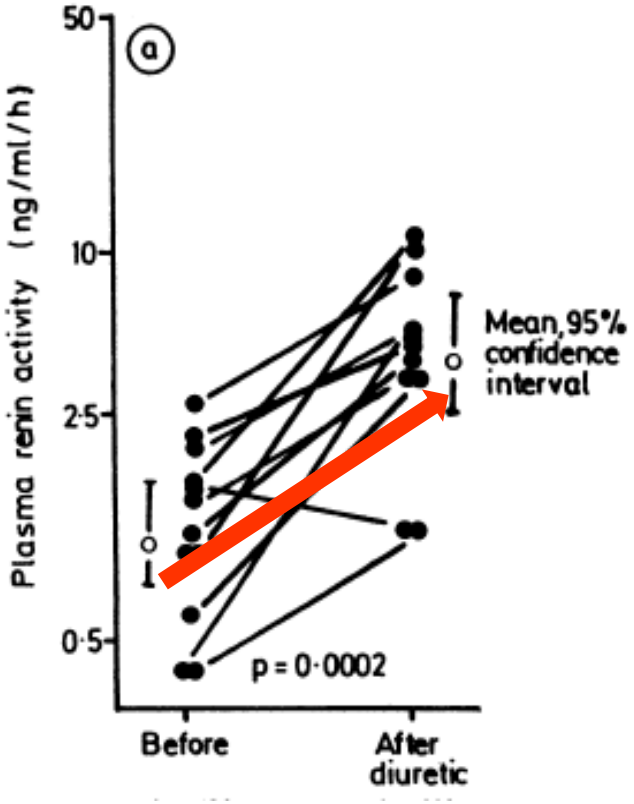
	Prior	Following	*P*
Plasma volume, ml/kg	37.2 ± 2.9	43.1 ± 2.3	<0.05
Hct, %	42.8 ± 1.9	36.7 ± 1.8	<0.001
TP, g/dl	8.2 ± 0.3	6.9 ± 0.4	<0.001
COP, mm Hg	26.1 ± 0.9	21.5 ± 1.0	<0.002
Urine output-fluid intake		2823 ± 848	

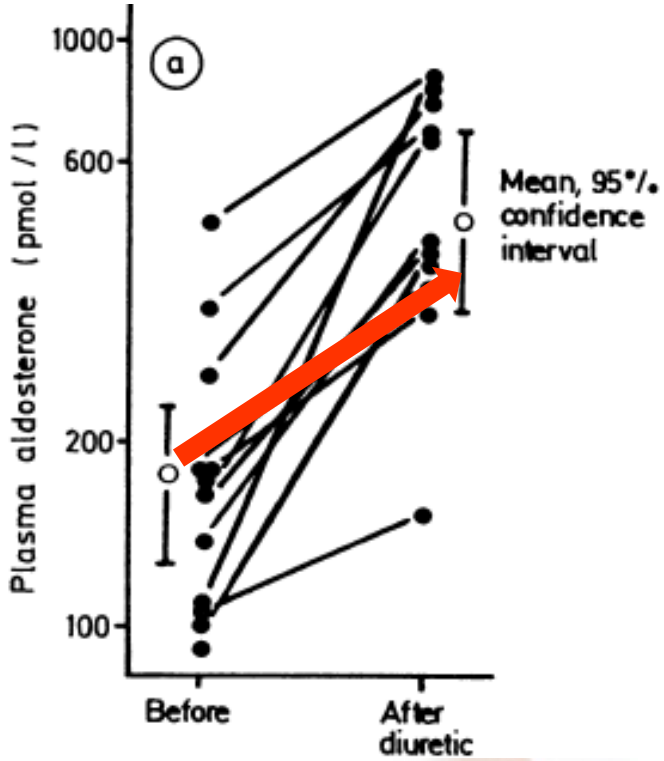


Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics

Bayliss J Br Heart J 1987; 57:17-22

Treatment : oxygen, furosemide, morphine sulfate





Effets hémodynamiques et neuroendocrines

Diurétiques

Effets neuroendocrines
Augmentation Nor epinephrine, ARP, Vasopressine, ANP
Vasoconstriction

Effets hémodynamiques : Immédiat
Augmentation des RVP, PAM (RVS)et PCP

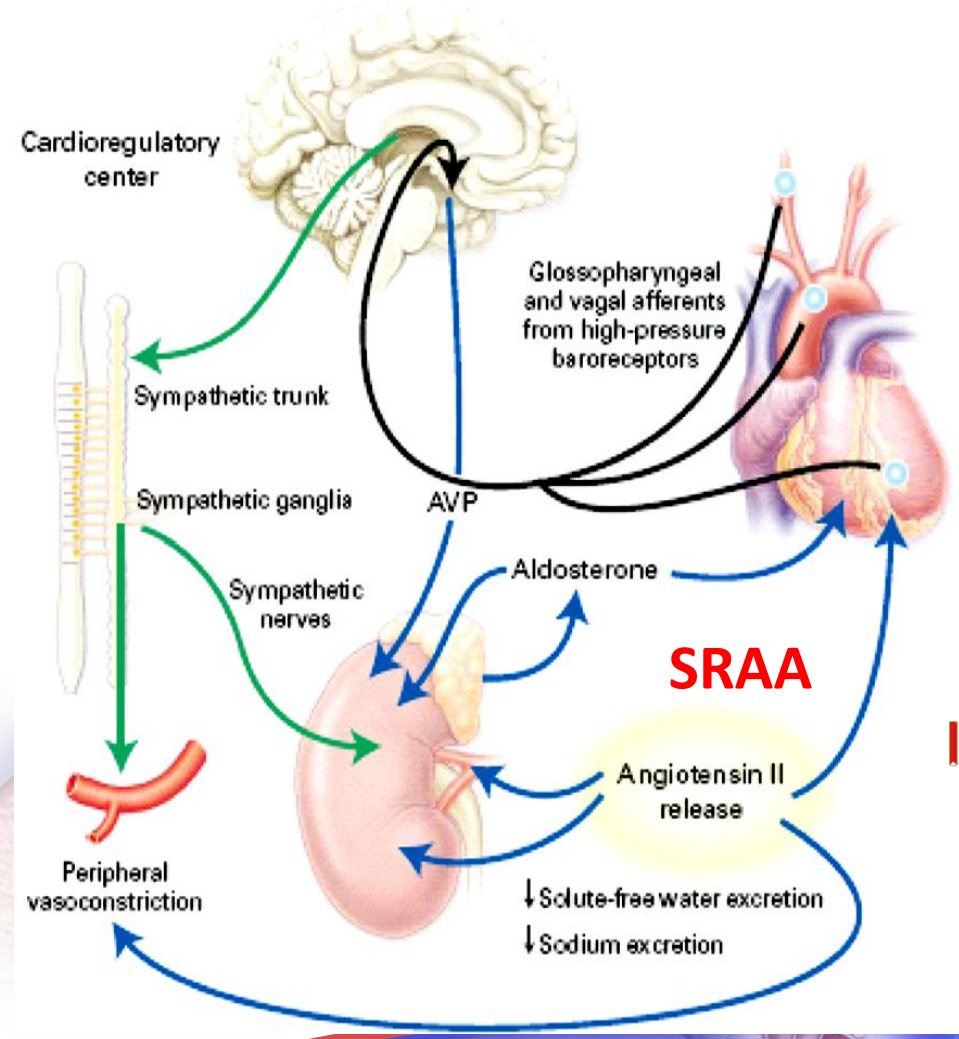
Facteurs aggravent la fonction pompe du VG

Non aux diurétiques dans tous les cas

Les arguments scientifiques

1. **Effets hémodynamiques et neuroendocrines**
2. **Diurétiques de l'anse et congestion pulmonaire**
3. **Résistance**
4. **Effets indésirables**
5. **Mortalité**

Rétention hydrosodée
Congestion pulmonaire



Diminution du Na au niveau du tube collecteur
site d'action de l'aldostérone et peptide Natriurétique

Activation récepteurs de l' épithélium du tube proximal → augmente réabsorption de Na+

Diurétiques de l'anse insuffisant pour traiter la congestion

- 25 % du sodium filtré
- →limite l'efficacité des diurétiques de l'anse à réduite le sodium total
- La persistance du Na en excès → réaccumulation de l'eau → congestion → dysfonction ventriculaire progressive et aggravation de l'insuffisance cardiaque

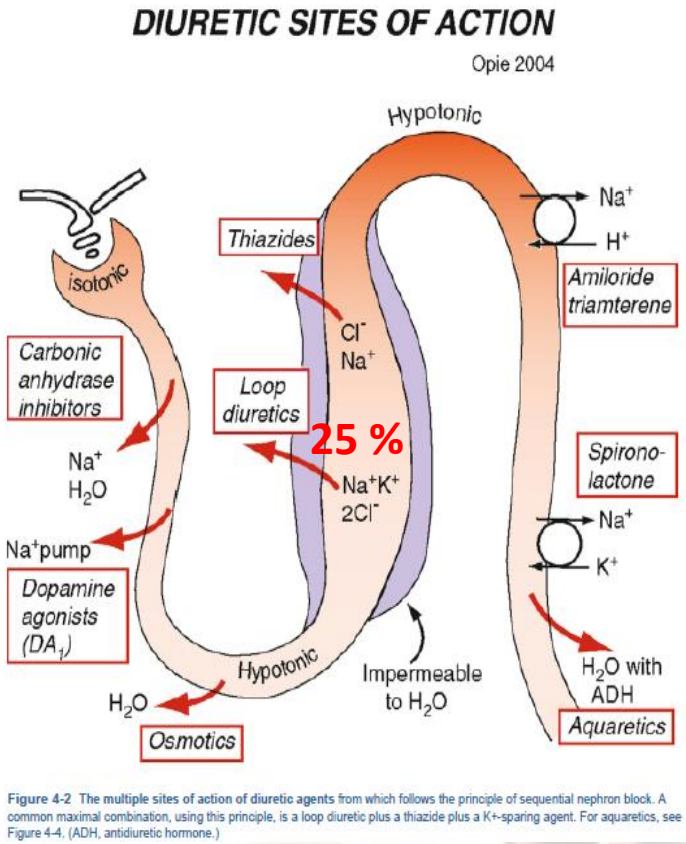
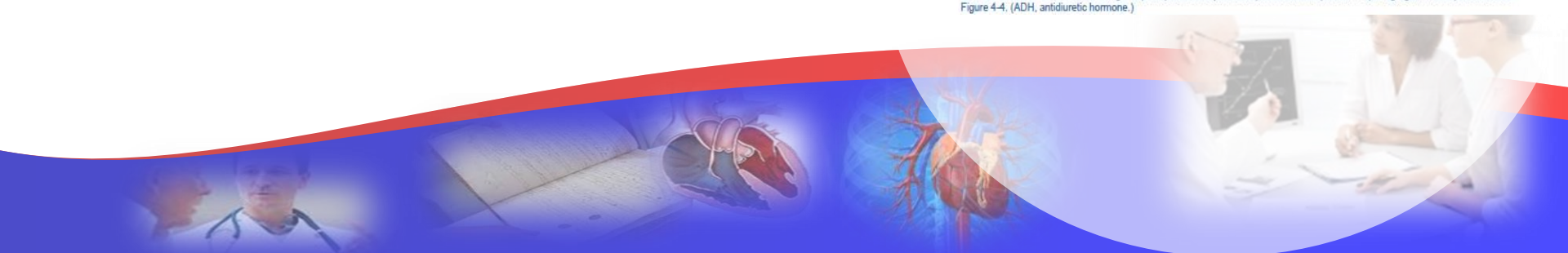


Figure 4-2 The multiple sites of action of diuretic agents from which follows the principle of sequential nephron block. A common maximal combination, using this principle, is a loop diuretic plus a thiazide plus a K+-sparing agent. For aquaretics, see Figure 4-4. (ADH, antidiuretic hormone.)



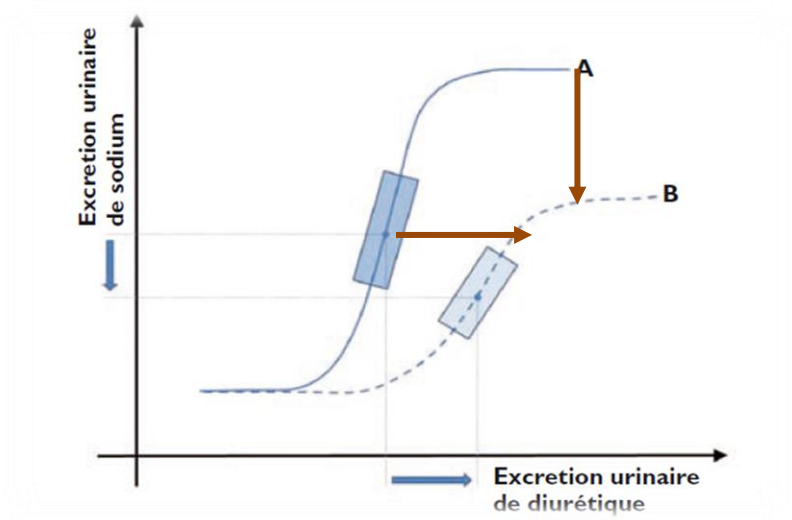
Non aux diurétiques dans tous les cas

Les arguments scientifiques

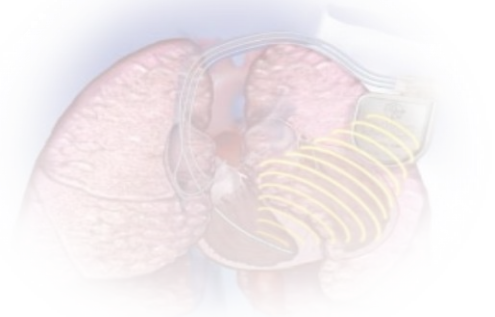
1. **Effets hémodynamiques et neuroendocrines**
2. **Diurétiques de l'anse et congestion pulmonaire**
3. **Résistance**
4. **Effets indésirables**
5. **Mortalité**

Résistance aux diurétiques

- Problème majeur
- Plusieurs mécanismes sont responsables de la résistance aux diurétiques :
  - ***diminution du débit sanguin rénal*** →baisse de la concentration intrarénale des diurétiques → diminution importante de l'excrétion sodée

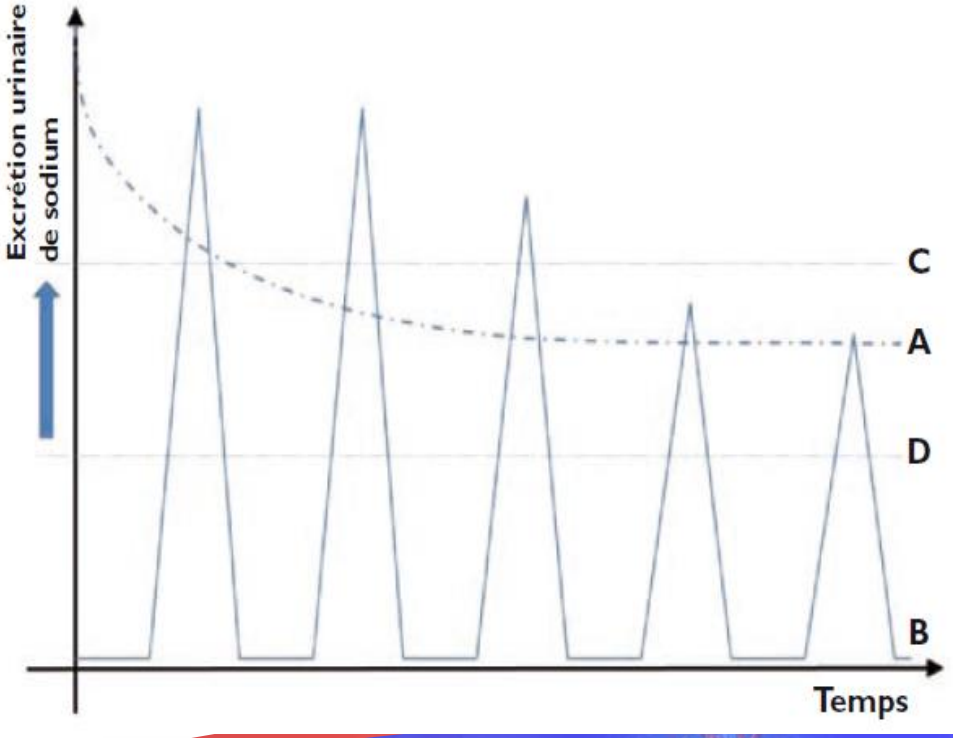


- ***Activation neuro-hormonale,***
  - Réabsorption hydro sodée
  - Résistance aux diurétique en induisant une vasoconstriction (rénale)
- ***Diminution de la sécrétion tubulaire des diurétiques,***
- ***Réabsorption sodée compensatrice***
- ***Hypertrophie des cellules du tube contourné distal.***



Résistance aux diurétiques

- ***Effet tolérance (braking phenomenon) :*** baisse progressive de la réponse aux diurétiques



Non aux diurétiques dans tous les cas

Les arguments scientifiques

1. Effets hémodynamiques et neuroendocrines
2. Diurétiques de l'anse et congestion pulmonaire
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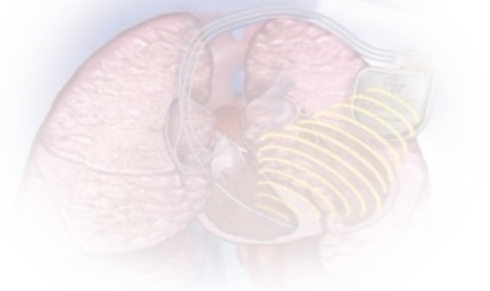
4. Effets indésirables
5. Mortalité



Autres limites des diurétiques

- Réduction de la filtration glomérulaire
- Troubles électrolytiques
- Autres
  - Photo sensibilité
  - Rash cutané
  - Complications auditives

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

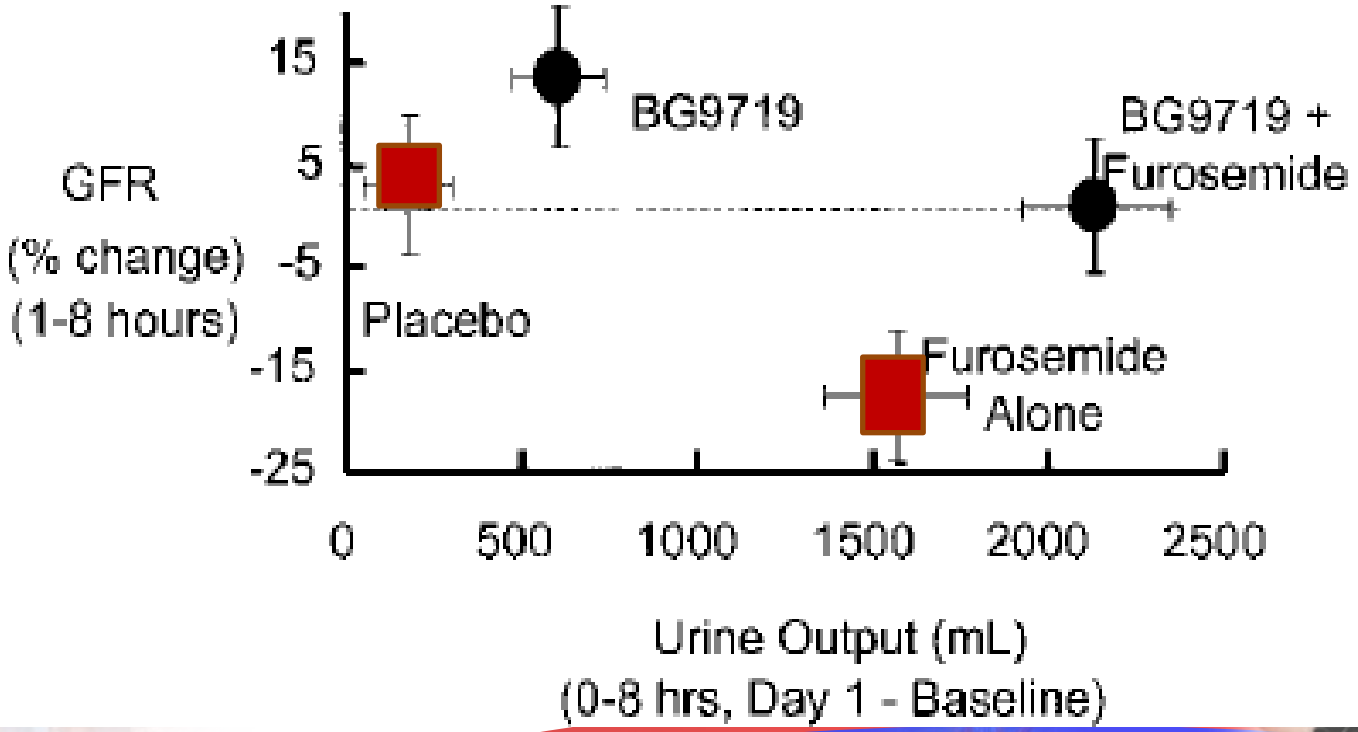
American Heart Association®

BG9719 (CVT-124), an A_1 Adenosine Receptor Antagonist, Protects Against the Decline in Renal Function Observed With Diuretic Therapy

Stephen S. Gottlieb, D. Craig Brater, Ignatius Thomas, Edward Havranek, Robert Bourge, Steven Goldman, Farere Dyer, Miguel Gomez, Donald Bennett, Barry Ticho, Evan Beckman and William T. Abraham

Circulation. 2002;105:1348-1353;

Furosemide Monotherapy Causes Significant Decline in Renal Function (GFR)



Worsening renal function in patients hospitalised for acute heart failure: Clinical implications and prognostic significance

Marco Metra [a,*], Savina Nodari [a], Giovanni Parrinello [b], Tania Bordonali [a], Silvia Bugatti [a], Rossella Danesi [a], Benedetta Fontanella [a], Carlo Lombardi [a], Patrizia Milani [a], Giulia Verzura [a], Gadi Cotter [c], Howard Dittrich [d], Barry M. Massie [e], Livio Dei Cas [a]

European Journal of Heart Failure 10 (2008) 188–195

318 Patients

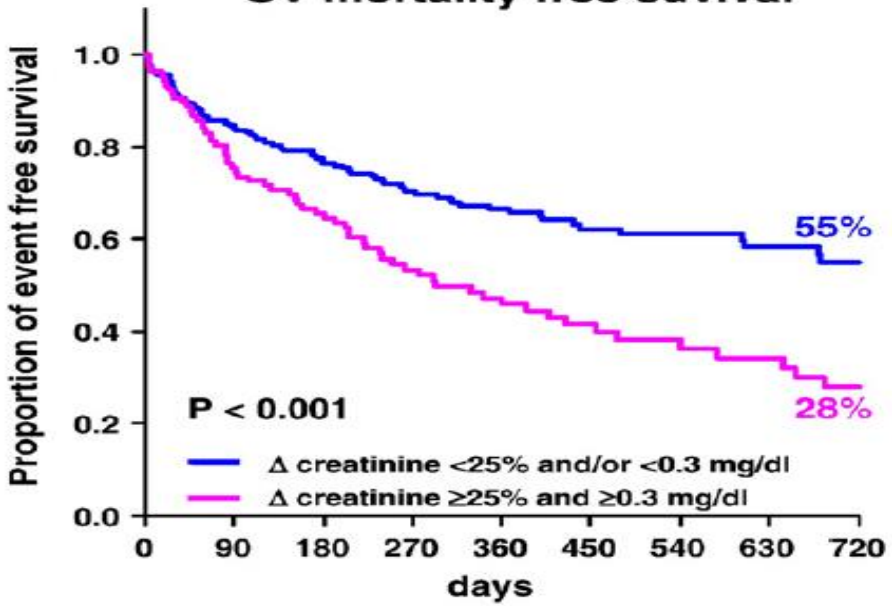
Aggravation fonction rénale: $\uparrow creat > 25\%$ *et plus de* $0,3 \frac{mg}{dl}$

107 (34%)

Table 3
Baseline determinants of WRF-Abs-% at multivariable analysis

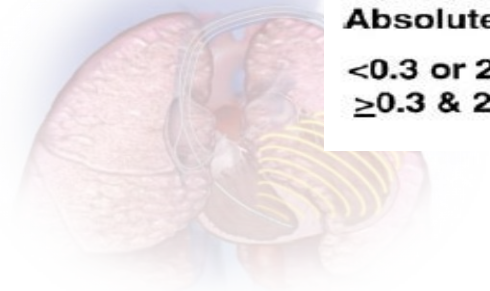
Predictors	Odds ratio (95% CI)	*p* value
Analysis with LVEF and furosemide dose as continuous variables		
History of chronic kidney disease	3.66 (1.61–8.33)	0.002
LV ejection fraction	0.97 (0.95–0.99)	0.012
I.v. furosemide daily dose on admission	1.001 (1.000–1.003)	0.034
NYHA class	1.79 (0.99–1.79)	0.052
Analysis with LVEF and furosemide dose as categorical variables		
History of chronic kidney disease	1.84 (1.04–3.27)	<0.0001
I.v. furosemide dose >100 mg/day	2.18 (1.27–3.73)	0.004
NYHA class (IV versus III)	2.07 (1.24–3.45)	0.005
LV ejection fraction<30%	1.66 (1.01–2.75)	0.047

HF Hospitalisations and CV mortality free suvival



Pts. at risk
Absolute and percent s-Cr change:

<0.3 or 25%	211	143	92	55	36
≥0.3 & 25%	107	64	36	19	14



Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Diuretics and Risk of Arrhythmic Death in Patients With Left Ventricular Dysfunction

Howard A. Cooper, Daniel L. Dries, C. E. Davis, Yuan Li Shen and Michael J. Domanski

Circulation. 1999;100:1311-1315

TABLE 3. Distribution of Events According to Diuretic Use at Baseline

	Diuretic (n=2901)		No Diuretic (n=3896)		
	n (%)	Incidence	n (%)	Incidence	*P*
Death from any cause	1013 (34.9)	12.8	586 (15.0)	5.3	0.001
Cardiovascular death	903 (31.1)	11.4	510 (13.1)	4.6	0.001
Arrhythmic death	241 (8.3)	3.1	183 (4.7)	1.7	0.001

Incidence is expressed as number of events per 100 patient-years of follow-up.

Non aux diurétiques dans tous les cas

Les arguments scientifiques

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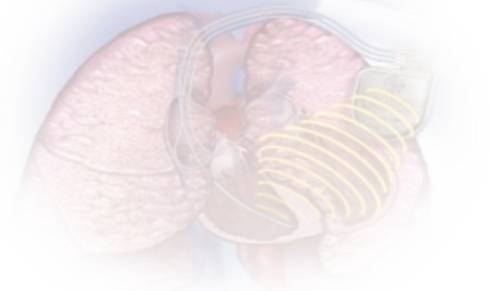
5. Mortalité



Intensive Care Med (2011) 37:290–301
DOI 10.1007/s00134-010-2073-4

ORIGINAL

Alexandre Mebazaa
John Parissis
Raphael Porcher
Etienne Gayat
Maria Nikolaou
Fabio Vilas Boas
J. F. Delgado
Ferenc Follath

Short-term survival by treatment among patients hospitalized with acute heart failure: the global ALARM-HF registry using propensity scoring methods

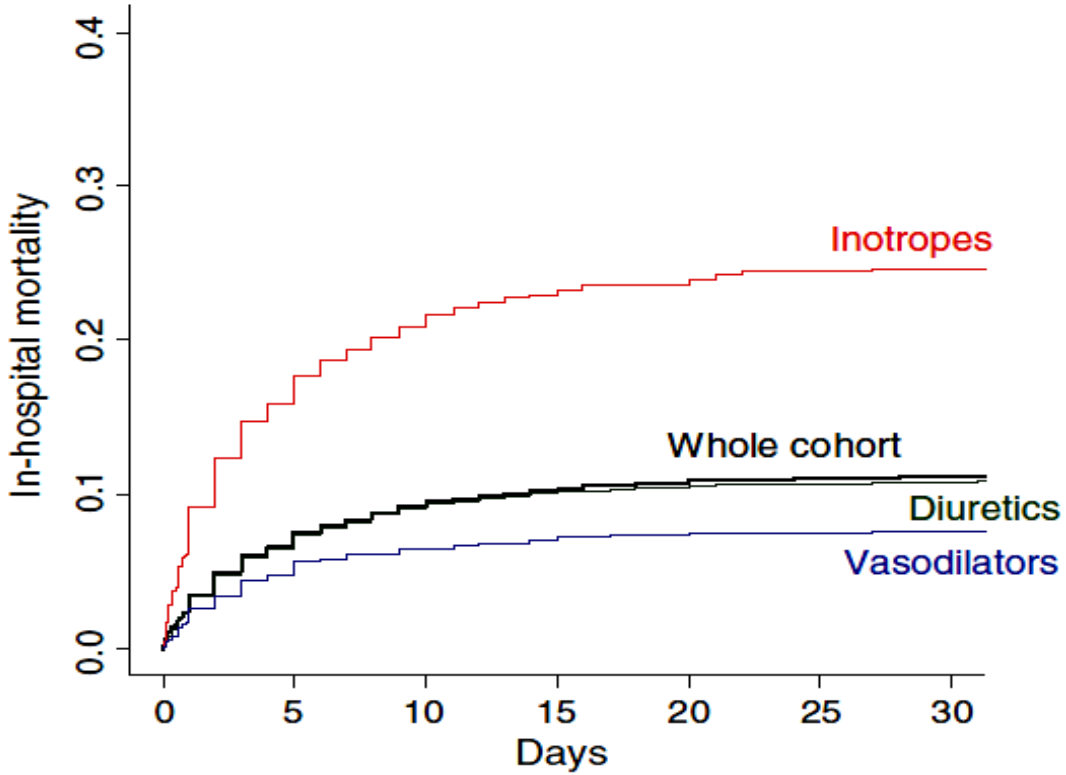


Fig. 1 Effect of the main intravenous (IV) drugs administered during first 48 h in acute heart failure (AHF) patients on in-hospital mortality. Whole cohort ($n = 4{,}953$), IV diuretics ($n = 4{,}167$), IV vasodilators (mostly nitrates, $n = 1{,}930$), IV inotropes and/or IV vasopressors ($n = 1{,}617$)

Loop Diuretics in Acute Decompensated Heart Failure

Necessary? Evil? A Necessary Evil?

G. Michael Felker, MD, MHS; Christopher M. O'Connor, MD; Eugene Braunwald, MD; for the Heart Failure Clinical Research Network Investigators*

Circ Heart Fail 2009;2:56-62;

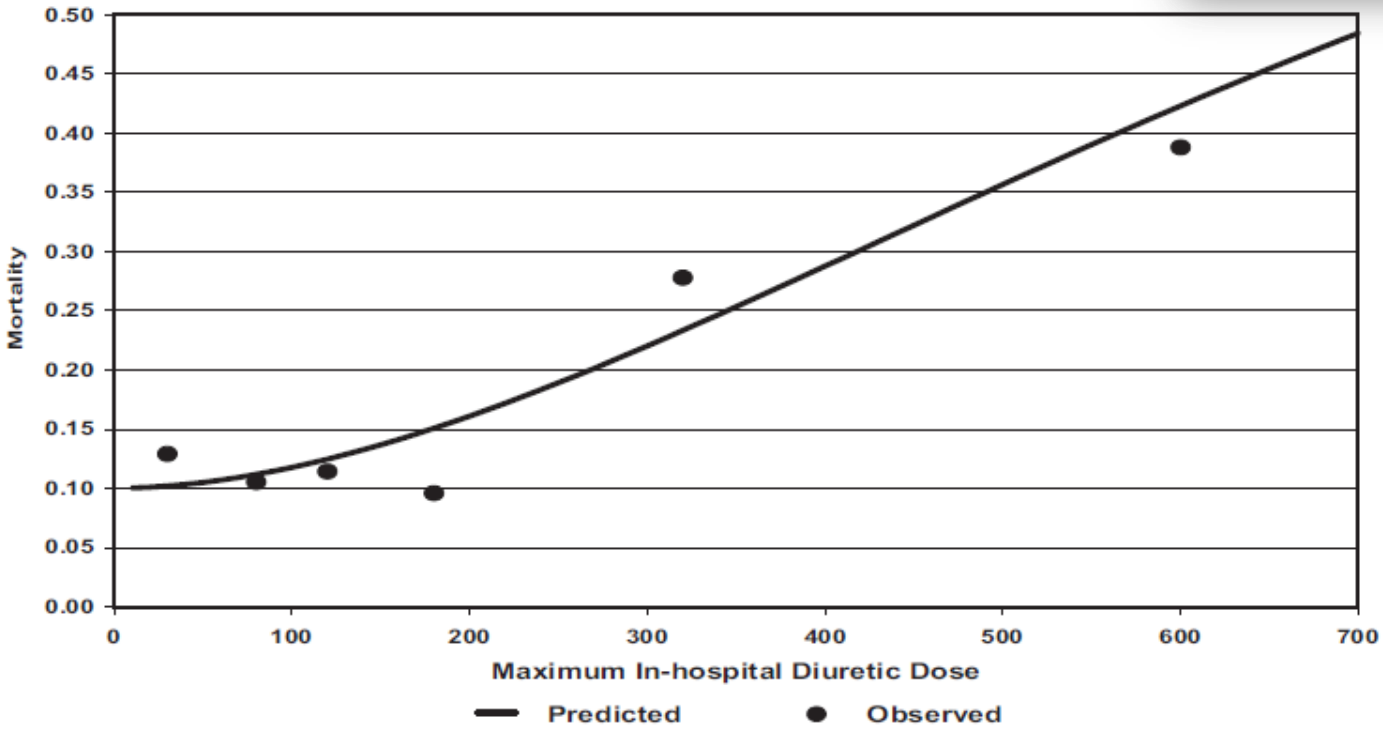
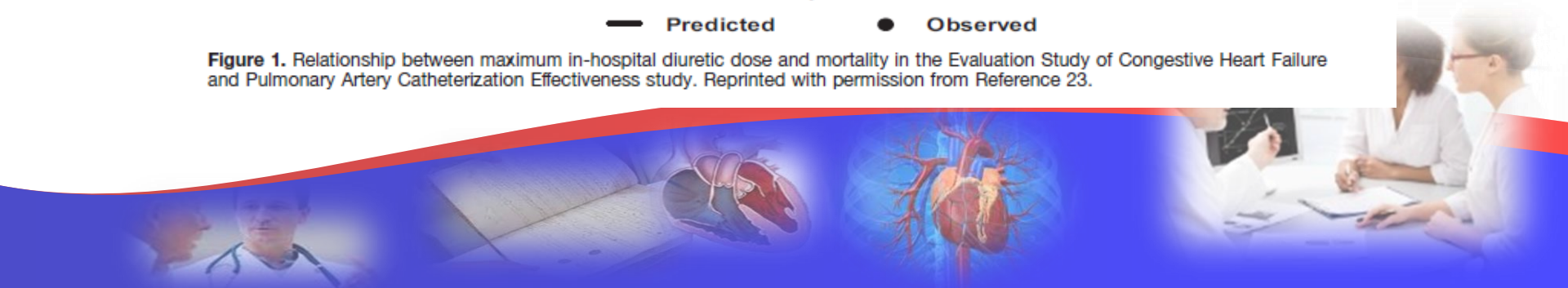


Figure 1. Relationship between maximum in-hospital diuretic dose and mortality in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness study. Reprinted with permission from Reference 23.

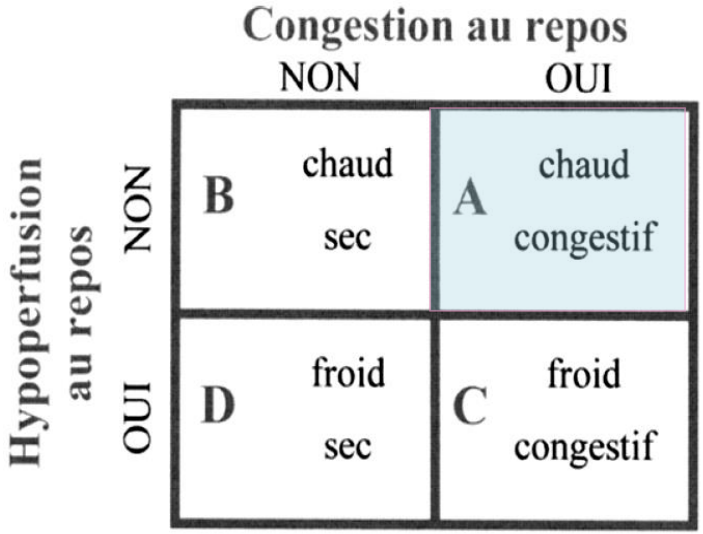


Diurétique

- Pour quels patients : profils hémodynamiques?

  →Niveau de pression de remplissage (sec ou congestif)

  →Perfusion tissulaire : chaud ou froid



Signes de congestion :

Orthopnée, dyspnée paroxystique nocturne
Turgescence ou reflux jugulaire
Hépatomégalie
Œdèmes déclives
Crépitants pulmonaires
PA élevée

Signes en faveur d'une hypoperfusion :

Pression pulsée basse
Somnolence, obnubilation
Hyponatrémie
Extrémités froides
Hypotension sous IEC
Insuffisance rénale

Alternatives :

- Vasodilatateurs
- Natriurétiques
- Ultrafiltration

Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema

Gad Cotter, Einat Metzkor, Edo Kaluski, Zwi Faigenberg, Rami Miller, Avi Simovitz, Ori Shaham, Doron Marghitay, Maya Koren, Alex Blatt, Yaron Moshkovitz, Ronit Zaidenstein, Ahuva Golik

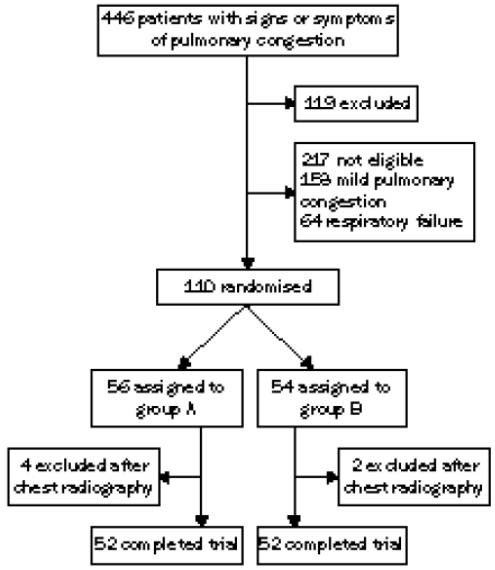


Figure 1: **Trial profile**

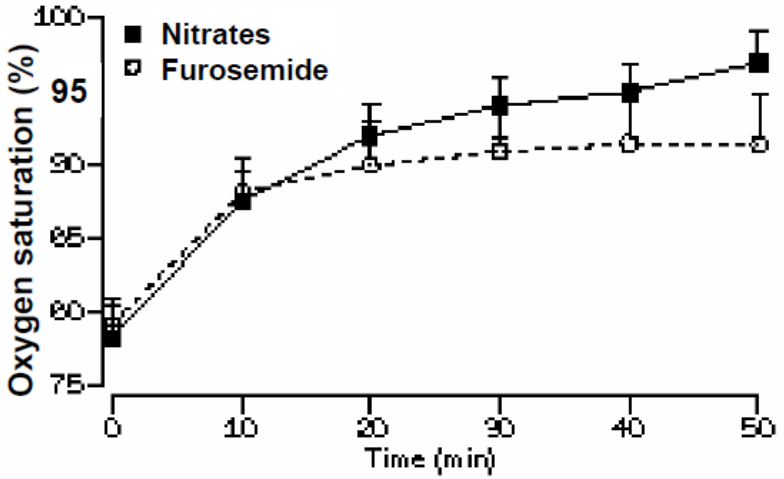


Figure 2: **Change in oxygen saturation during treatment in group A (predominant isosorbide dinitrate) and group B (predominant furosemide)**

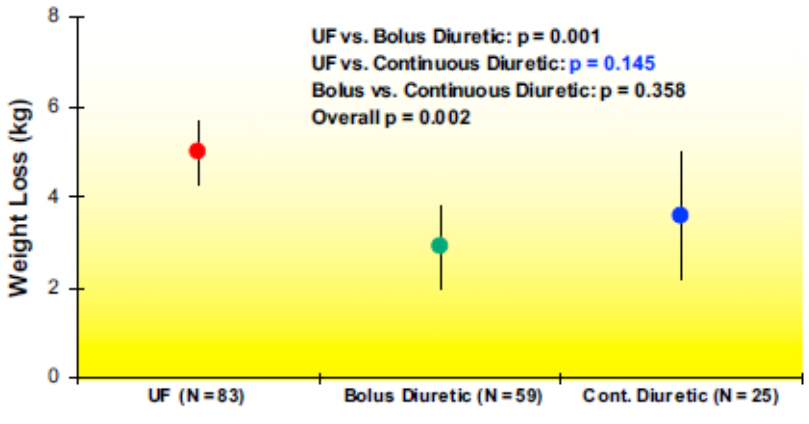
Primary outcome	Group A (n=52)	Group B (n=52)	p
Died	1 (2%)	3 (6%)	0·61
Required mechanical ventilation	7 (13%)	21 (40%)	0·0041
Myocardial infarction	9 (17%)	19 (37%)	0·047
Any adverse event	13 (25%)	24 (46%)	0·041

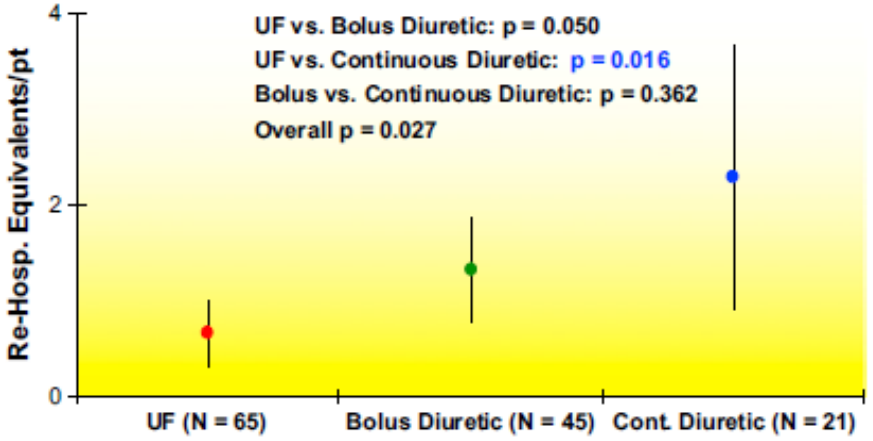
Alexandre Mebazaa MD, PhD
Département d'Anesthésie-Réanimation-SMUR, Hôpital Lariboisiere, Université Paris 7 Paris
Diderot, France

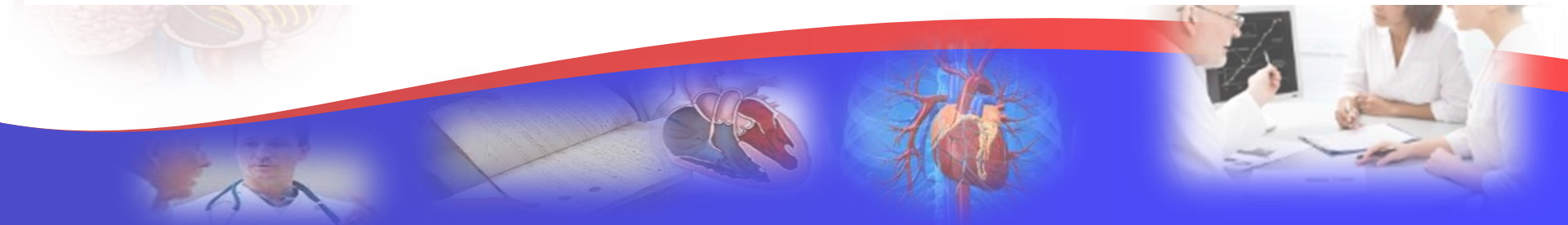
Ultrafiltration is Associated With Fewer Rehospitalizations than Continuous Diuretic Infusion in Patients With Decompensated Heart Failure: Results From UNLOAD

Journal of Cardiac Failure Vol. 16 No. 4 2010

UNLOAD
200 patients









Conclusions

- **Non aux diurétiques dans tous les cas**
  - Intérêt surtout chez les patients insuffisants cardiaques chroniques congestives et en cas de décompensation avec signes droit
  - Ne pas utiliser des diurétiques seuls
  - Pas besoin de forte doses de diurétiques

- **Utilisation des vasodilatateurs le plus rapidement possible**
  - Effet démontré sur le pronostic des patients
  - La PAS basse ne contre-indique pas en tant que telle leur utilisation