Heart Failure and the Cardiomyopathies for the USMLE Step One Exam
Part II: *the* ***Neurohumoral Response*** ***and*** ***Applied Pharmacology***

PDF available at
12DaysinMarch.com


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Ernest Starling

Tutorial Services
(check website for details)

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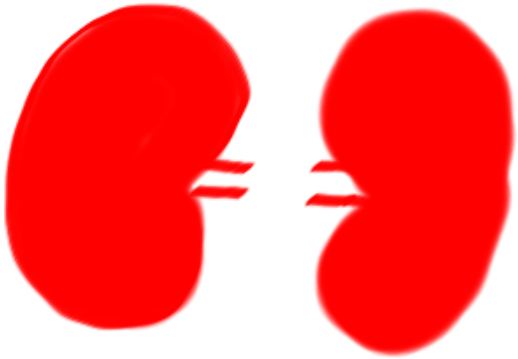
CHF:

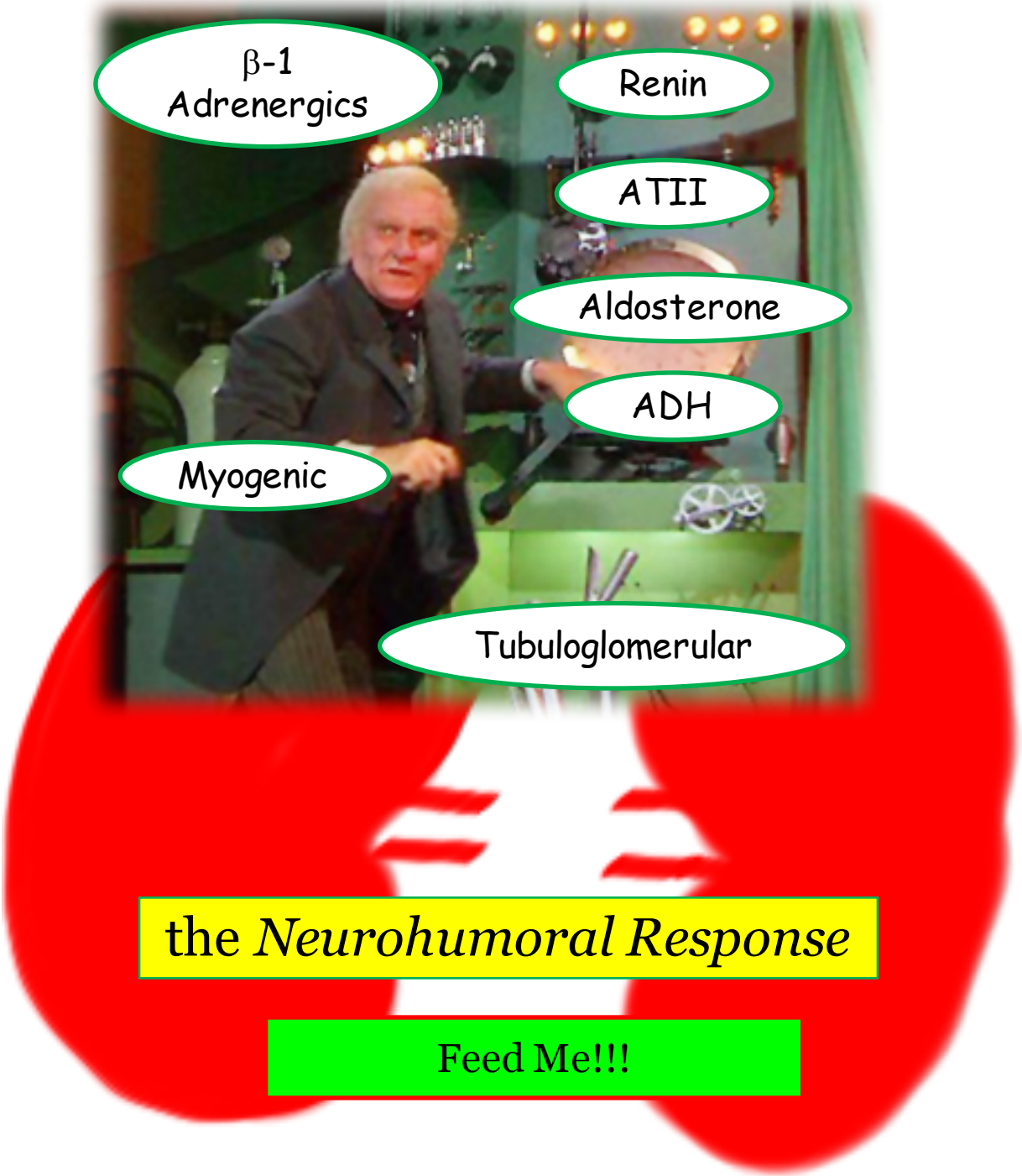
Heart is Failing

Work Harder!!!

Feed Me!!!



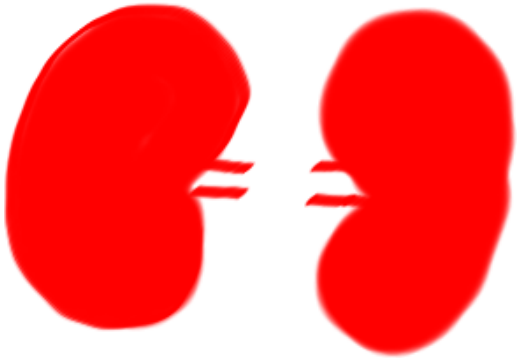
the *Neurohumoral Response*


β-1 Adrenergics
Renin
ATII
Aldosterone
ADH
Myogenic
Tubuloglomerular
the *Neurohumoral Response*
Feed Me!!!

CHF:
Heart is Failing

Work Harder!!!

Feed Me!!!



Sympathetic Nerves

Renin-AT-Aldo-*ADH*

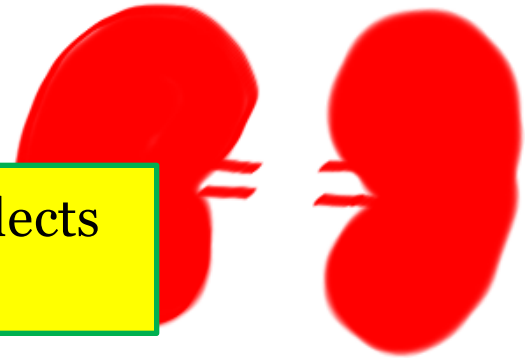
Neuro.....*Humoral*

Response

CHF:
Heart is Failing

Work Harder!!!

Feed Me!!!

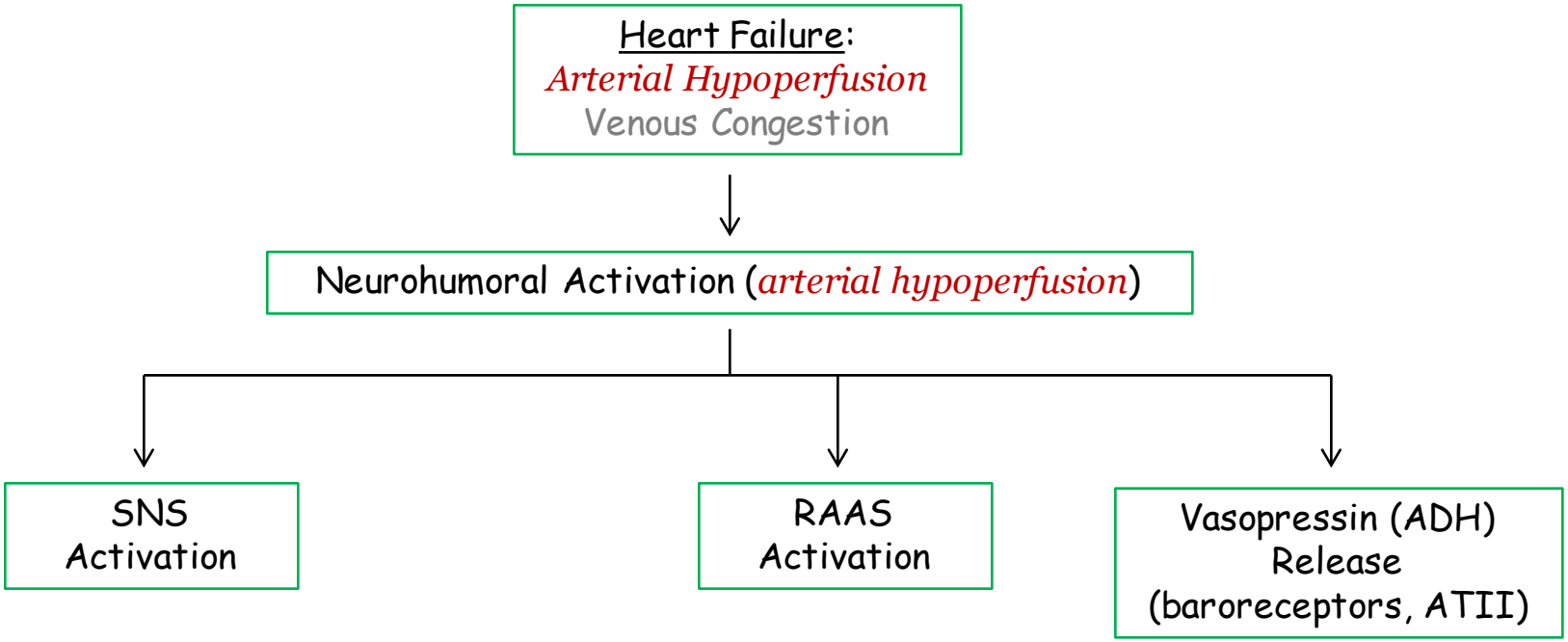


Applied Pharmacology

PharmacoRx Underscores/Reflects Pathophysiology

Sympathetic Nerves

Renin-AT-Aldo-*ADH*



The response is similar to any other cause of renal (or visceral) hypoperfusion

Heart Failure:
Arterial Hypoperfusion
Venous Congestion

↓

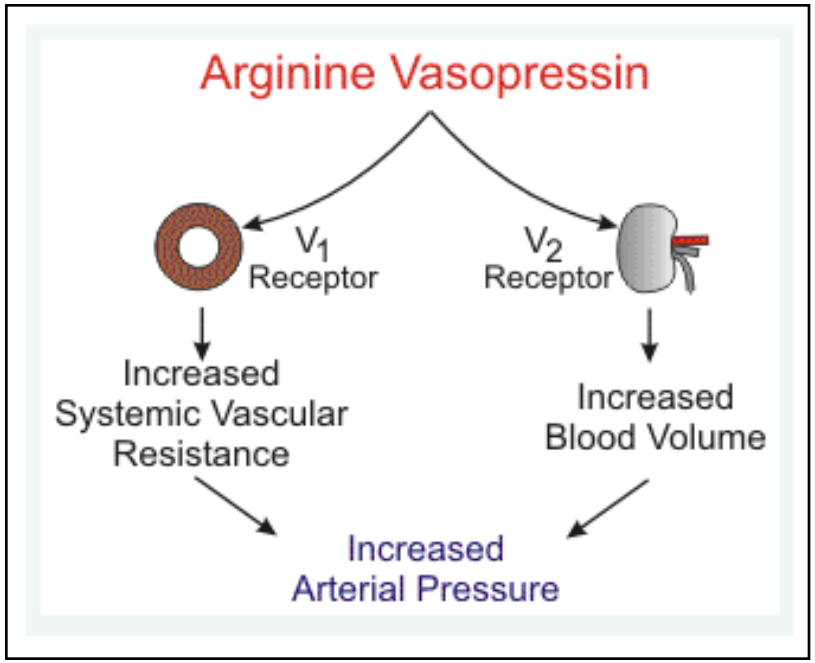
Neurohumoral Activation (*arterial hypoperfusion*)

↓

SNS Activation

RAAS Activation

Vasopressin (ADH) Release (baroreceptors, ATII)



V_1 receptor = Vasopressin (vasopressor functions)
V_2 receptor = ADH

Heart Failure:
Arterial Hypoperfusion
Venous Congestion

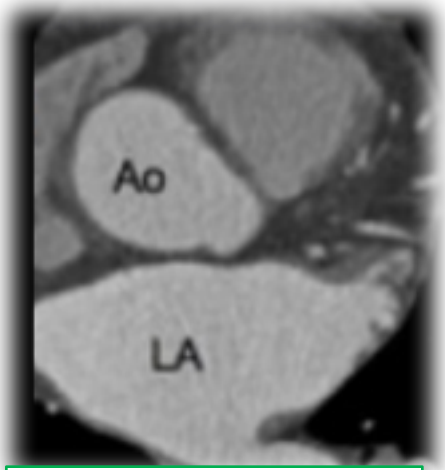
→ Atrial Natriuretic Peptide

↓

Neurohumoral Activation (arterial hypoperfusion)

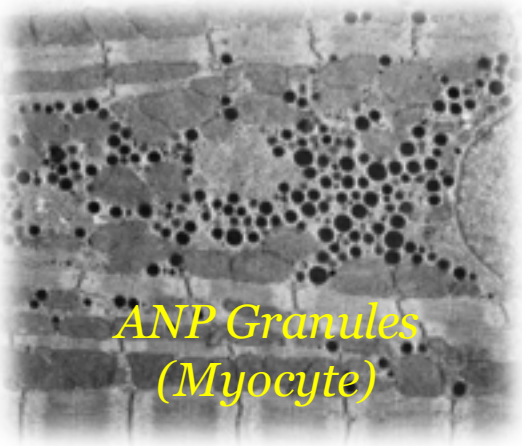
↓

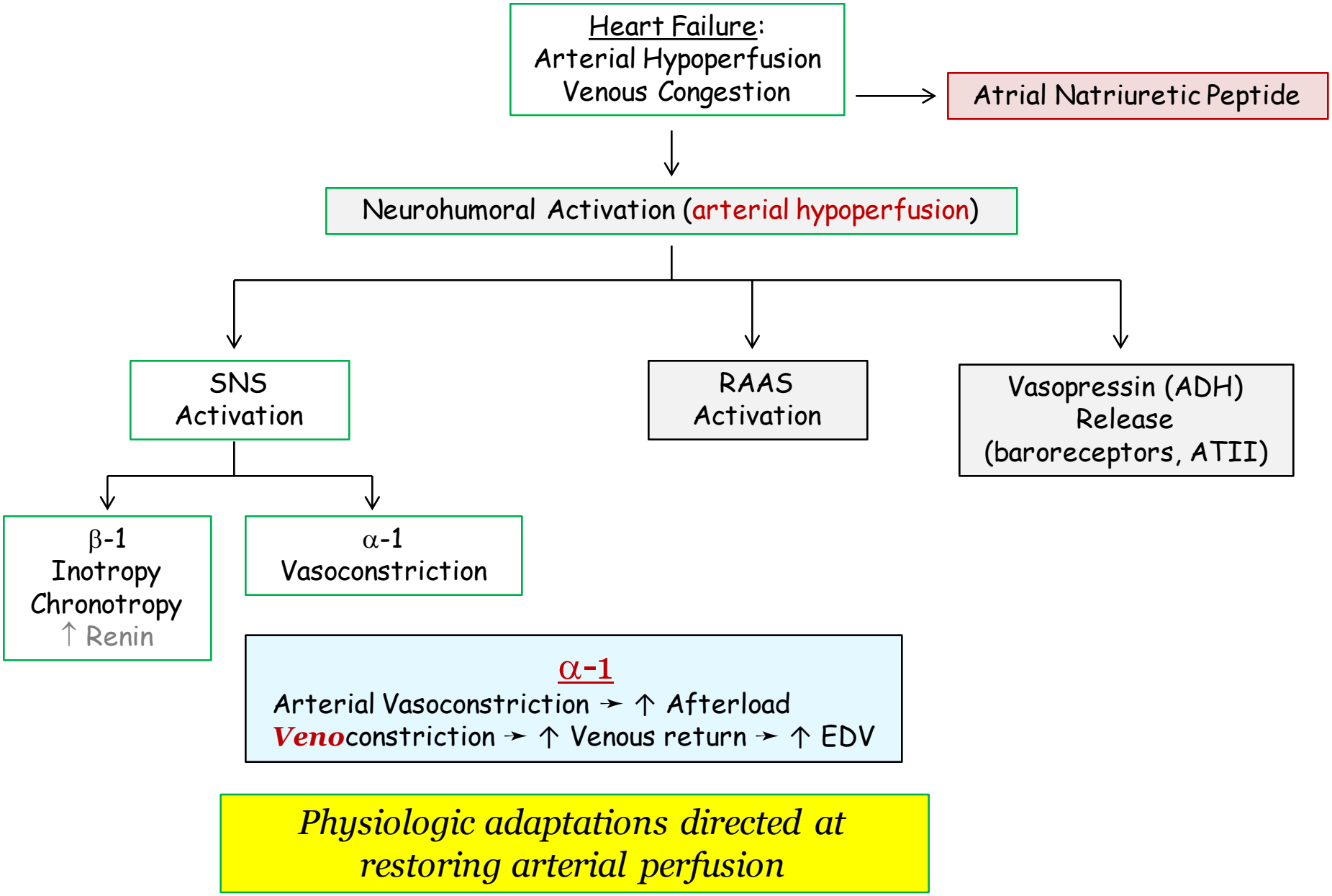
- SNS Activation
- RAAS Activation
- Vasopressin (ADH) Release (baroreceptors, ATII)



Stretching of Cardiac Myocytes

→




Heart Failure:
Arterial Hypoperfusion
Venous Congestion
Atrial Natriuretic Peptide
Neurohumoral Activation (arterial hypoperfusion)
SNS Activation
RAAS Activation
Vasopressin (ADH) Release (baroreceptors, ATII)
β-1 Inotropy Chronotropy ↑ Renin
α-1 Vasoconstriction
α-1
Arterial Vasoconstriction ➔ ↑ Afterload
Venoconstriction ➔ ↑ Venous return ➔ ↑ EDV
Physiologic adaptations directed at restoring arterial perfusion

Heart Failure:
Arterial Hypoperfusion
Venous Congestion

→ Atrial Natriuretic Peptide

↓

Neurohumoral Activation (arterial hypoperfusion)

↓

SNS Activation

↓

β-1
Inotropy
Chronotropy
↑ Renin

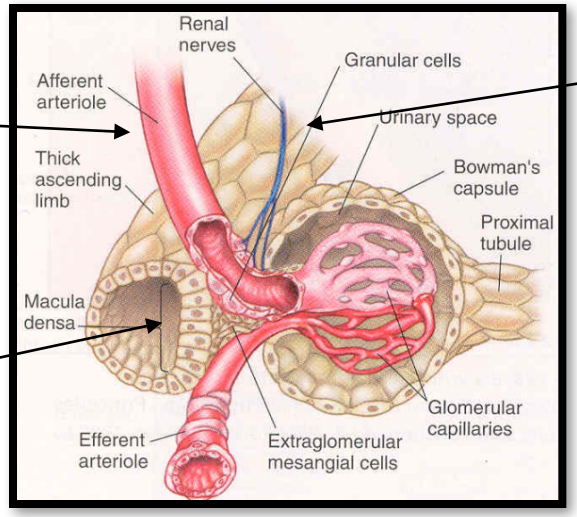
RAAS Activation

↓

Renin
(β-1, MD, myogenic)

Afferent Arteriole:
Vasoconstriction

Macula Densa:
↓ NaCL



Renal Autonomic Nvs:
β-1 Stimulation

Heart Failure:
Arterial Hypoperfusion
Venous Congestion

→ Atrial Natriuretic Peptide

↓

Neurohumoral Activation (arterial hypoperfusion)

↓

SNS Activation

↓

β-1
Inotropy
Chronotropy
↑ Renin

α-1
Vasoconstriction

RAAS Activation

↓

Renin
(β-1, MD, myogenic)

↓

Angiotensin II
Vasoconstriction

→ ↑ *Afterload*

↓

Aldosterone
Na+ Retention

→ *Volume Overload*

Vasopressin (ADH) Release
(baroreceptors, ATII)

Otto Frank

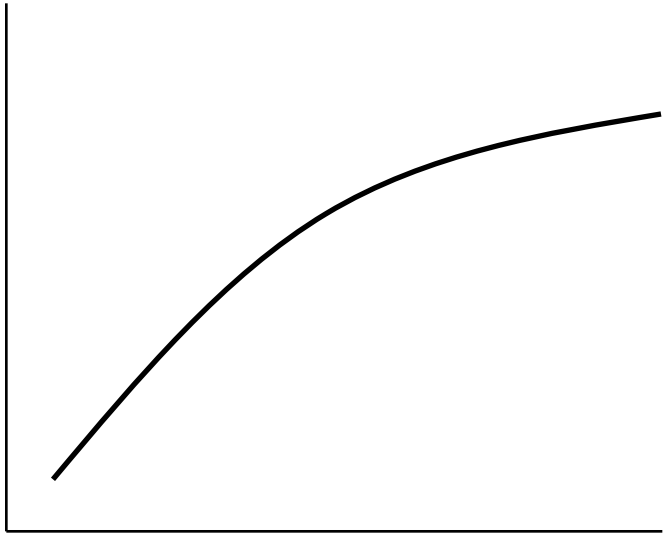
~The Volume of Blood Ejected Depends on the Volume of Blood Present at EDV~

Preload

Ernest Starling

Definition:
Maximum tension depends on resting length

Tension
Pressure

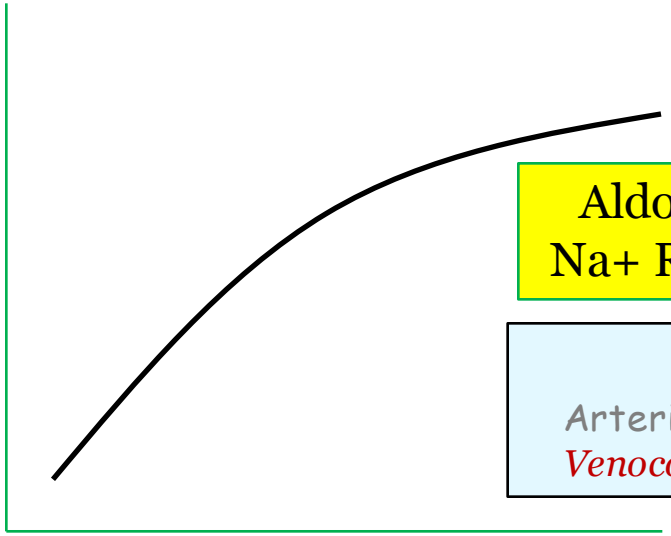


End Diastolic Volume
Preload

Sarcomere Length

Definition:
Maximum tension depends on resting length

Tension
Pressure

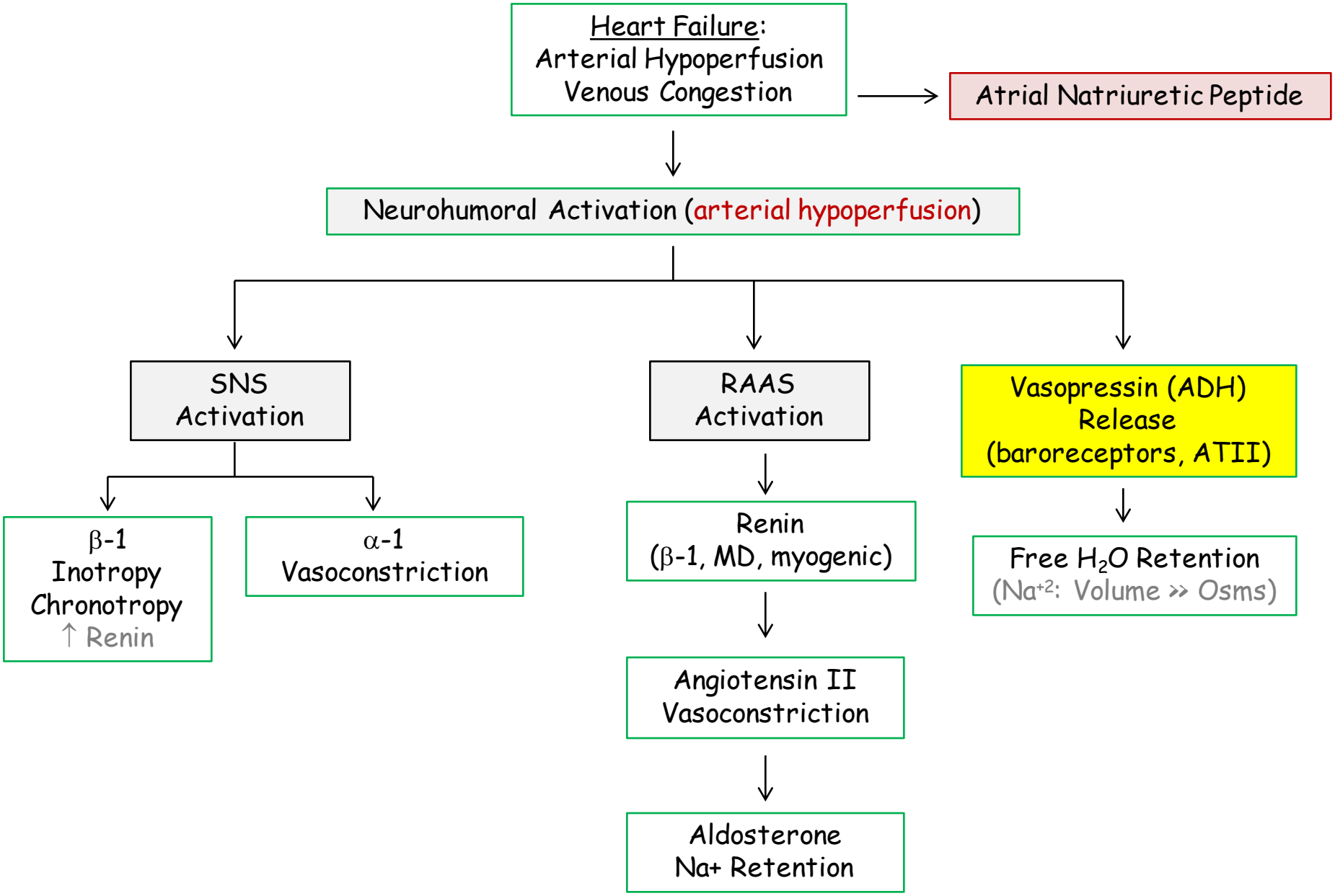


Aldosterone
Na+ Retention

α-1
Arterial Vasoconstriction ➛ ↑ Afterload
Venoconstriction ➛ ↑ Venous return ➛ ↑ EDV

End Diastolic Volume
Preload

Sarcomere Length


Heart Failure:
Arterial Hypoperfusion
Venous Congestion
Atrial Natriuretic Peptide
Neurohumoral Activation (arterial hypoperfusion)
SNS Activation
RAAS Activation
Vasopressin (ADH) Release (baroreceptors, ATII)
β-1 Inotropy Chronotropy ↑ Renin
α-1 Vasoconstriction
Renin (β-1, MD, myogenic)
Angiotensin II Vasoconstriction
Aldosterone Na+ Retention
Free H2O Retention (Na+2: Volume >> Osms)

Heart Failure:
Arterial Hypoperfusion
Venous Congestion

→ Atrial Natriuretic Peptide

↓

Neurohumoral Activation

Arterial Hypoperfusion

↓

SNS Activation

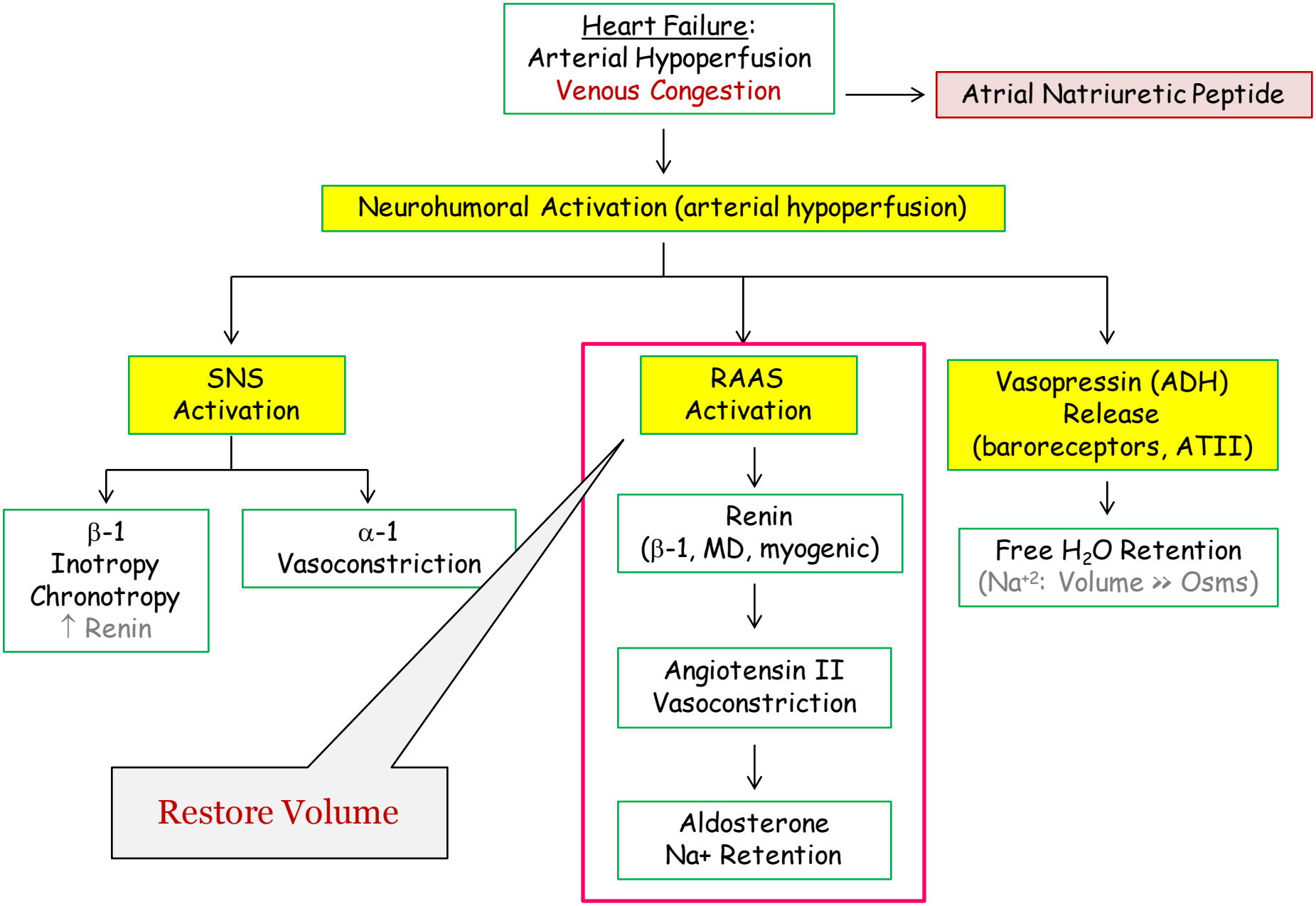
R… Act…tion

Vasopressin (ADH) Release (baroreceptors, ATII)

↓

Free H_2O Retention
(Na^{+2}: Volume » Osms)

	Ref Range & Units	
NA	135 - 145 mmol/L	129 (L)
K	3.5 - 5.3 mmol/L	4.3
Cl	97 - 110 mmol/L	95 (L)
CO2	24 - 32 mmol/L	29
Anion Gap	5 - 15	5
Glucose	70 - 99 mg/dL	85
Creatinine	0.50 - 1.20 mg/dL	0.52


Heart Failure:
Arterial Hypoperfusion
Venous Congestion
Atrial Natriuretic Peptide
Neurohumoral Activation (arterial hypoperfusion)
SNS Activation
RAAS Activation
Vasopressin (ADH) Release (baroreceptors, ATII)
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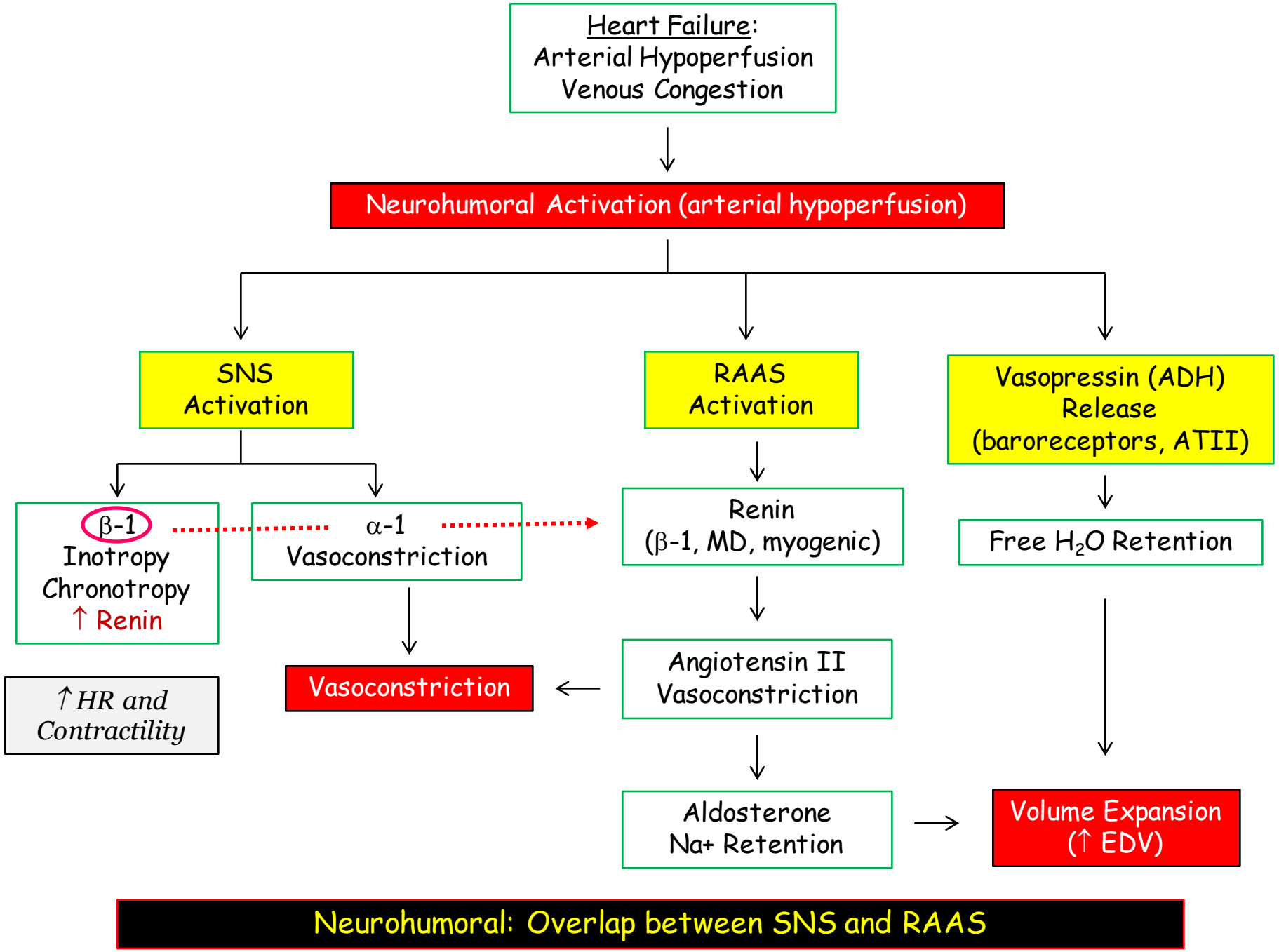
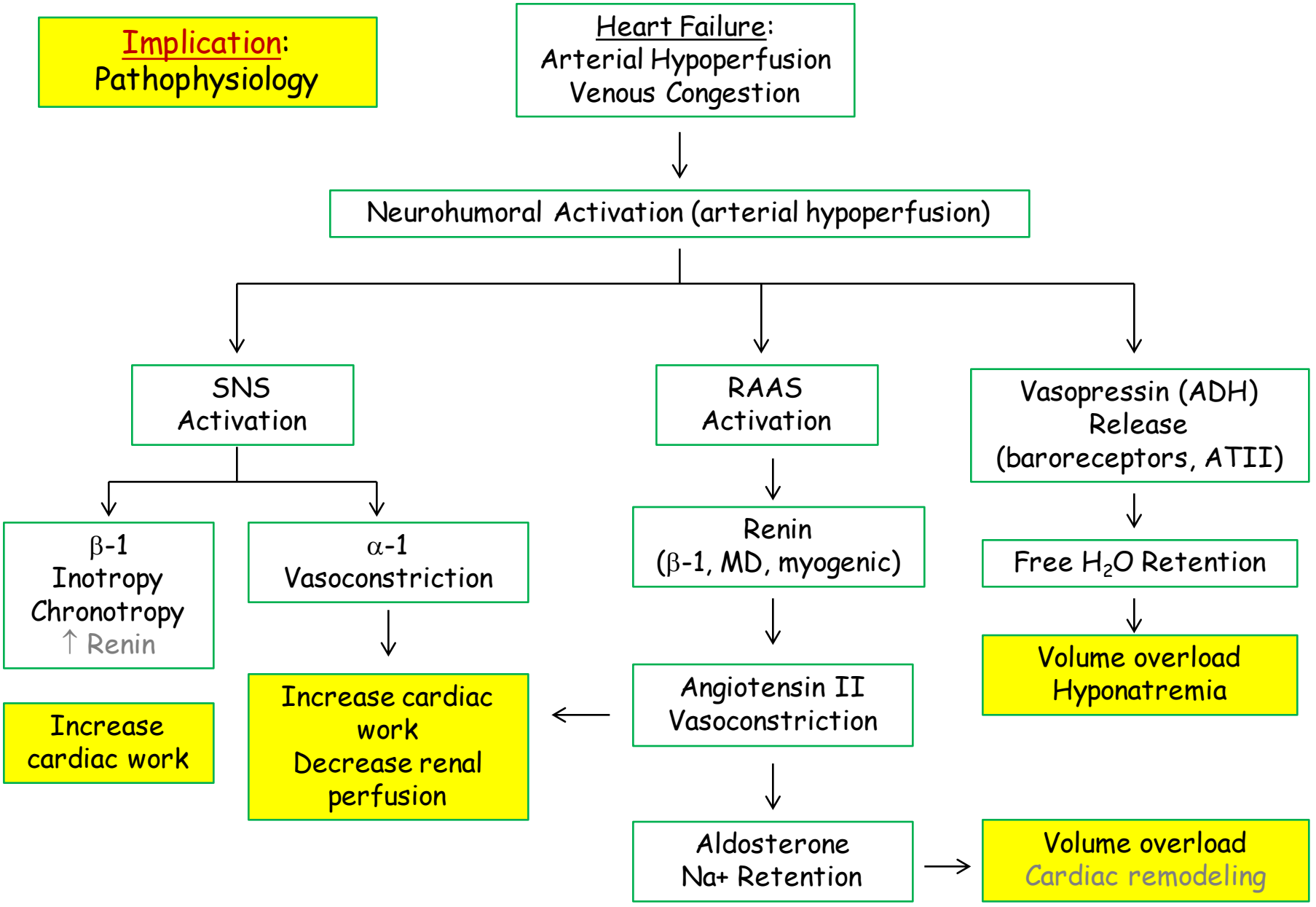
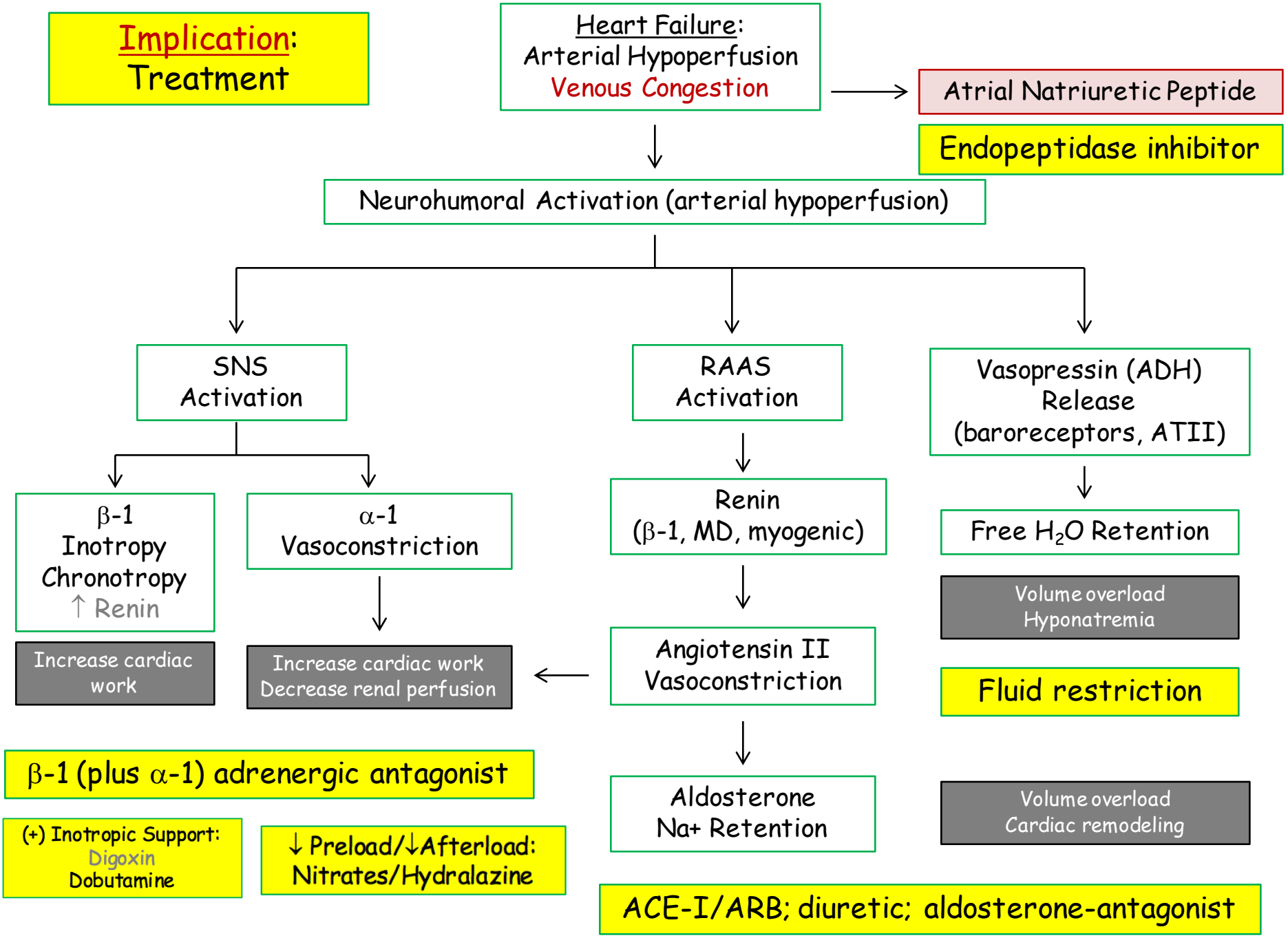
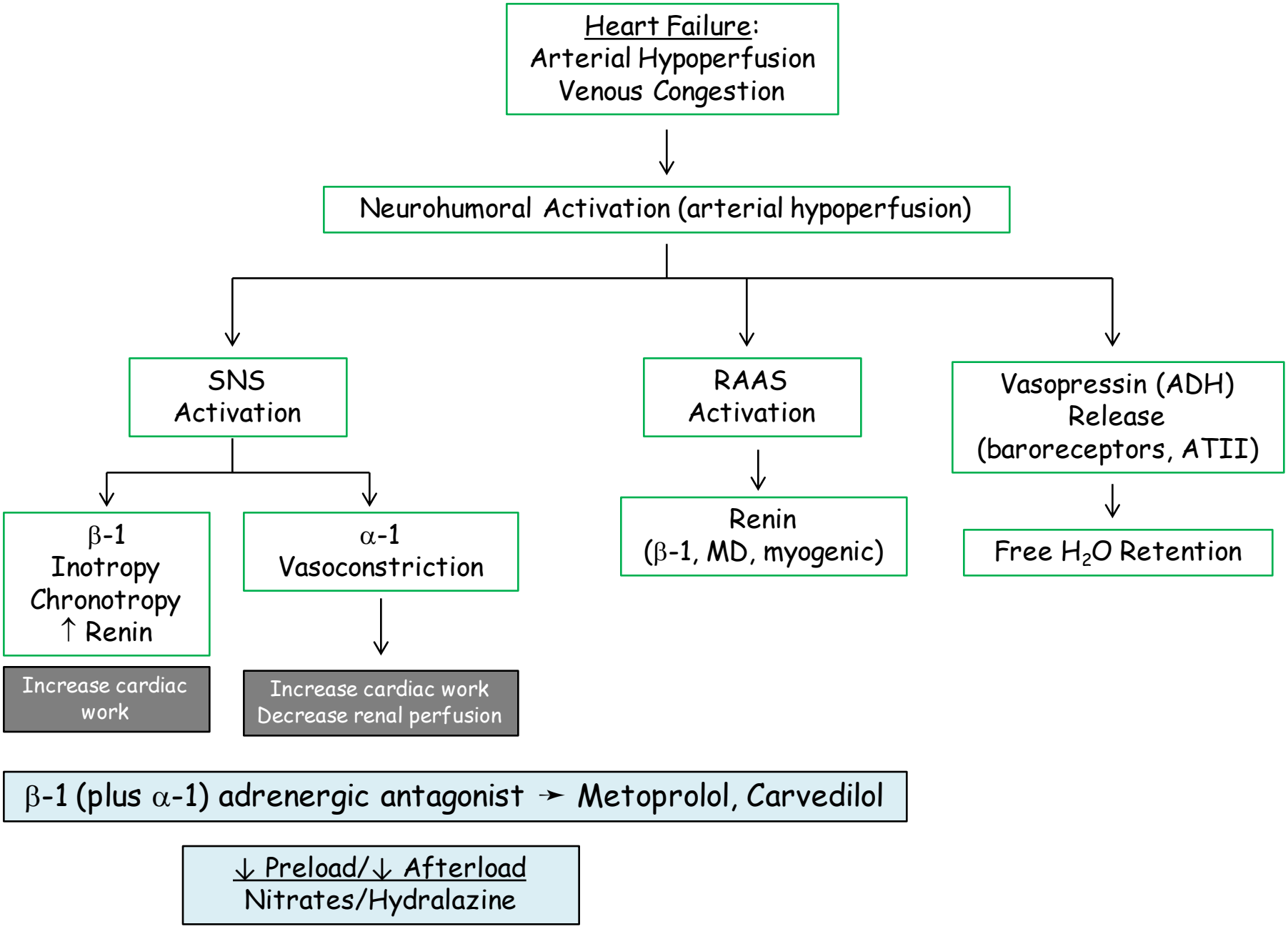
α-1 Vasoconstriction
Renin (β-1, MD, myogenic)
Angiotensin II Vasoconstriction
Aldosterone Na+ Retention
Free H2O Retention (Na+2: Volume >> Osms)
Restore Volume


Heart Failure:
Arterial Hypoperfusion
Venous Congestion
Neurohumoral Activation (arterial hypoperfusion)
SNS Activation
RAAS Activation
Vasopressin (ADH) Release (baroreceptors, ATII)
β-1
Inotropy
Chronotropy
↑ Renin
α-1
Vasoconstriction
Renin
(β-1, MD, myogenic)
Free H2O Retention
↑ HR and Contractility
Vasoconstriction
Angiotensin II
Vasoconstriction
Aldosterone
Na+ Retention
Volume Expansion
(↑ EDV)
Neurohumoral: Overlap between SNS and RAAS


Implication:
Pathophysiology
Heart Failure:
Arterial Hypoperfusion
Venous Congestion
Neurohumoral Activation (arterial hypoperfusion)
SNS
Activation
RAAS
Activation
Vasopressin (ADH)
Release
(baroreceptors, ATII)
β-1
Inotropy
Chronotropy
↑ Renin
α-1
Vasoconstriction
Renin
(β-1, MD, myogenic)
Free H2O Retention
Increase
cardiac work
Increase cardiac
work
Decrease renal
perfusion
Angiotensin II
Vasoconstriction
Volume overload
Hyponatremia
Aldosterone
Na+ Retention
Volume overload
Cardiac remodeling


Implication:
Treatment
Heart Failure:
Arterial Hypoperfusion
Venous Congestion
Atrial Natriuretic Peptide
Endopeptidase inhibitor
Neurohumoral Activation (arterial hypoperfusion)
SNS
Activation
RAAS
Activation
Vasopressin (ADH)
Release
(baroreceptors, ATII)
β-1
Inotropy
Chronotropy
↑ Renin
α-1
Vasoconstriction
Renin
(β-1, MD, myogenic)
Free H2O Retention
Increase cardiac work
Increase cardiac work
Decrease renal perfusion
Angiotensin II
Vasoconstriction
Volume overload
Hyponatremia
Fluid restriction
β-1 (plus α-1) adrenergic antagonist
Aldosterone
Na+ Retention
Volume overload
Cardiac remodeling
(+) Inotropic Support:
Digoxin
Dobutamine
↓ Preload/↓Afterload:
Nitrates/Hydralazine
ACE-I/ARB; diuretic; aldosterone-antagonist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RAAS Activation
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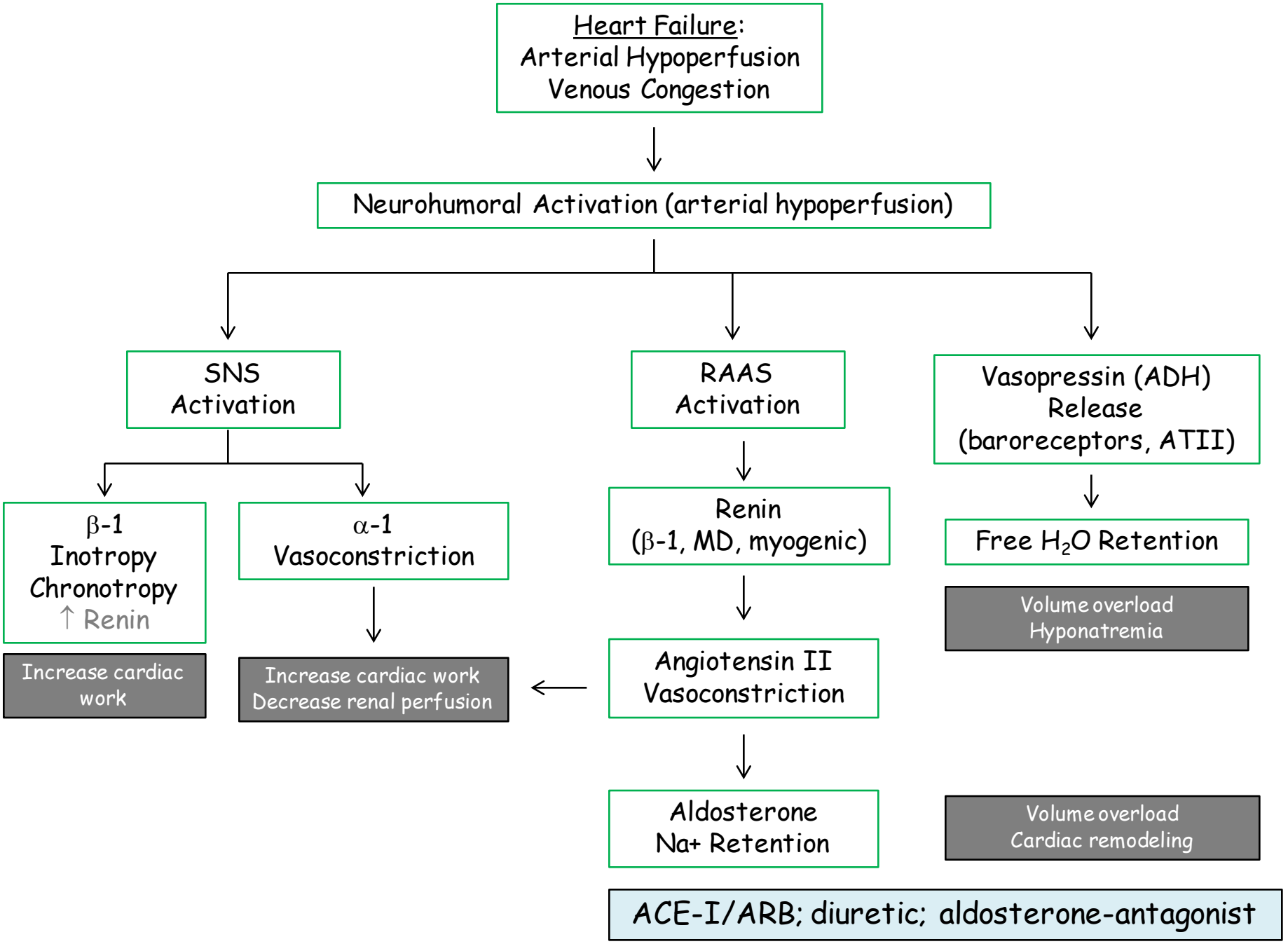
β-1 Inotropy Chronotropy ↑ Renin
α-1 Vasoconstriction
Renin (β-1, MD, myogenic)
Free H_2O Retention
Increase cardiac work
Increase cardiac work Decrease renal perfusion
β-1 (plus α-1) adrenergic antagonist ➛ Metoprolol, Carvedilol
↓ Preload/↓ Afterload
Nitrates/Hydralazine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Arterial Hypoperfusion
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Neurohumoral Activation (arterial hypoperfusion)
SNS Activation
RAAS Activation
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β-1 Inotropy Chronotropy ↑ Renin
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Renin (β-1, MD, myogenic)
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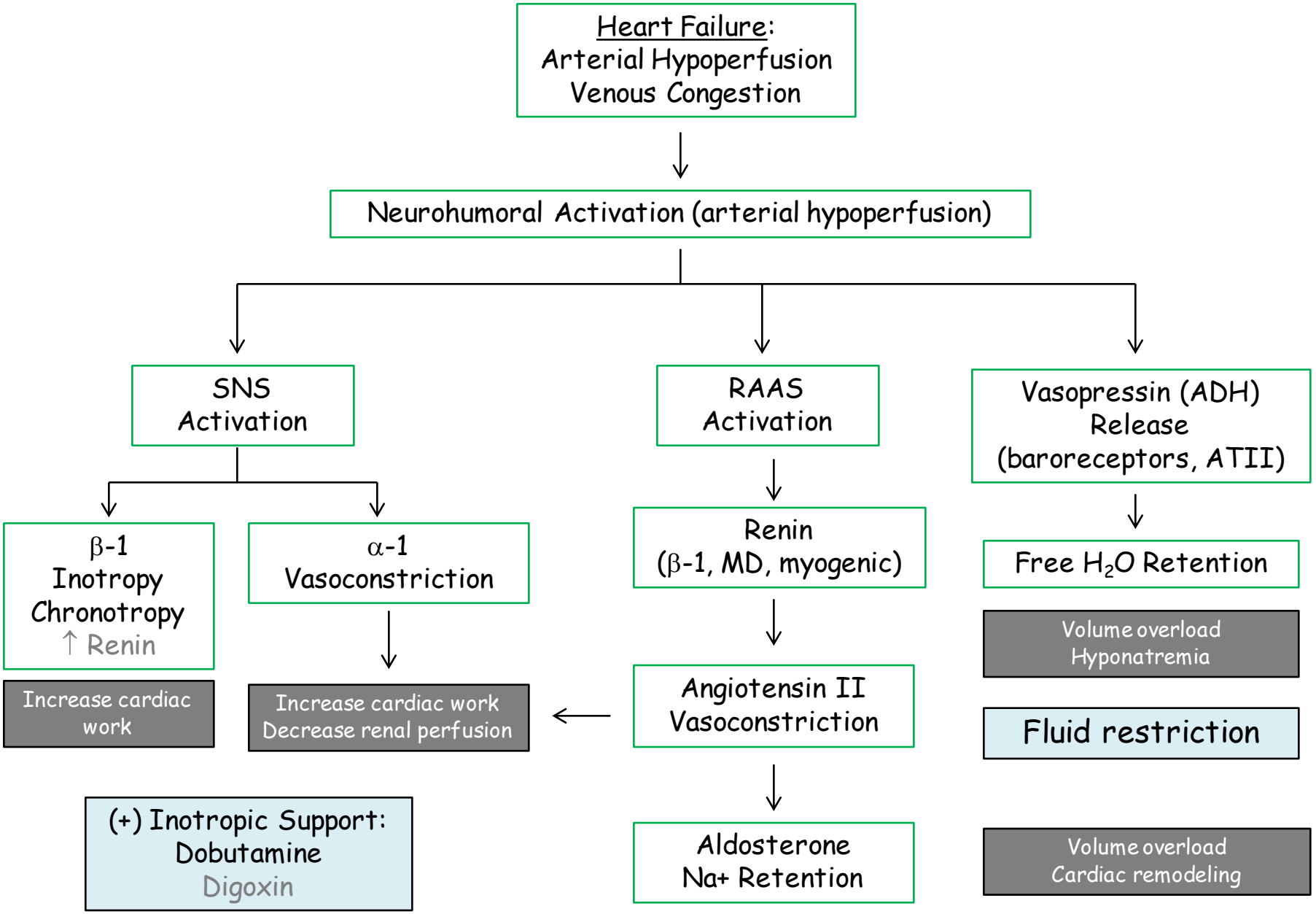
Increase cardiac work
Increase cardiac work Decrease renal perfusion
Angiotensin II Vasoconstriction
Volume overload Hyponatremia
Aldosterone Na+ Retention
Volume overload Cardiac remodeling
ACE-I/ARB; diuretic; aldosterone-antagonist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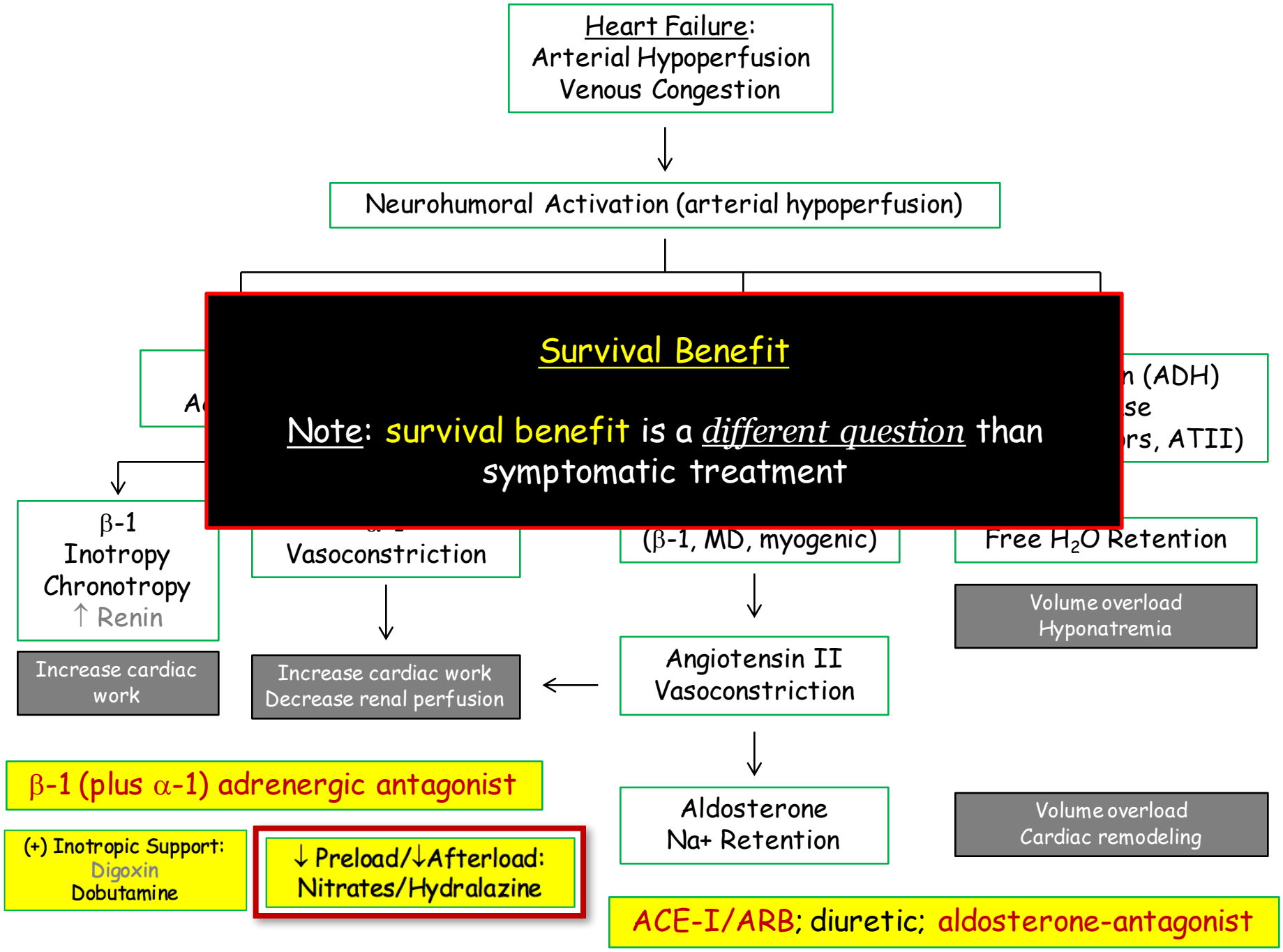
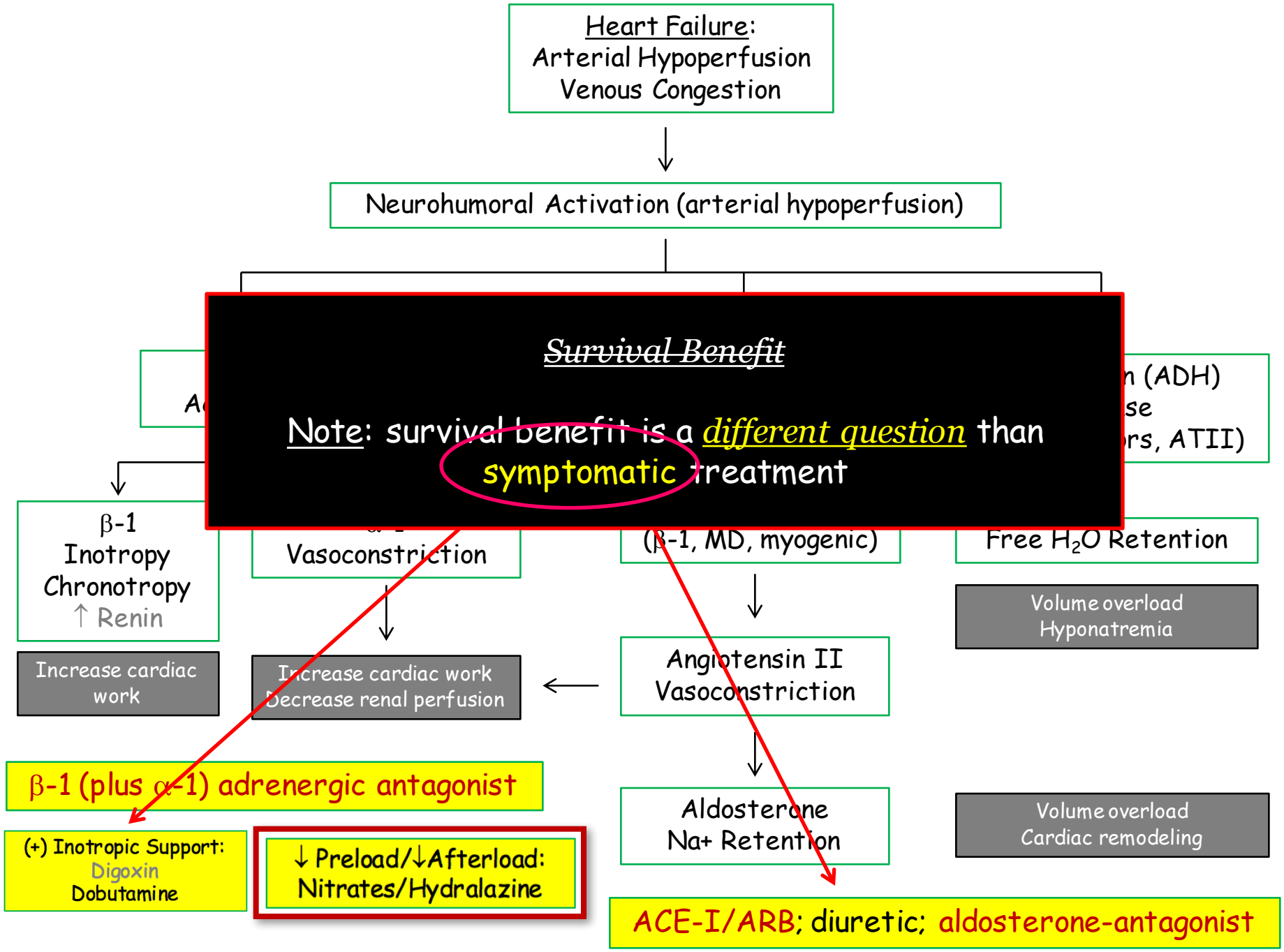
Free H2O Retention
Increase cardiac work
Increase cardiac work Decrease renal perfusion
Angiotensin II Vasoconstriction
Volume overload Hyponatremia
Fluid restriction
(+) Inotropic Support:
Dobutamine
Digoxin
Aldosterone Na+ Retention
Volume overload Cardiac remodeling


Heart Failure:
Arterial Hypoperfusion
Venous Congestion
Neurohumoral Activation (arterial hypoperfusion)
Survival Benefit
Note: survival benefit is a different question than symptomatic treatment
β-1
Inotropy
Chronotropy
↑ Renin
Vasoconstriction
(β-1, MD, myogenic)
Free H2O Retention
Increase cardiac work
Increase cardiac work
Decrease renal perfusion
Angiotensin II
Vasoconstriction
Volume overload
Hyponatremia
β-1 (plus α-1) adrenergic antagonist
Aldosterone
Na+ Retention
Volume overload
Cardiac remodeling
(+) Inotropic Support:
Digoxin
Dobutamine
↓ Preload/↓Afterload:
Nitrates/Hydralazine
ACE-I/ARB; diuretic; aldosterone-antagonist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Vasoconstriction
Increase cardiac work
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(β-1, MD, myogenic)
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Vasoconstriction
Aldosterone
Na+ Retention
Free H2O Retention
Volume overload
Hyponatremia
Volume overload
Cardiac remodeling
β-1 (plus α-1) adrenergic antagonist
(+) Inotropic Support:
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↓ Preload/↓Afterload:
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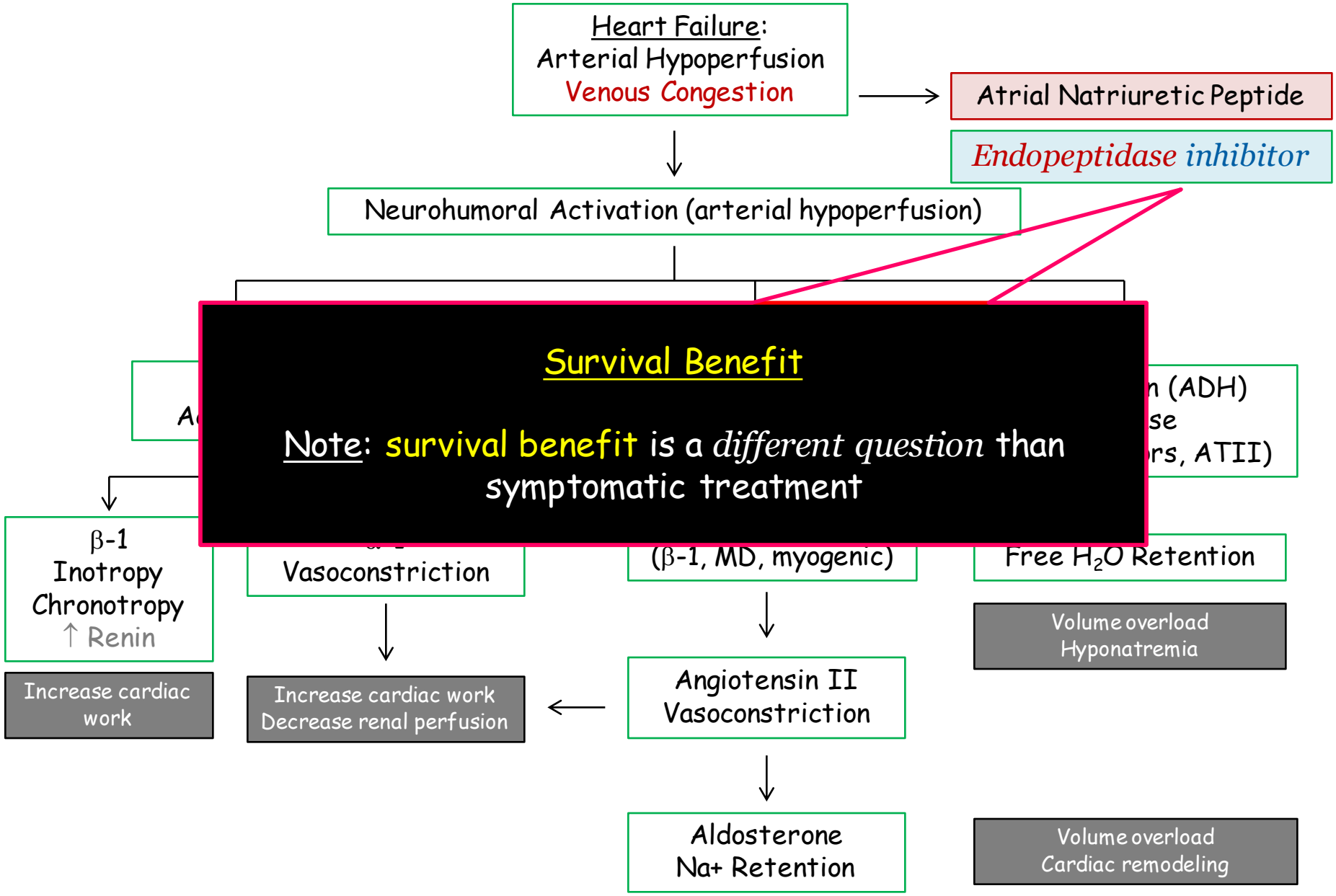
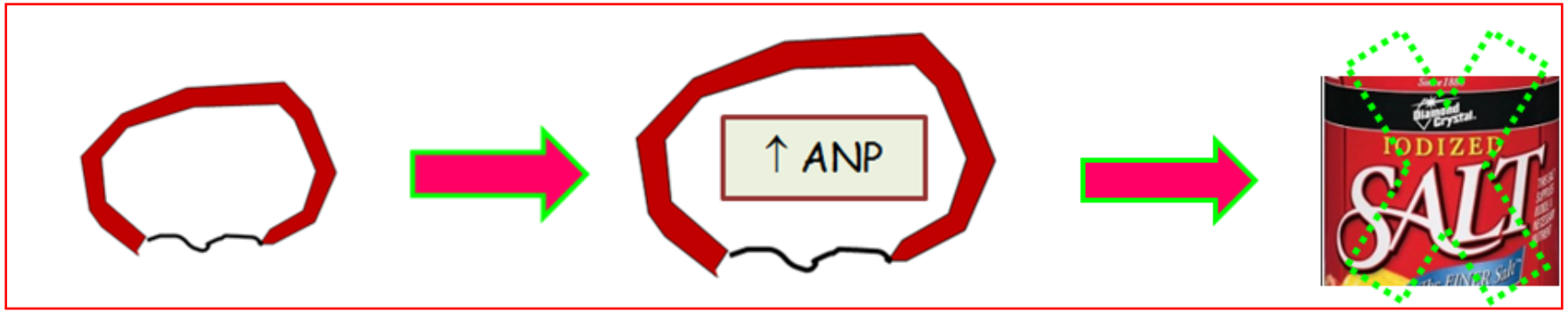
ACE-I/ARB; diuretic; aldosterone-antagonist

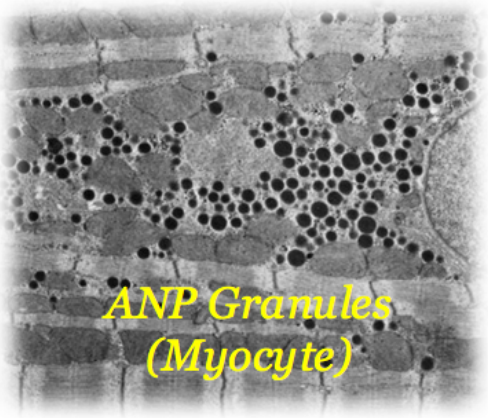

Heart Failure:
Arterial Hypoperfusion
Venous Congestion
Atrial Natriuretic Peptide
Endopeptidase inhibitor
Neurohumoral Activation (arterial hypoperfusion)
Survival Benefit
Note: survival benefit is a different question than symptomatic treatment
β-1
Inotropy
Chronotropy
↑ Renin
Increase cardiac work
Vasoconstriction
Increase cardiac work
Decrease renal perfusion
(β-1, MD, myogenic)
Angiotensin II
Vasoconstriction
Aldosterone
Na+ Retention
Free H2O Retention
Volume overload
Hyponatremia
Volume overload
Cardiac remodeling

Heart Failure:
Arterial Hypoperfusion
Venous Congestion → Atrial Natriuretic Peptide

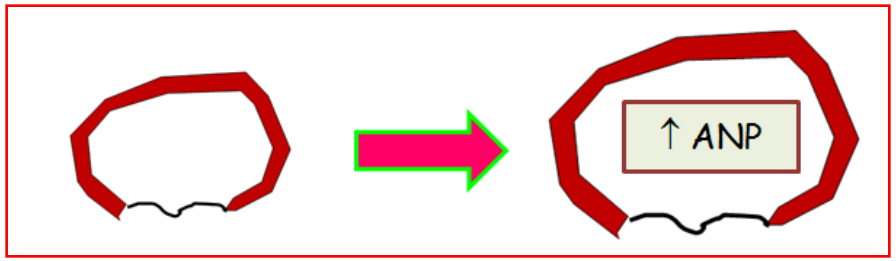
Atrial Natriuretic Peptide

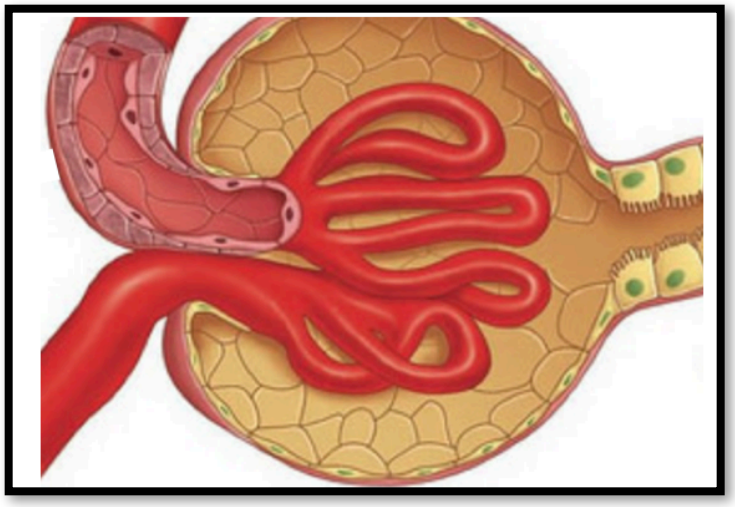


- ANP/BNP is rarely mentioned as a diagnostic test (for CHF).
- They allude to it in setting of decompensated HF as a peptide with X, Y, Z *properties* (TBD…)
- *Released in response to myocardial wall stretch (volume expansion).*



ANP: The Perfect Response



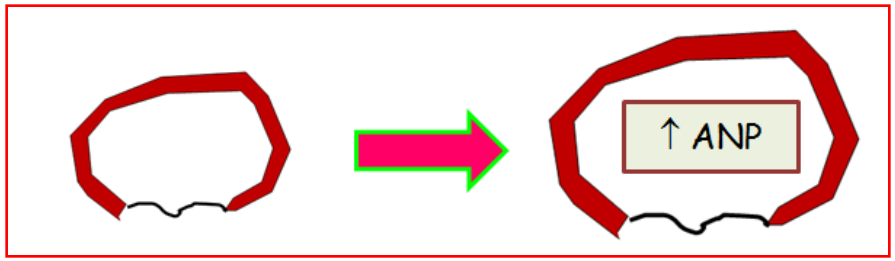


Afferent vasodilation with efferent vasoconstriction

Result: ↑ **GFR** → ↓ **Renin** (*inhibit ATII, aldosterone, ADH*)

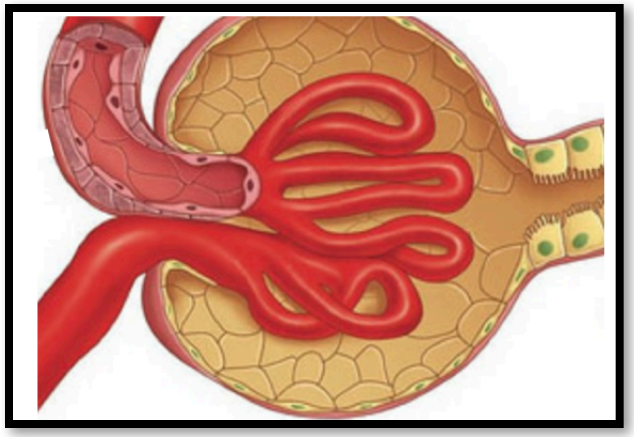
Natriuresis: Directly inhibits Na^{+2} reabsorption in the PCT

ANP: The Perfect Response



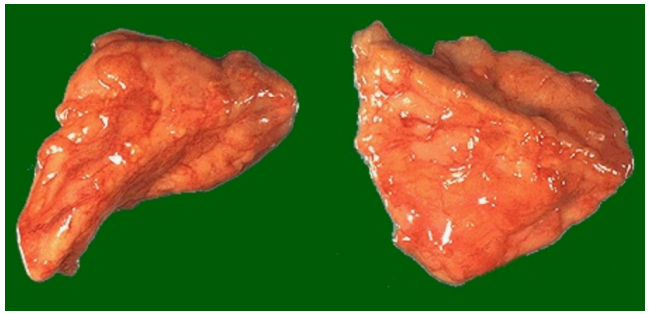
Directly inhibits

aldosterone release



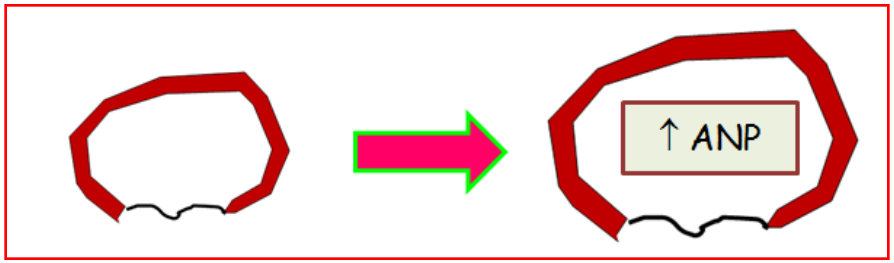
Indirectly (via ↓ renin) decreases

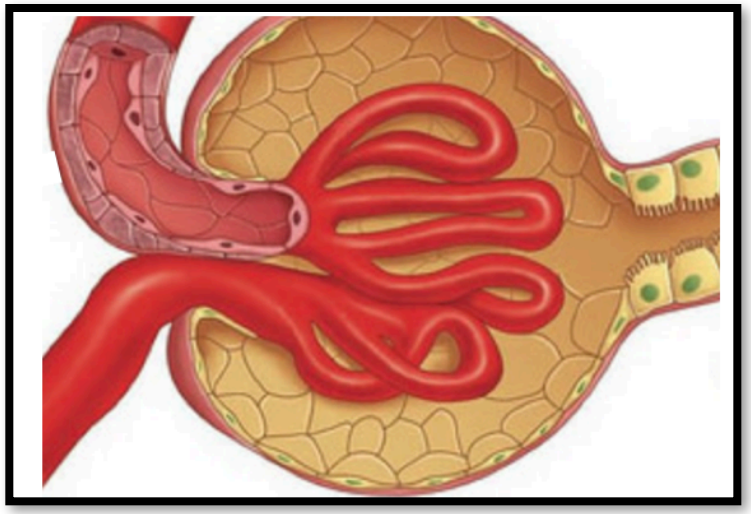
aldosterone synthesis



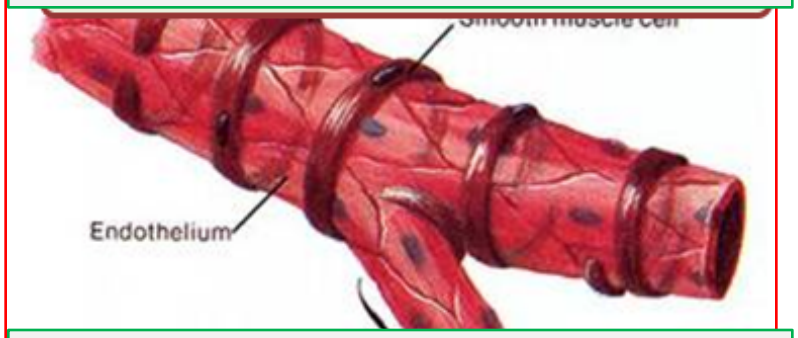
Result: Decrease Na/water absorption

ANP: The Perfect Response



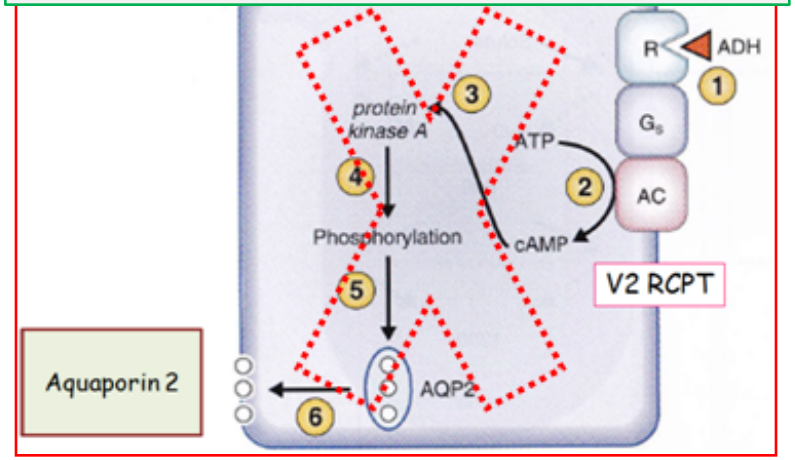


Arteriolar Vasodilation
(↓ *Afterload*)



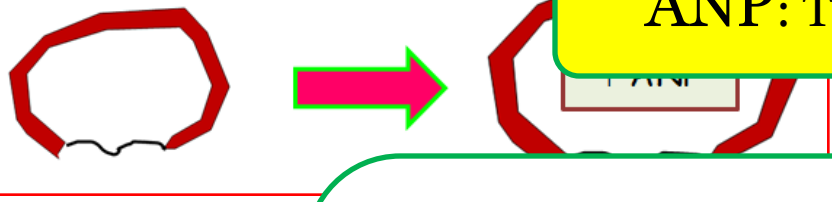
Direct (↑cGMP) and
indirect (↓ ATII)

Suppresses ADH Release (↓ ATII)
Attenuates ADH binding to V2 receptor



ANP: The Perfect Response

Arteriolar Vasodilation
(↓ *afterload*)



ANP: an exercise in cardio-renal physiology

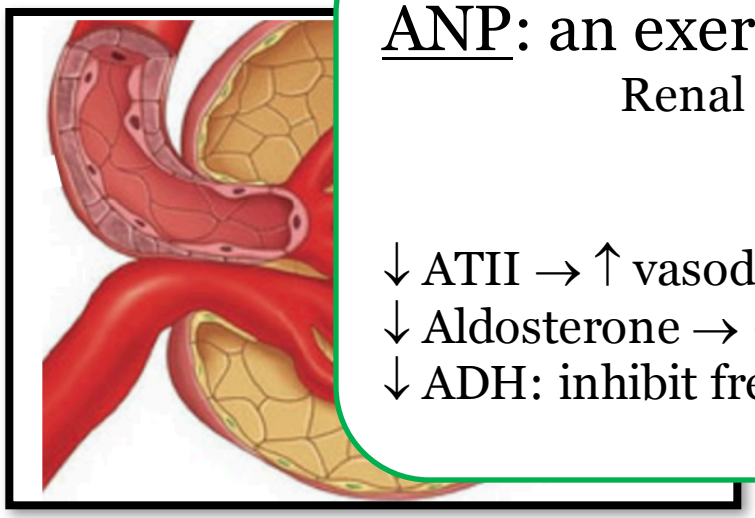
Renal afferent vasodilation (↑ cGMP)

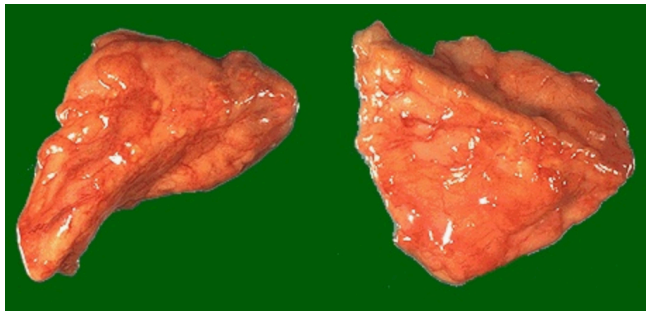
↑ GFR → ↓ RAAS:

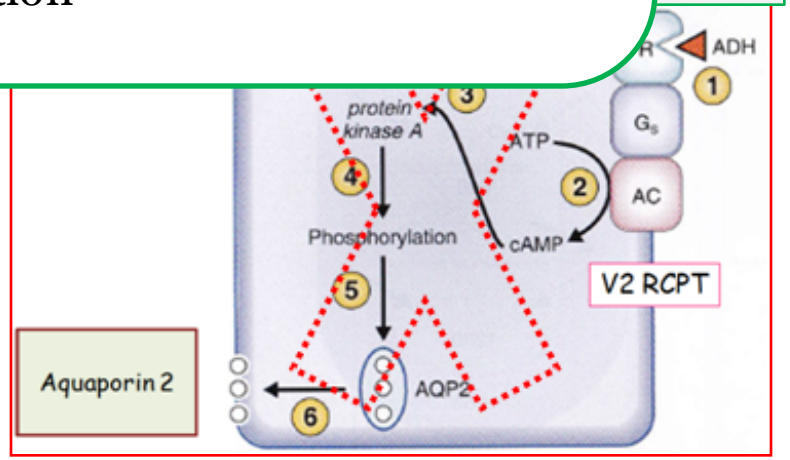
↓ ATII → ↑ vasodilation and ↓ ADH stimulation

↓ Aldosterone → ↓ Na retention

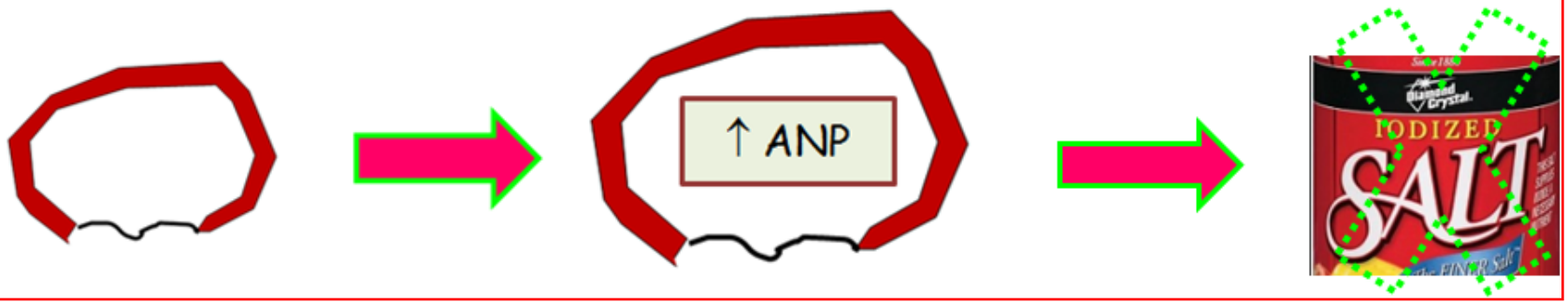
↓ ADH: inhibit free H2O retention







Natriuretic Peptide Therapeutic Implications



Natriuretic peptides are metabolized by a 'neutral endopeptidase' (also described as a *metalloprotease*) - *neprilysin.*

Neprilysin Inhibitors prevent degradation of ANP with net result: *natriuresis, vasodilation*

Language: 'an endopeptidase inhibitor is initiated resulting in prolonged activity of an endogenous polypeptide hormone'

Whereas rx with Synthetic Natriuretic Peptide (*nesiritide*) did NOT produce favorable clinical trial results, sacubitril (*in combination with valsartan*) resulted in:

Decreased Mortality and Readmission for CHF (HF**r**EF only)

Implication: Treatment

Heart Failure:
Arterial Hypoperfusion
Venous Congestion

→ Atrial Natriuretic Peptide

Endopeptidase inhibitor
PLUS ARB

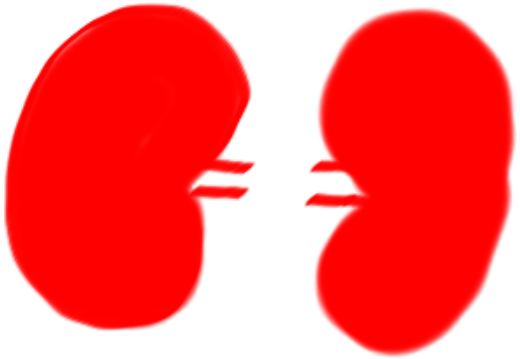
Survival Benefit

Note: survival benefit is a *different question* than symptomatic treatment.

CHF:
Heart is Failing

Work Harder!!!

Feed Me!!!



Sympathetic Nerves

Renin-AT-Aldo-*ADH*

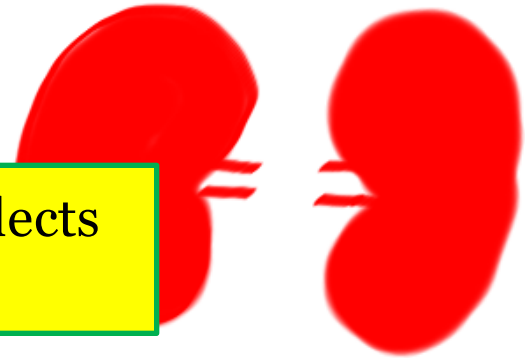
Neuro.....*Humoral*

Response

CHF:
Heart is Failing

Work Harder!!!

Feed Me!!!

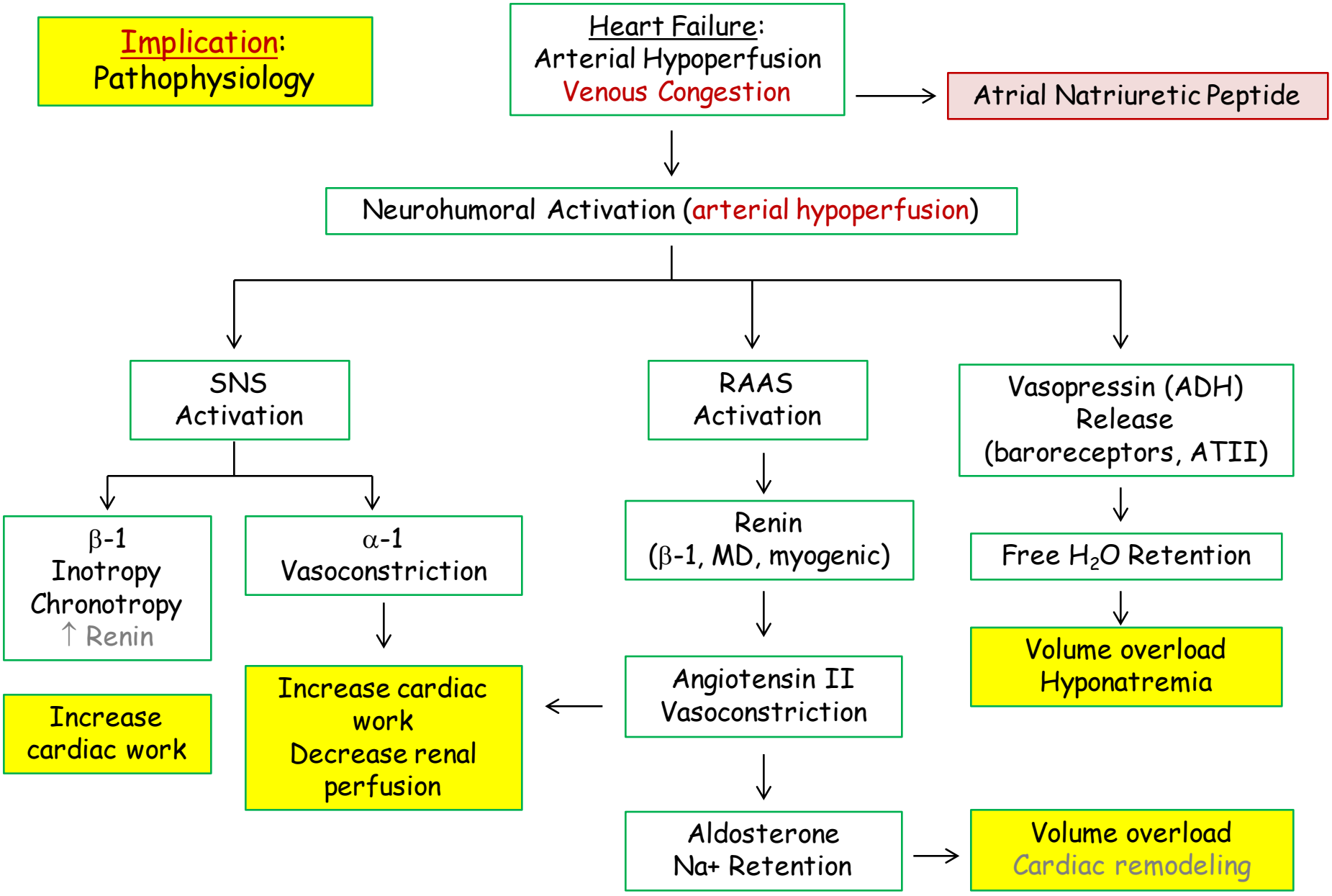


Applied Pharmacology

PharmacoRx Underscores/Reflects Pathophysiology

Sympathetic Nerves

Renin-AT-Aldo-*ADH*


Implication:
Pathophysiology
Heart Failure:
Arterial Hypoperfusion
Venous Congestion
Atrial Natriuretic Peptide
Neurohumoral Activation (arterial hypoperfusion)
SNS
Activation
RAAS
Activation
Vasopressin (ADH)
Release
(baroreceptors, ATII)
β-1
Inotropy
Chronotropy
↑ Renin
α-1
Vasoconstriction
Renin
(β-1, MD, myogenic)
Free H2O Retention
Increase
cardiac work
Increase cardiac
work
Decrease renal
perfusion
Angiotensin II
Vasoconstriction
Volume overload
Hyponatremia
Aldosterone
Na+ Retention
Volume overload
Cardiac remodeling

Heart Failure and the Cardiomyopathies for the USMLE Step One Exam
Part II: *the* ***Neurohumoral Response*** ***and*** ***Applied Pharmacology***

PDF available at
12DaysinMarch.com


Otto Frank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Tutorial Services
(check website for details)

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