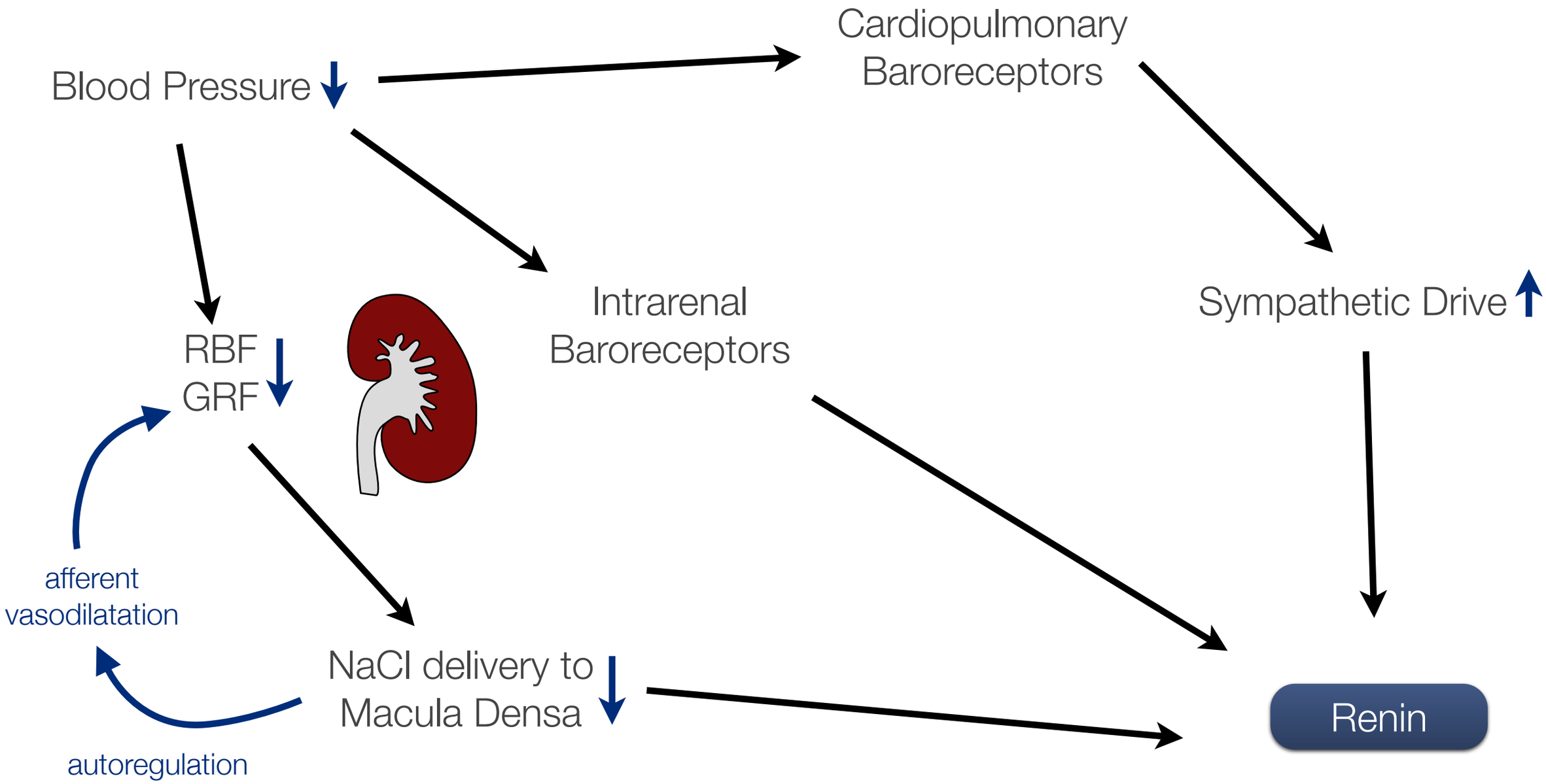
Acute Renal Failure

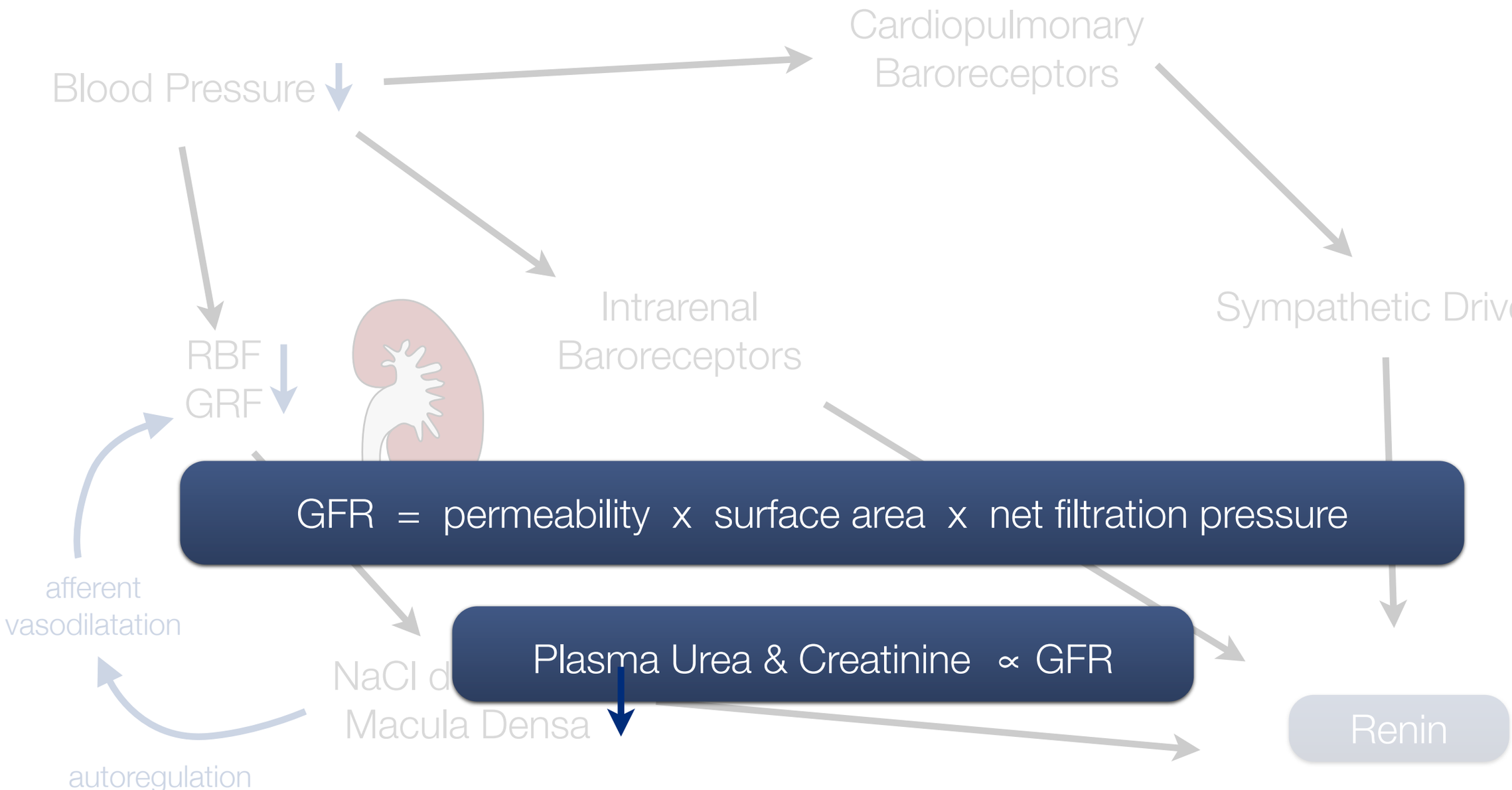
usually a consequence

- Definitions
- Pathogenisis
- Classification
- ICU Incidence/ Significance
- Treatments

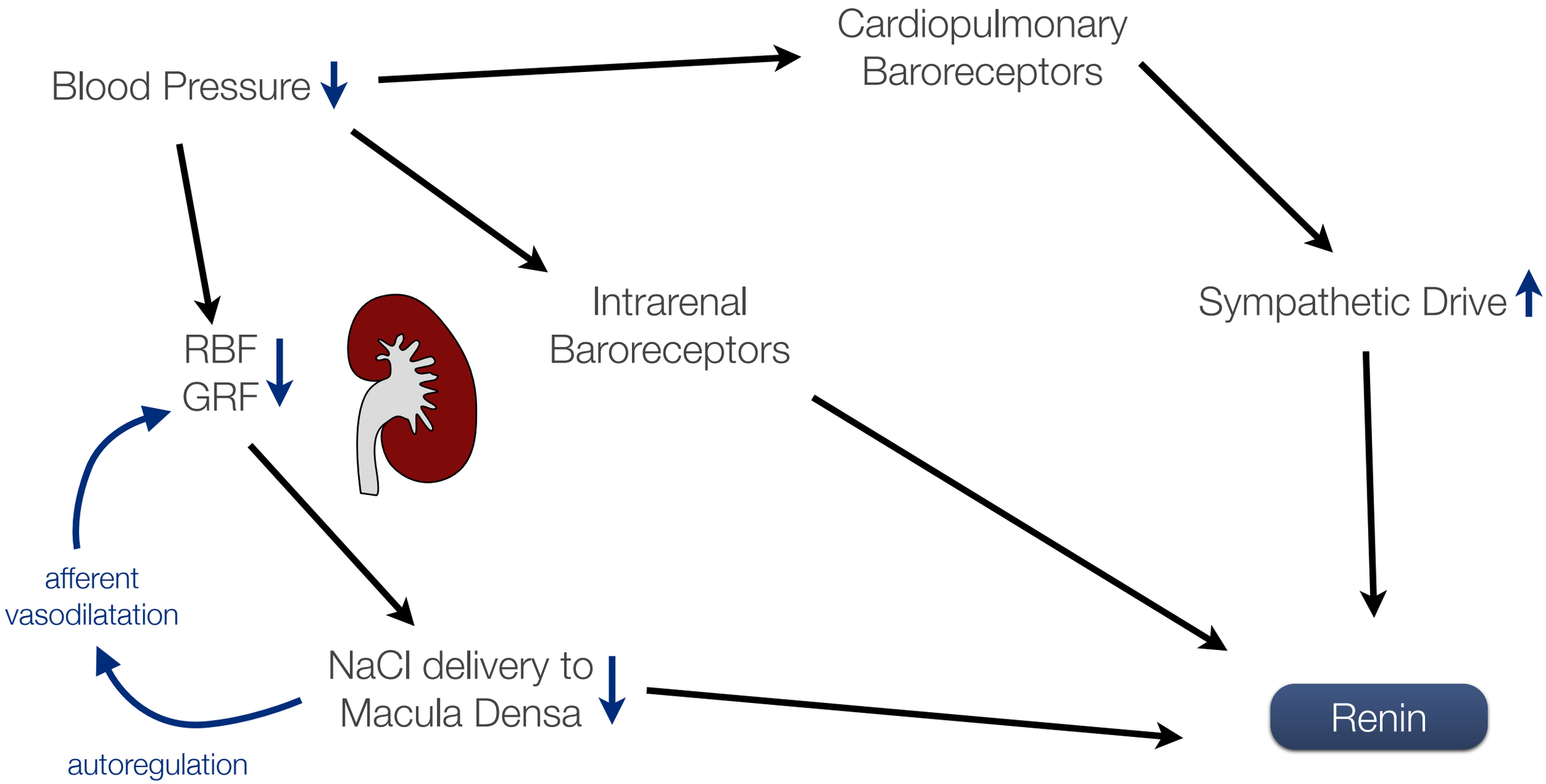
Prerenal Azotaemia

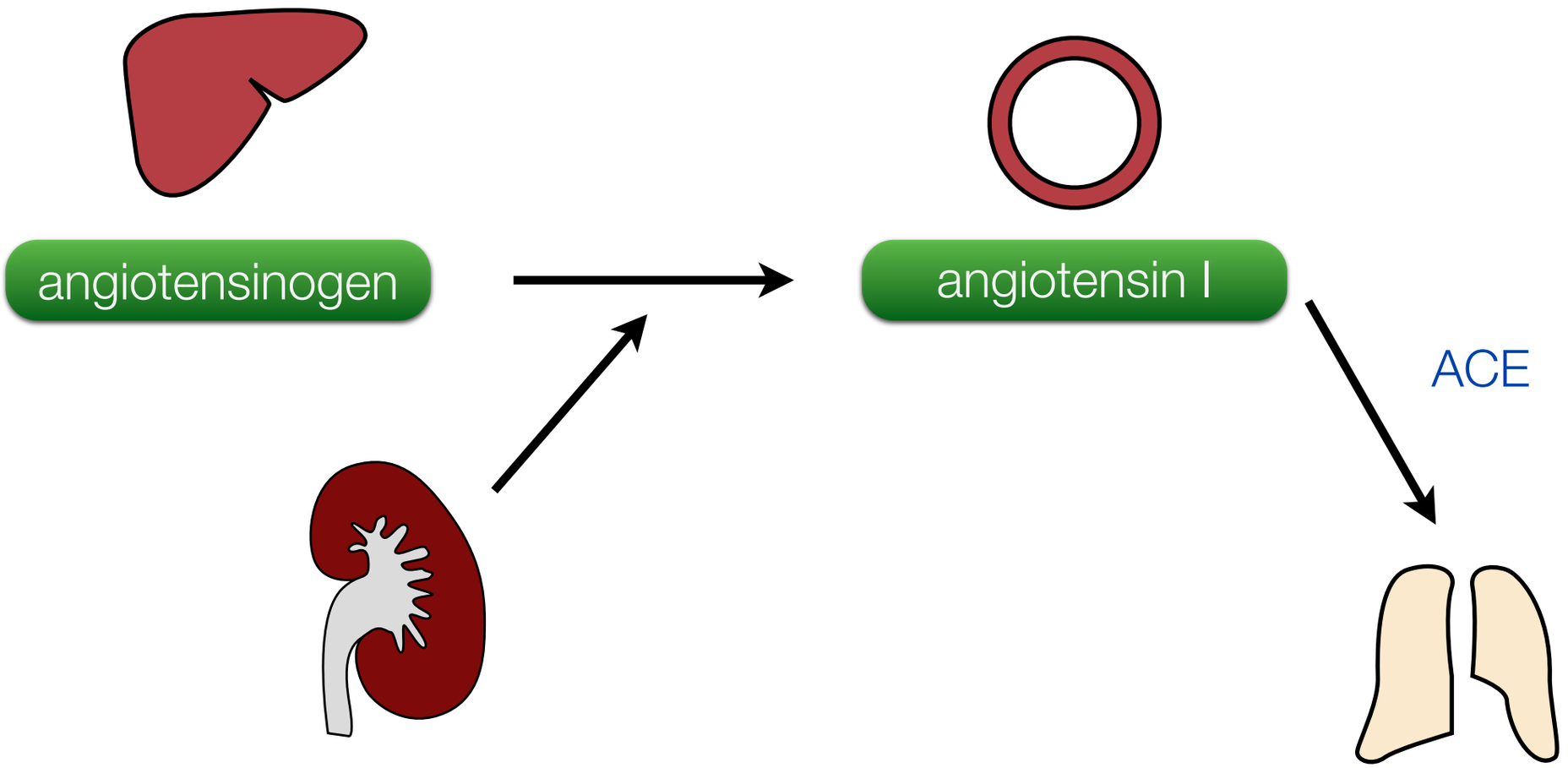


Prerenal Azotaemia

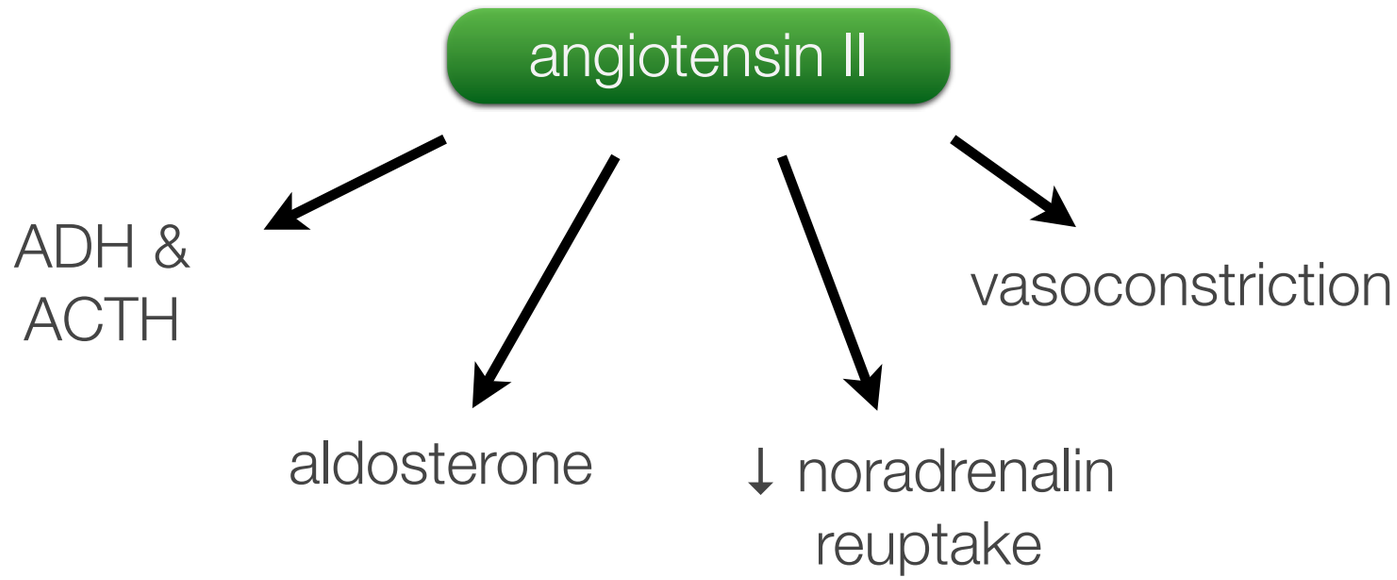


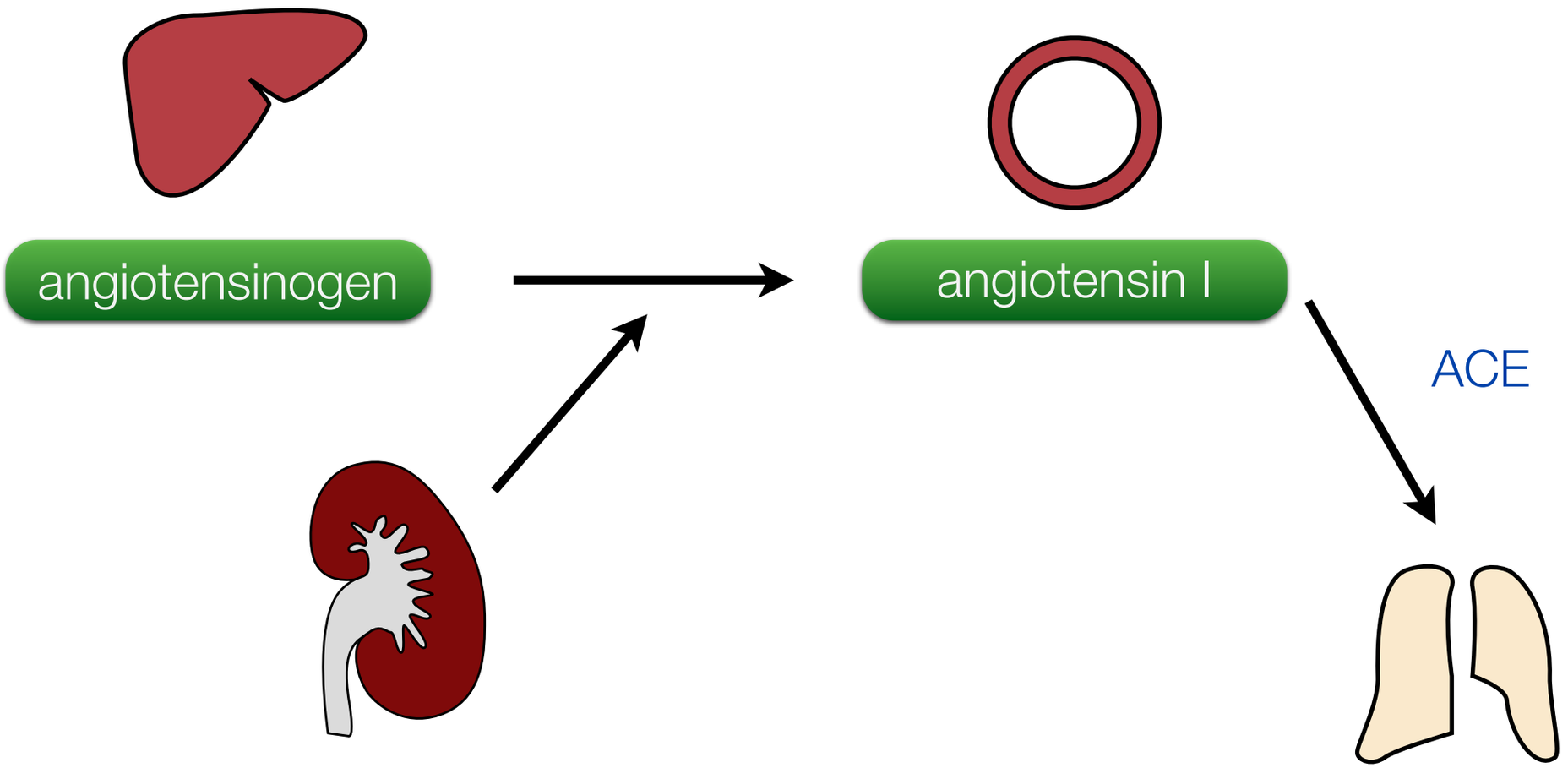
Prerenal Azotaemia



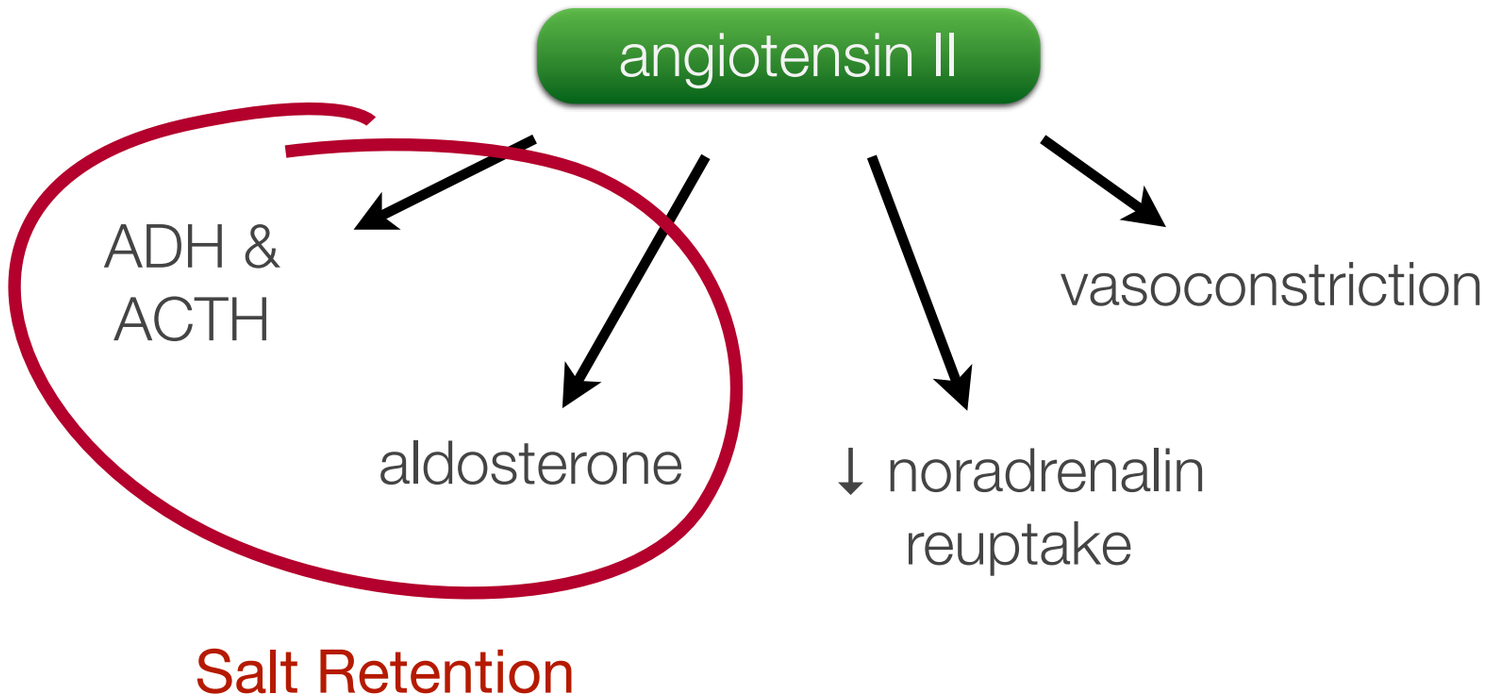

angiotensinogen
angiotensin I
ACE

Renin


angiotensin II
ADH &
ACTH
aldosterone
↓ noradrenalin
reuptake
vasoconstriction


angiotensinogen
angiotensin I
ACE

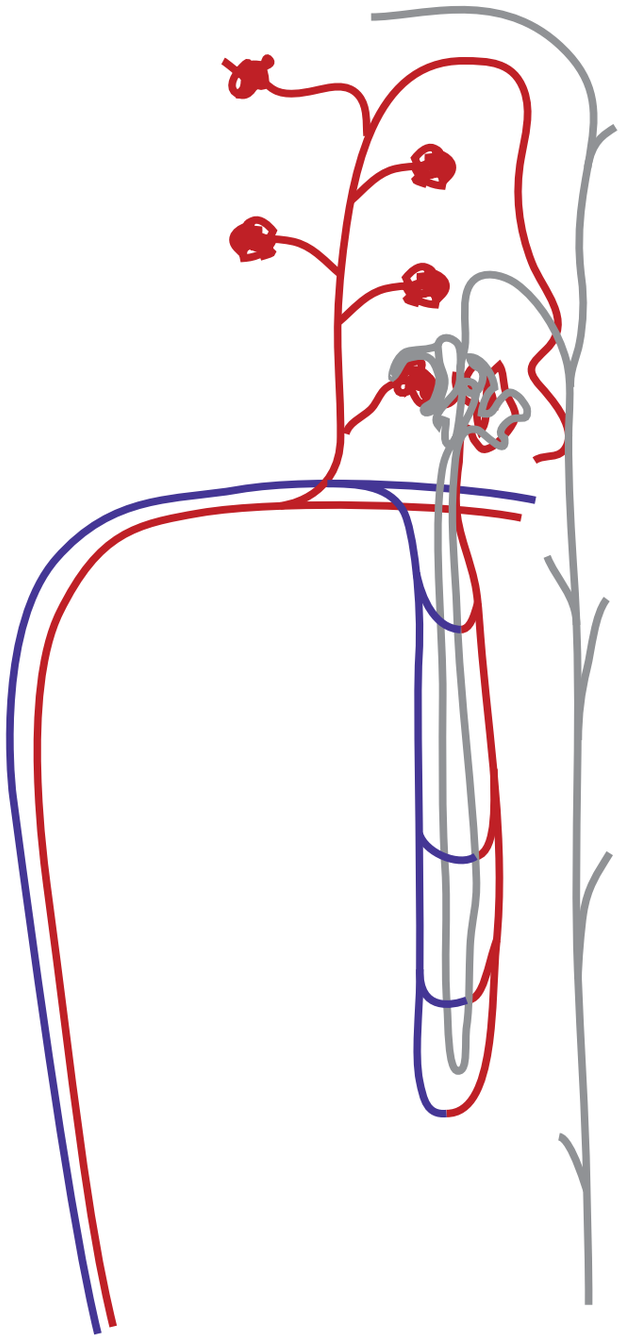
Renin


angiotensin II
ADH &
ACTH
aldosterone
vasoconstriction
↓ noradrenalin
reuptake
Salt Retention

Prerenal Azotaemia

	Prerenal Azotaemia
Urine Osmolality (mOsm/Kg)	>500
Urine Sodium (mmol/l)	<20
Urine/ Plasma Creatinine ratio	>40
FE_{Na}	<1%
FE_{Urea}	<35%
Urinary Sediment	occasional hyaline or fine granular casts

Pathogenesis: Vascular Factors



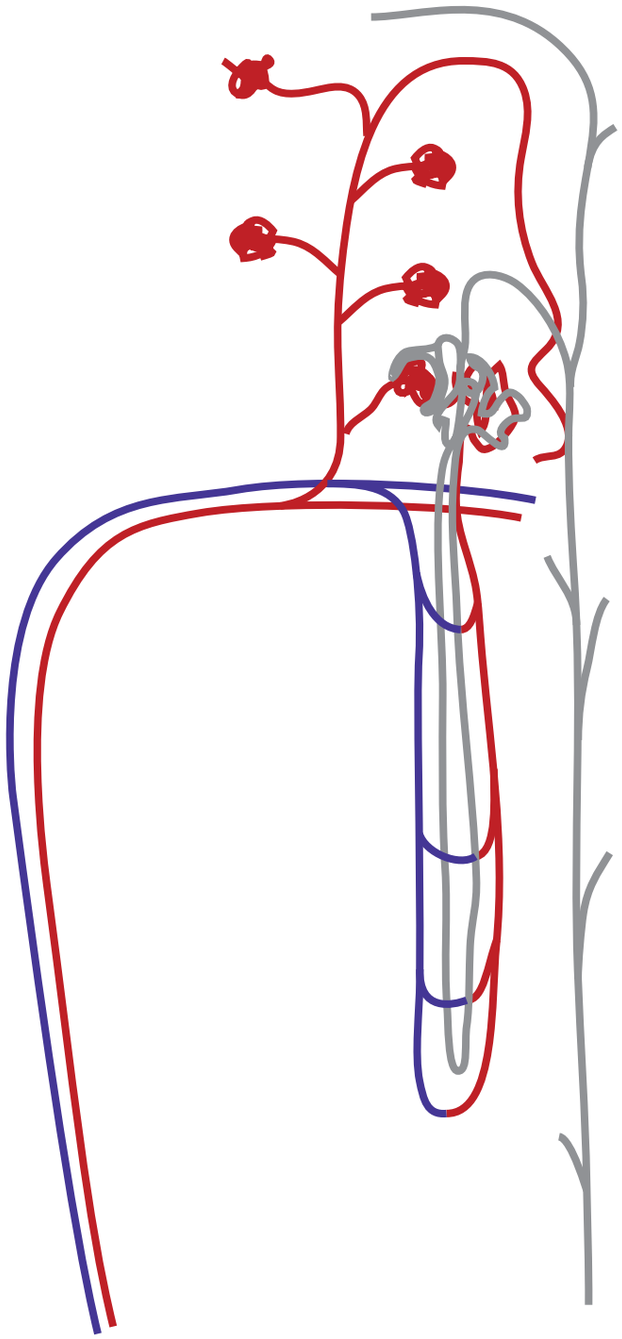
Cortex

70% O_2 requirement
90% Blood supply

Medulla

30% O_2 requirement
10% Blood supply

Pathogenesis: Vascular Factors



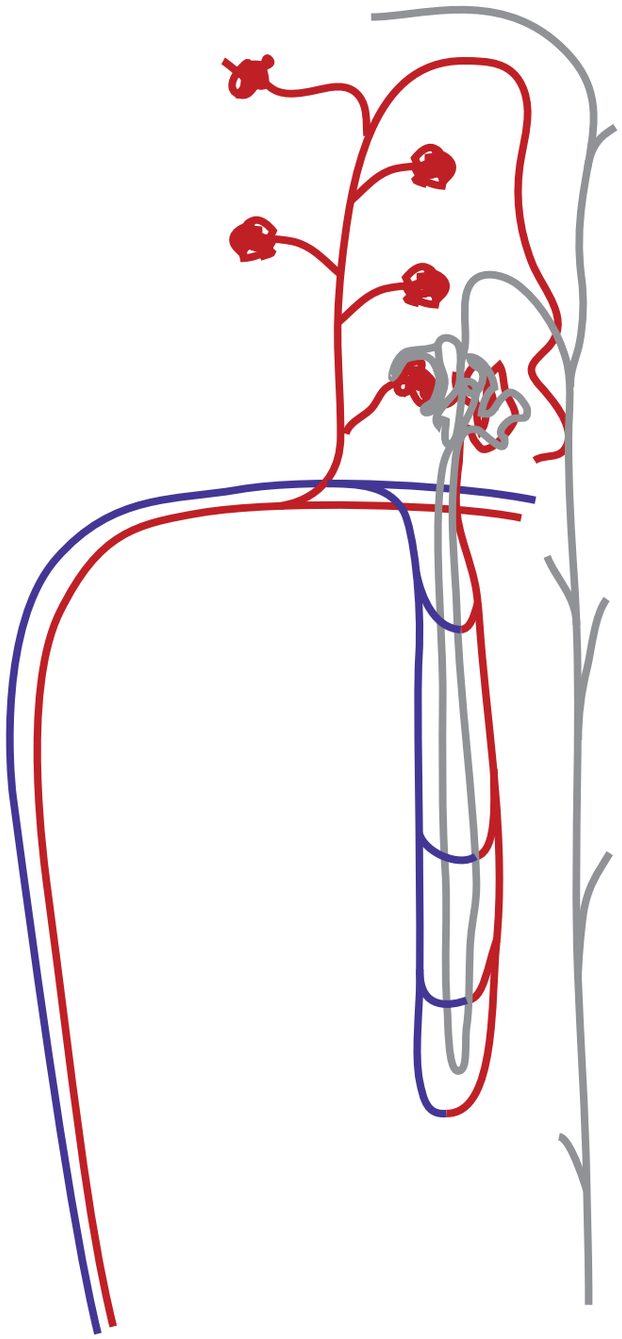
Cortex
70% O_2 requirement
90% Blood supply

Medulla
30% O_2 requirement
10% Blood supply

↓ Renal Blood Flow

Oxygen Demand ↑

Pathogenesis: Vascular Factors



Cortex

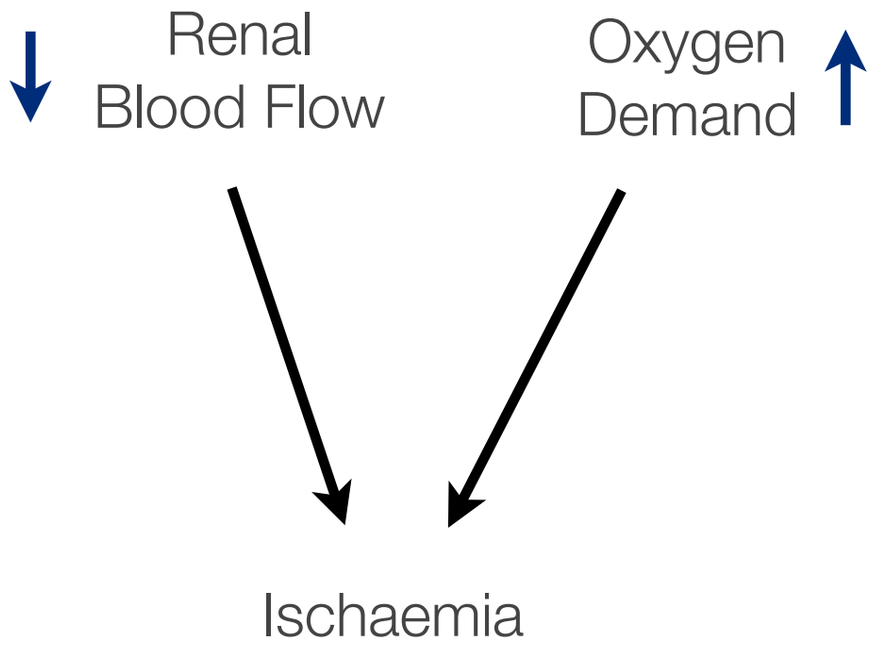
70% O_2 requirement

90% Blood supply

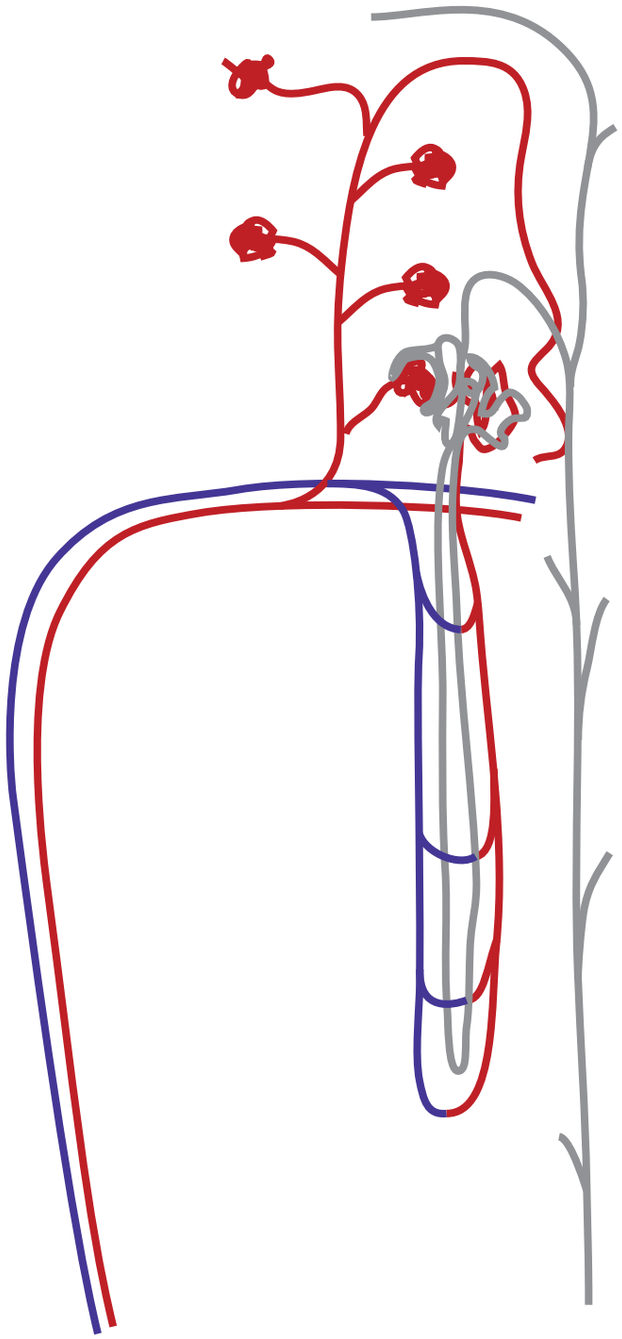
Medulla

30% O_2 requirement

10% Blood supply

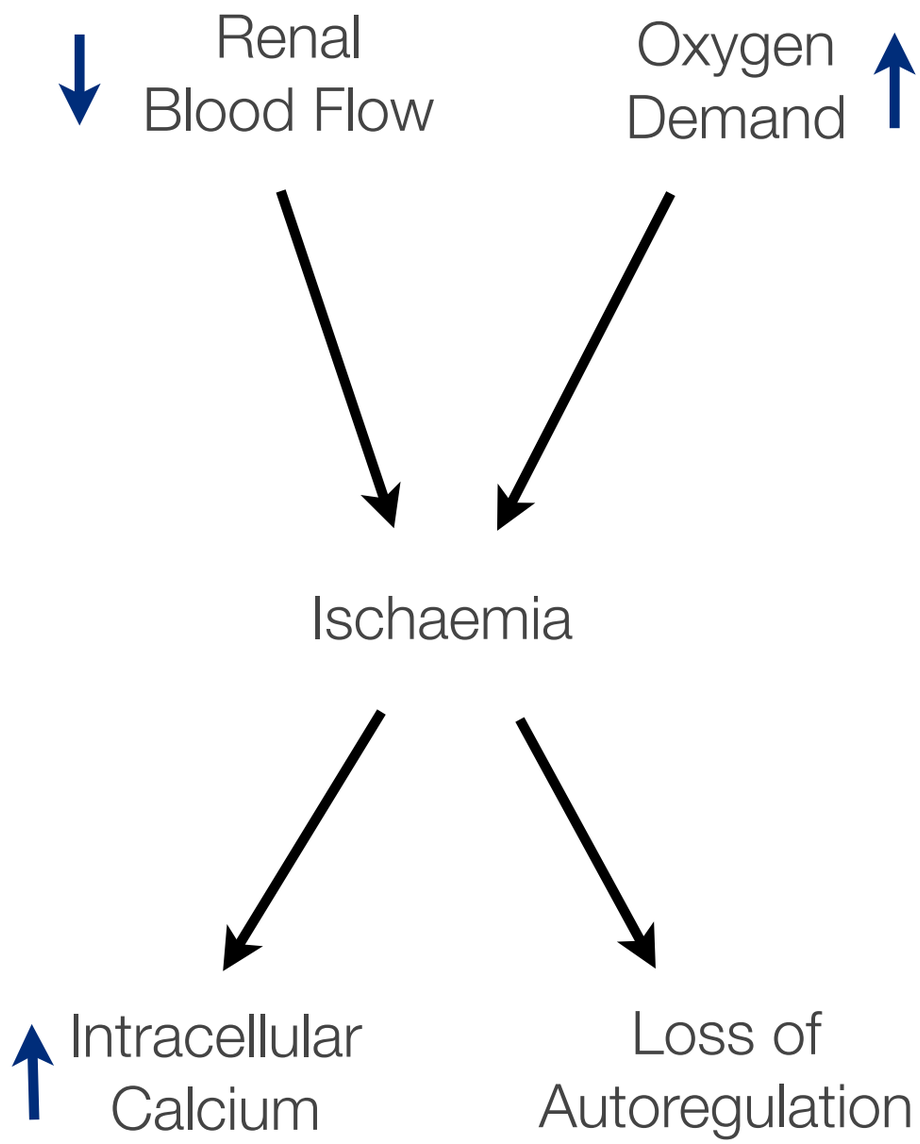


Pathogenesis: Vascular Factors

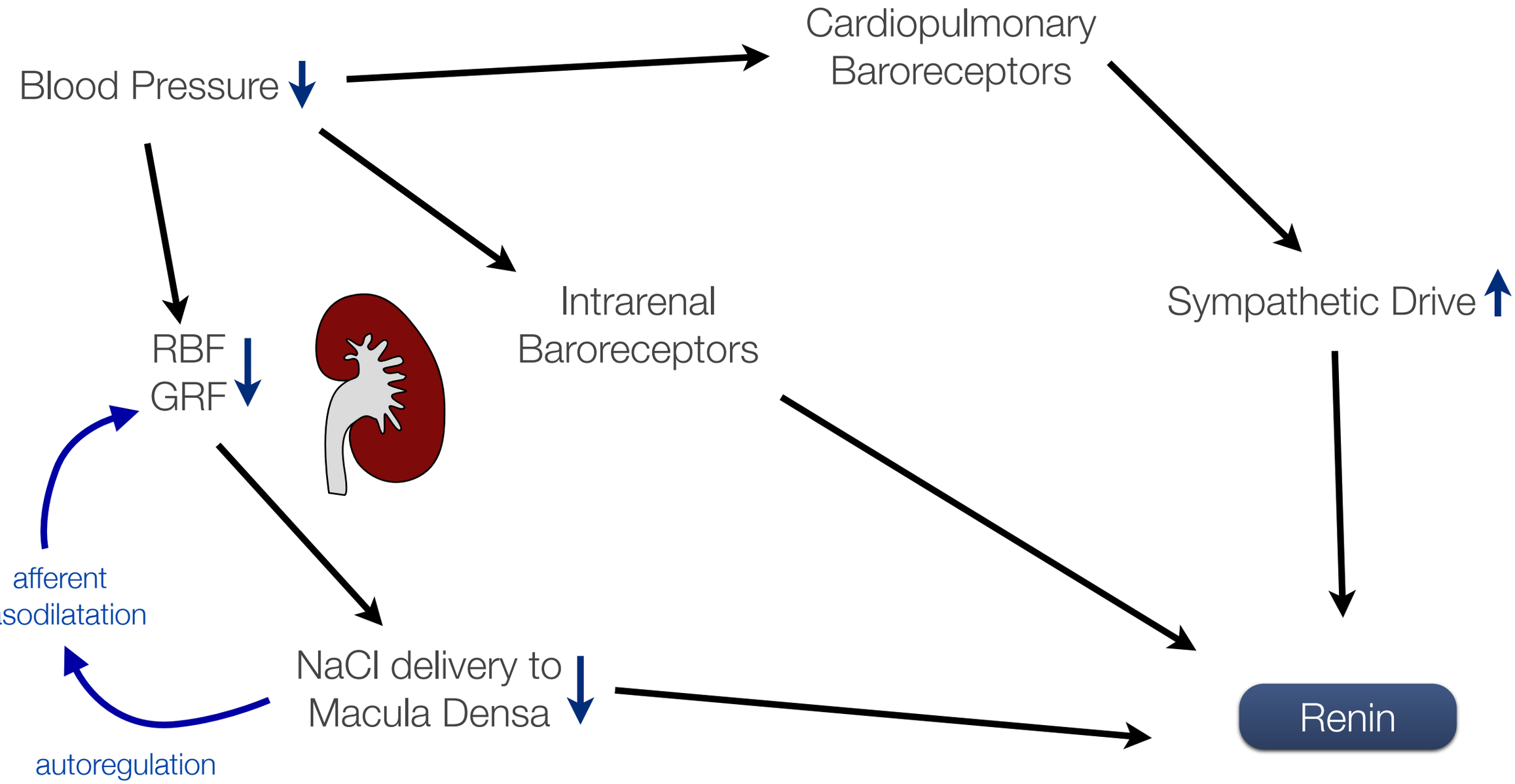


Cortex
70% O_2 requirement
90% Blood supply

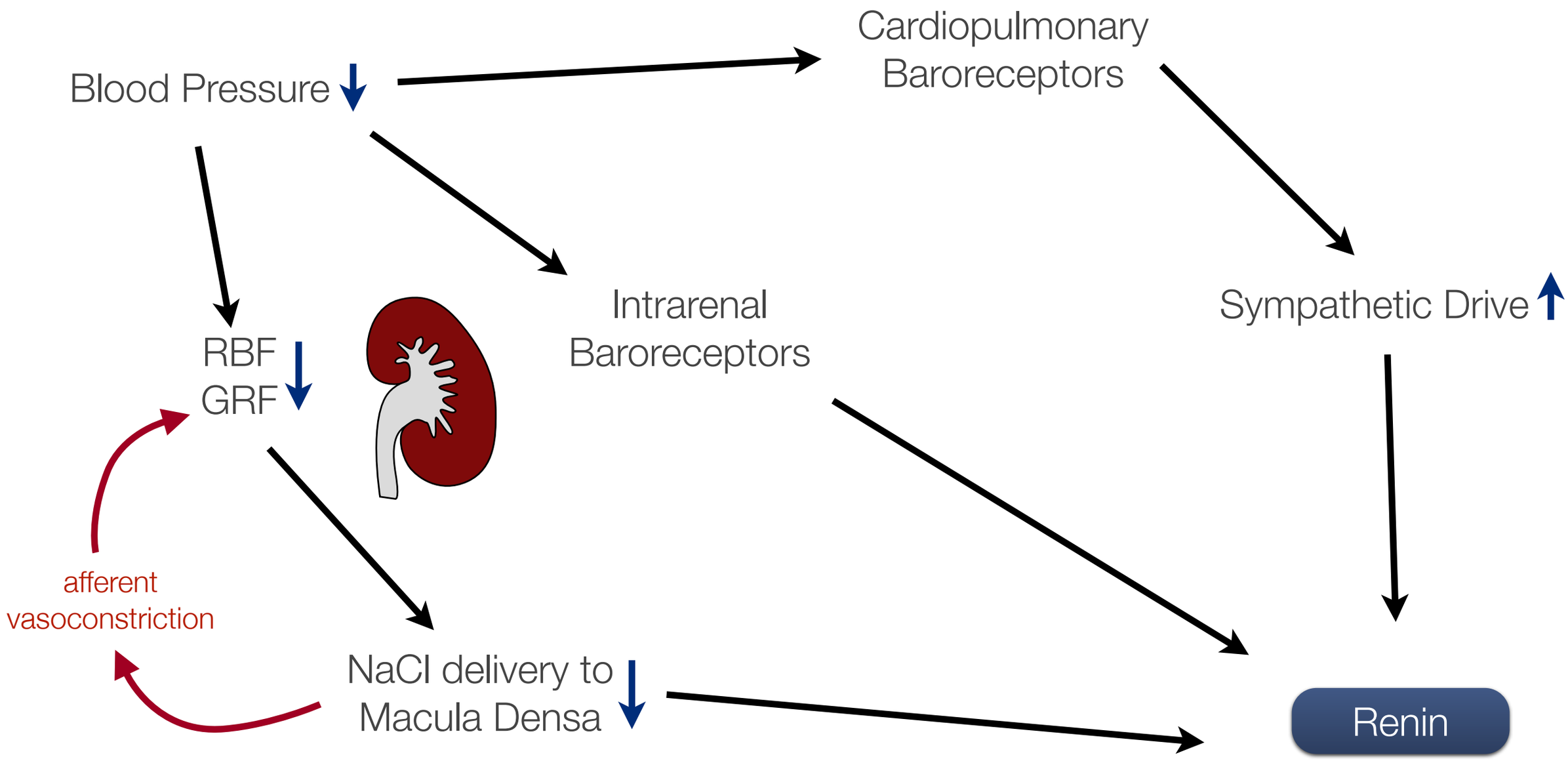
Medulla
30% O_2 requirement
10% Blood supply



Pathogenisis: Vascular Factors



Pathogenisis: Vascular Factors



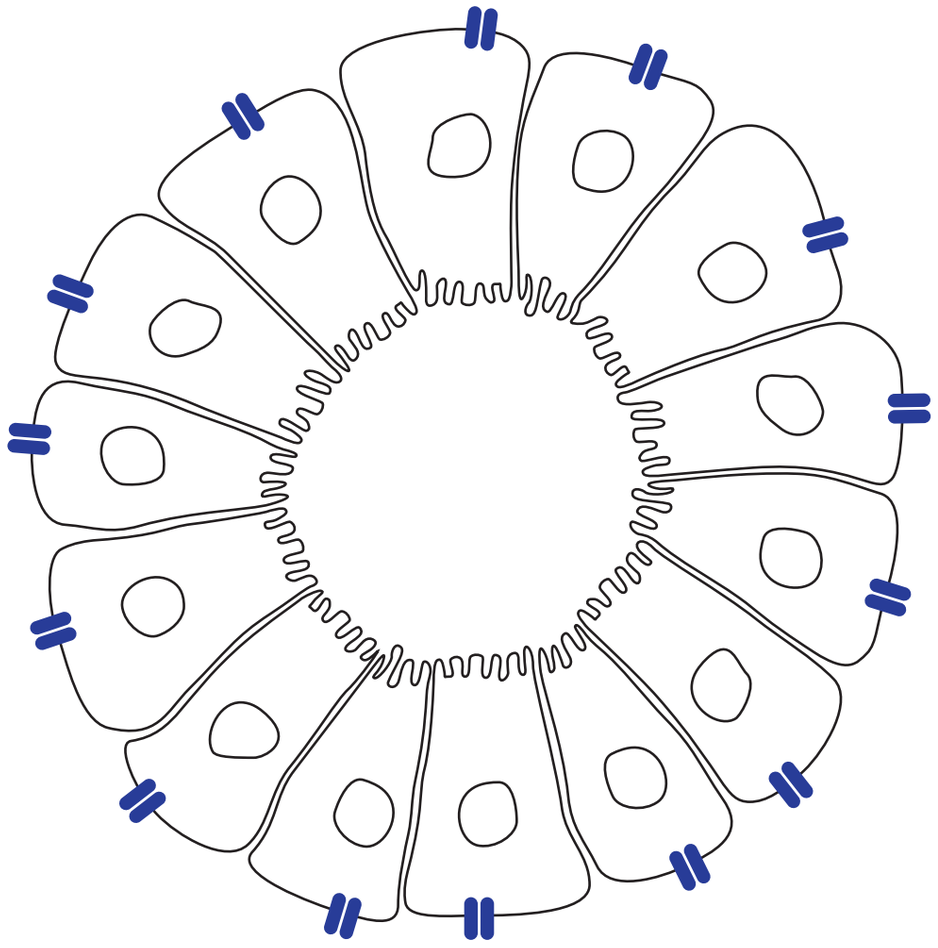
Acute Renal Failure

	Prerenal Azotaemia
Urine Osmolality (mOsm/Kg)	>500
Urine Sodium (mmol/l)	<20
Urine/ Plasma Creatinine ratio	>40
FE_{Na}	<1%
FE_{Urea}	<35%
Urinary Sediment	occasional hyaline or fine granular casts

Acute Renal Failure

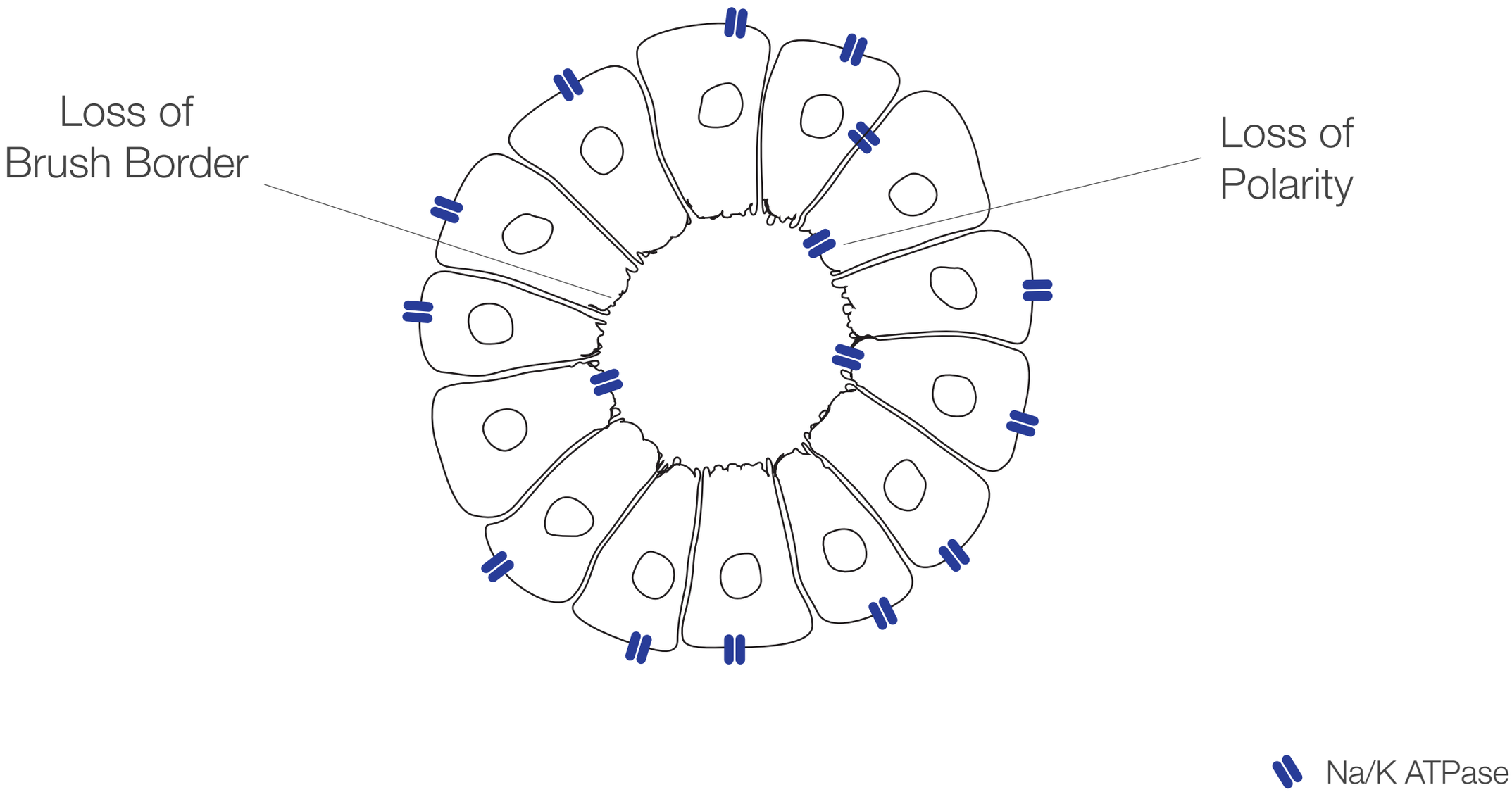
	Prerenal Azotaemia	Acute Renal failure
Urine Osmolality (mOsm/Kg)	>500	<400
Urine Sodium (mmol/l)	<20	>40
Urine/ Plasma Creatinine ratio	>40	<40
FE_{Na}	<1%	>2%
FE_{Urea}	<35%	>35%
Urinary Sediment	occasional hyaline or fine granular casts	tubular cells, coarse granular casts

Pathogenesis: Tubular Factors

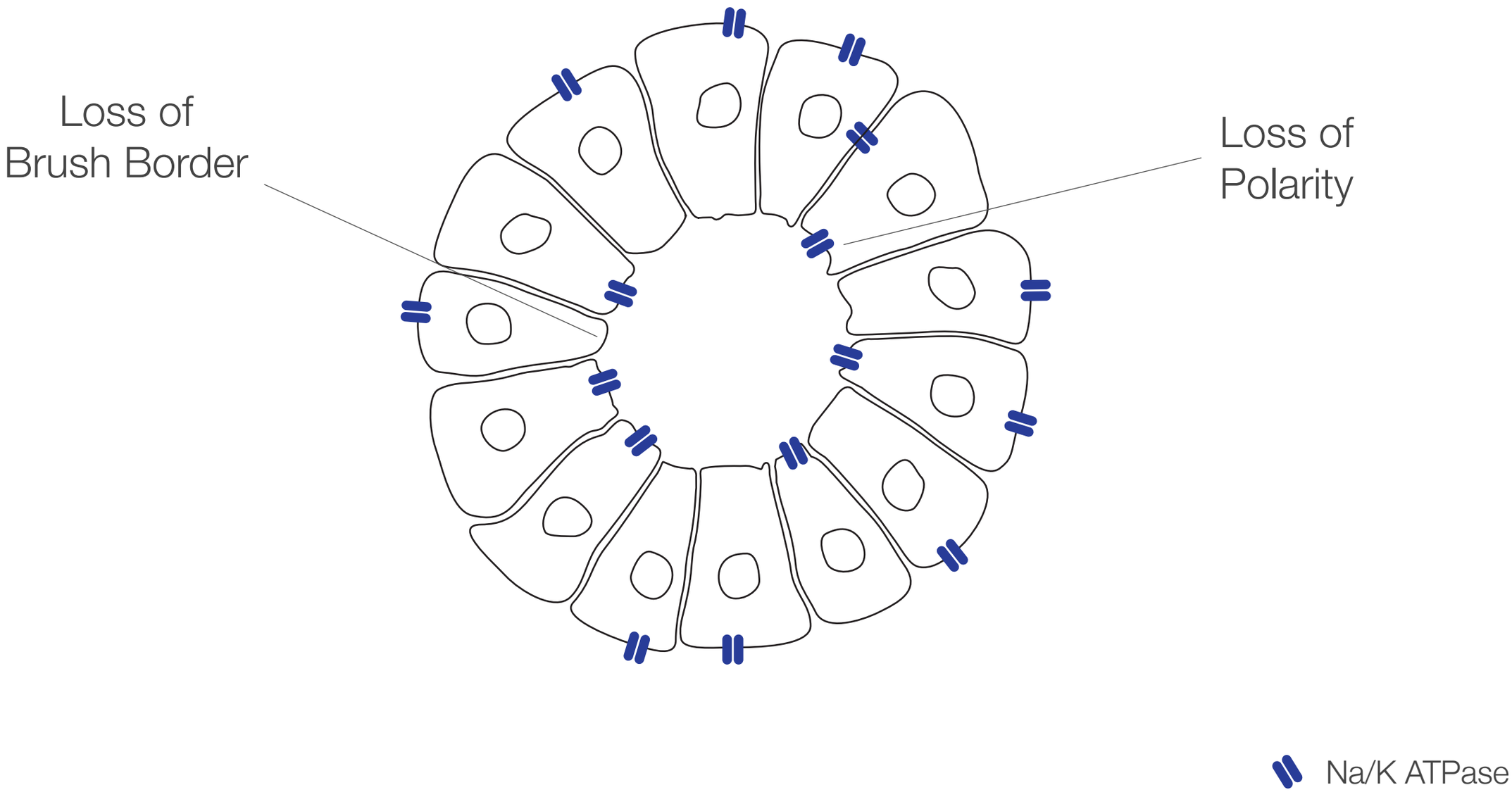


Na/K ATPase

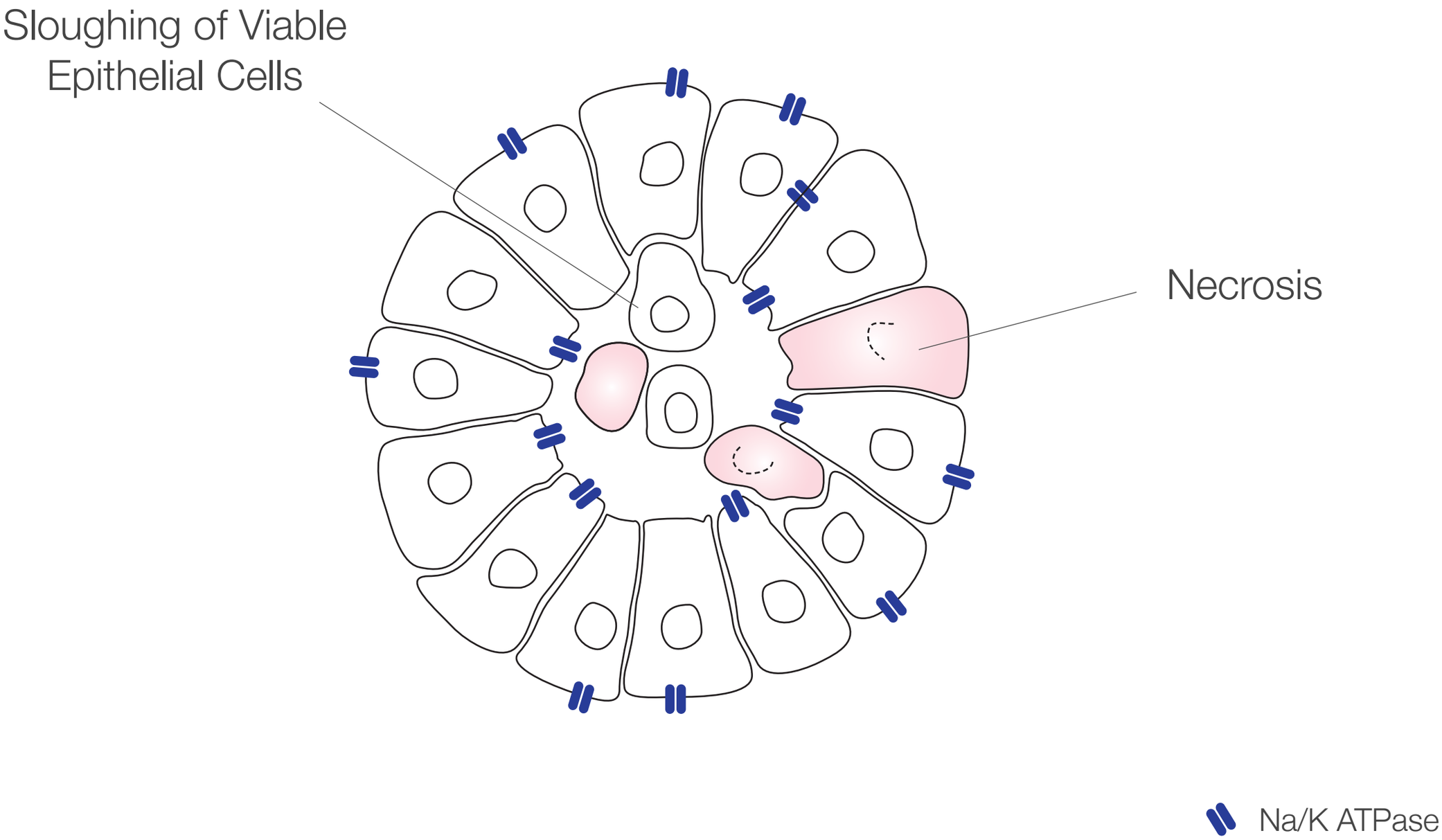
Pathogenesis: Tubular Factors



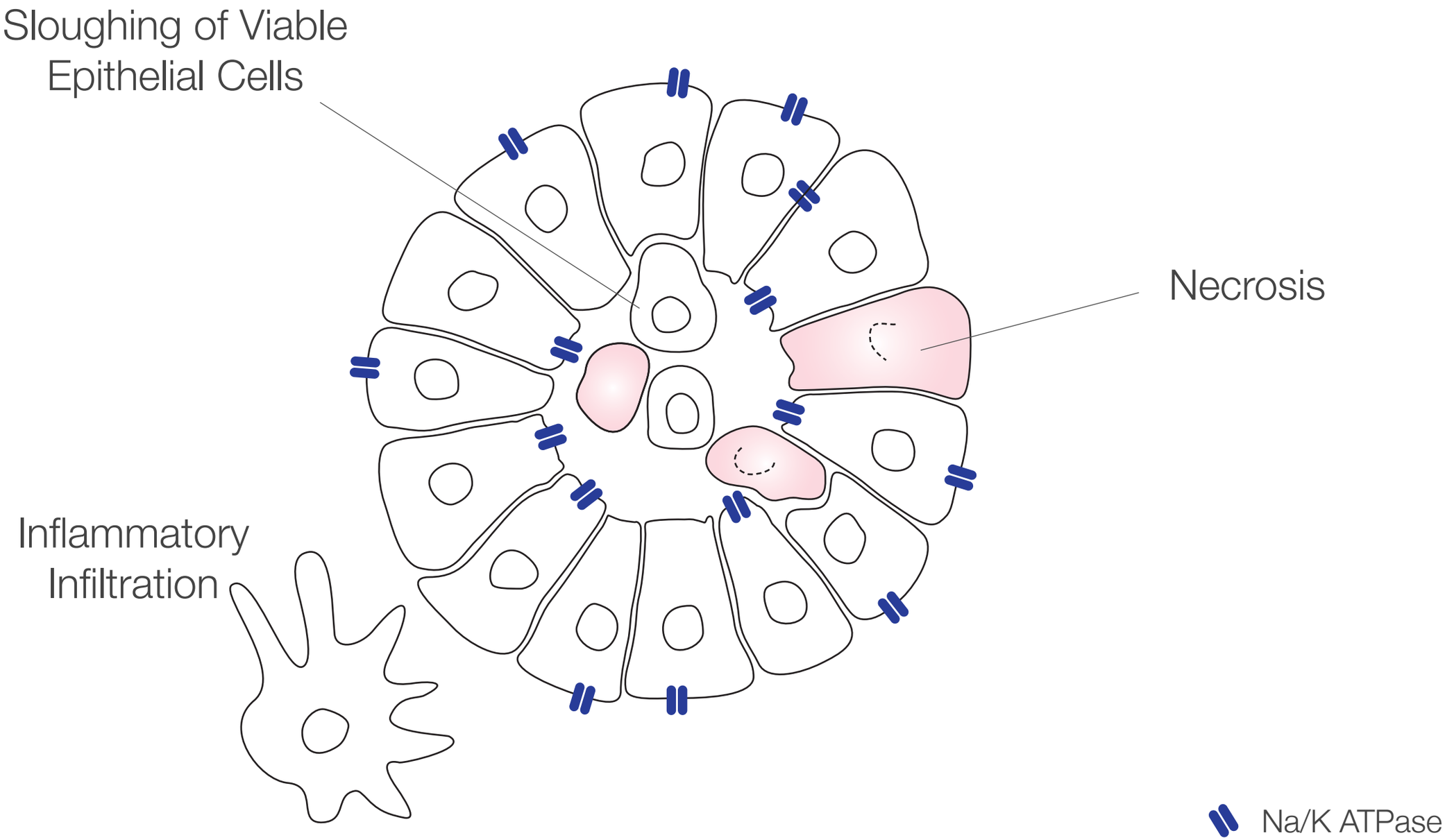
Pathogenesis: Tubular Factors



Pathogenesis: Tubular Factors

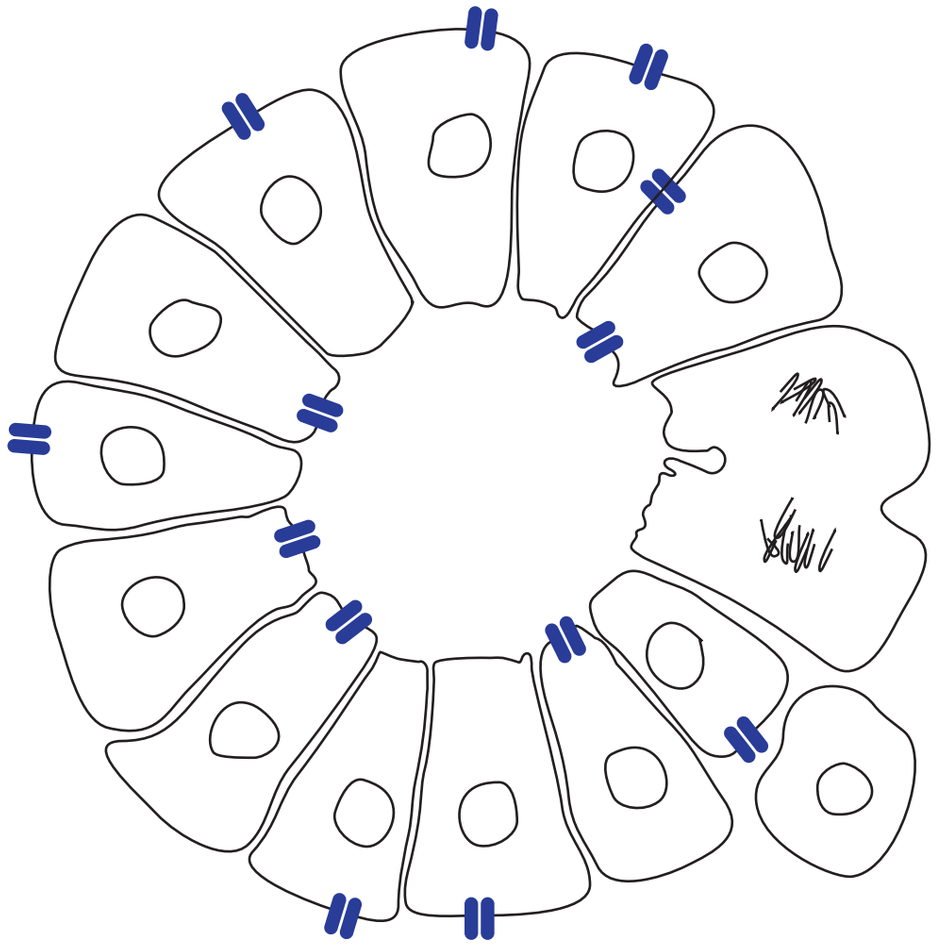


Pathogenesis: Tubular Factors



Pathogenesis: Tubular Factors

Kidney stem cells

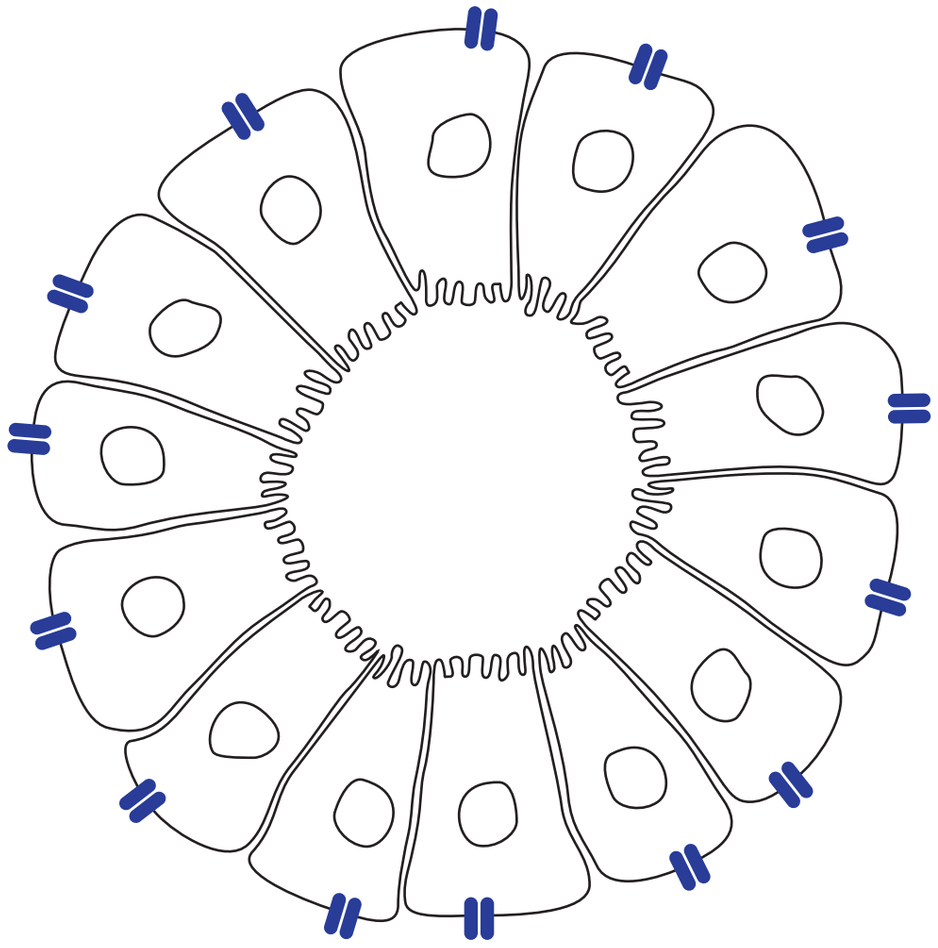


Adjacent tubule cells

Haematopoietic cells

Na/K ATPase

Pathogenesis: Tubular Factors

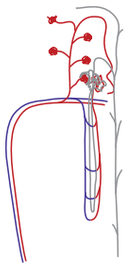


Na/K ATPase

Pathogenesis: Summary

Initiation

- Prerenal azotaemia
- Loss of autoregulation
- ↑ Intracellular calcium
- ATD Depletion
- Oxidative injury



Extension

- Loss of tubular cell polarity
- Cell necrosis
- Medullary congestion
- ↓↓ GFR
- Inflammatory infiltration

Maintenance

Tubular histology is rebuilt by:

- Adjacent tubule cells
- Kidney stem cells
- Haematopoietic cells

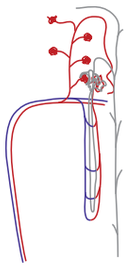
Repair

Polarity and function restored

Pathogenesis: Summary

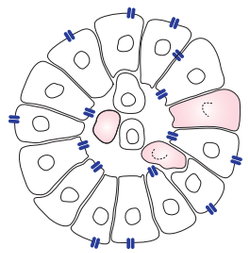
Initiation

- Prerenal azotaemia
- Loss of autoregulation
- ↑ Intracellular calcium
- ATD Depletion
- Oxidative injury



Extension

- Loss of tubular cell polarity
- Cell necrosis
- Medullary congestion
- ↓↓ GFR
- Inflammatory infiltration



Maintenance

Tubular histology is rebuilt by:

- Adjacent tubule cells
- Kidney stem cells
- Haematopoietic cells

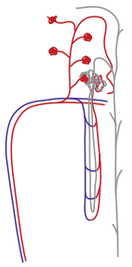
Repair

Polarity and function restored

Pathogenesis: Summary

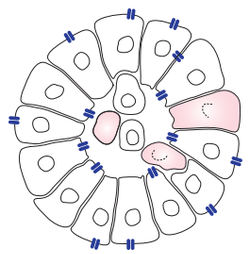
Initiation

- Prerenal azotaemia
- Loss of autoregulation
- ↑ Intracellular calcium
- ATD Depletion
- Oxidative injury



Extension

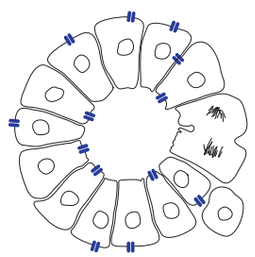
- Loss of tubular cell polarity
- Cell necrosis
- Medullary congestion
- ↓↓ GFR
- Inflammatory infiltration



Maintenance

Tubular histology is rebuilt by:

- Adjacent tubule cells
- Kidney stem cells
- Haematopoietic cells



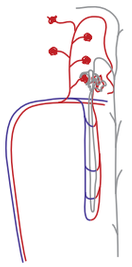
Repair

Polarity and function restored

Pathogenesis: Summary

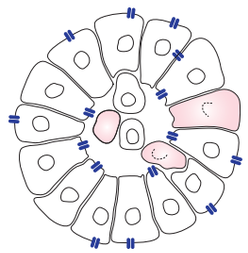
Initiation

- Prerenal azotaemia
- Loss of autoregulation
- ↑ Intracellular calcium
- ATD Depletion
- Oxidative injury



Extension

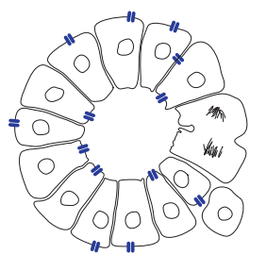
- Loss of tubular cell polarity
- Cell necrosis
- Medullary congestion
- ↓↓ GFR
- Inflammatory infiltration



Maintenance

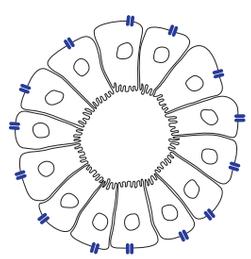
Tubular histology is rebuilt by:

- Adjacent tubule cells
- Kidney stem cells
- Haematopoietic cells



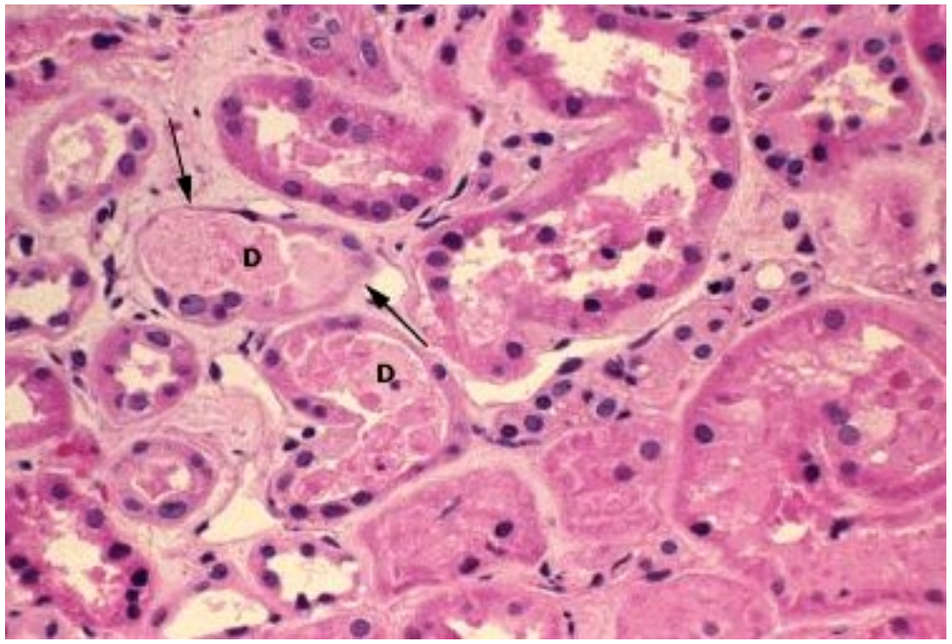
Repair

Polarity and function restored

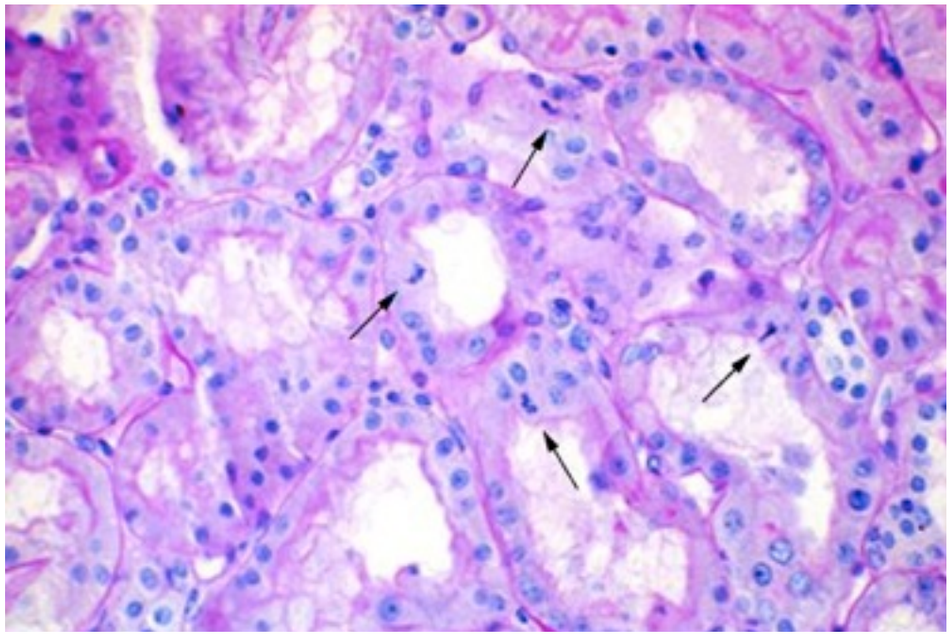


Pathogenesis: Tubular Factors

Extension Phase



Maintenance Phase



RIFLE

the Acute Dialysis Quality Initiative

RIFLE

the Acute Dialysis Quality Initiative

Risk

Injury

Failure

} Indicator Classes

RIFLE

the Acute Dialysis Quality Initiative

Risk

Injury

Failure

} Indicator Classes

Loss

End-stage Kidney Disease

} Outcome Classes

Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, the ADQI workgroup: **Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group.** *Crit Care* 2004, **8:**R204-R212

RIFLE: Classification

	GFR (Serum Creatinine)	Urine Output (ml/Kg/hr)
Risk	x 1.5	< 0.5 for 6 hours
Injury	6.1%	< 0.5 for 12 hours
Failure	4.4%	< 0.3 for 24 hours or anuria for 12 hours
Loss	Complete loss of kidney disease > 4 weeks	
End-stage	Complete loss of kidney disease > 3 months	

RIFLE: In Practice

- n = 5383 patients
- Pittsburg University Hospital 2006

E A Hoste, G Clermont, A Kersten et al: **RIFLE critereria for acute kidney injury.** *Crit Care* 2006, **10:**R73

	At Admission	Ever	Mortality (HR)
No ARF	78%	33%	
Risk	8%	12%	1.0 (0.68 - 1.56)
Injury	7%	27%	1.4 (1.02 - 1.88)
Failure	7%	28%	2.7 (2.03 - 3.55)

RIFLE: In Practice

- n = 5383 patients
- Pittsburg University Hospital 2006

E A Hoste, G Clermont, A Kersten et al: **RIFLE critereria for acute kidney injury.** *Crit Care* 2006, **10:**R73

	At Admission	Ever	Mortality (HR)
No ARF	78%	33%	
Risk	8%	12%	1.0 (0.68 - 1.56)
Injury	7%	27%	1.4 (1.02 - 1.88)
Failure	7%	28%	2.7 (2.03 - 3.55)

52%

Preventions

- Cause Prevention
- Loop Diuretics
- Osmotic Diuretics
- Ca Channel Blockers
- N-Acetylcysteine
- Theophyllines

Treatments

- Loop Diuretics
- Natriuretic Peptides
- Dopamine/ Fenoldopam
- Dialysis Mode
- Dialysis Dosing

Prevention & Treatment: Frusemide

- Inhibits Na/K/Cl channel in ascending Loop-of-Henley
- Reduced intracellular substrate for Na/K ATPase
- Reduced energy consumption in the critical outer medulla (by 45% in-vitro)
- Wash out tubular debris

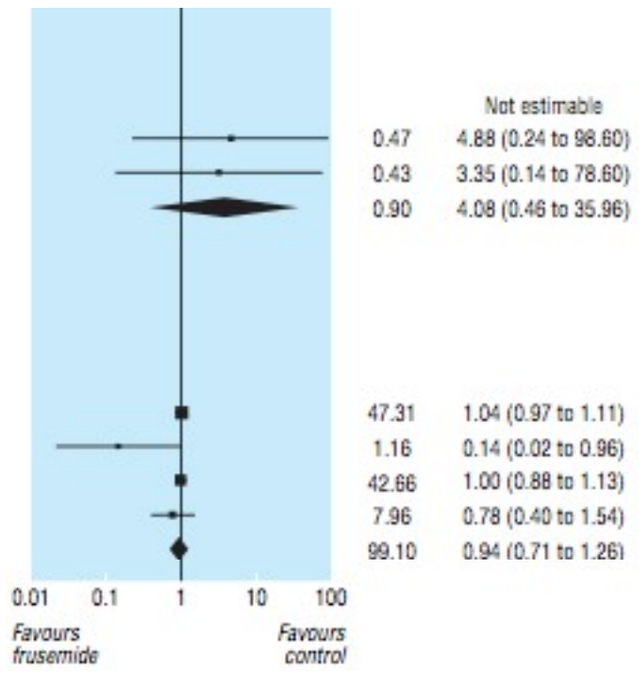
Prevention & Treatment: Frusemide

- 9 RCT
- n = 849
- In or at risk of ARF
- Heterogeneous selection criteria
- Many methodological problems
- Ototoxic

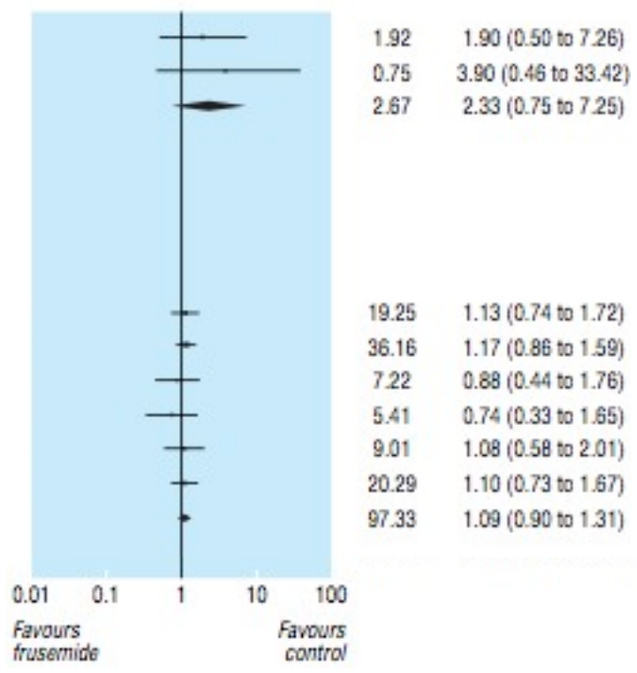
K M Ho, D J Sheridan: **Meta-analysis of frusemide to prevent or treat acute renal failre.** *BMJ* 2006, **doi:10.1136/bmj.38902.605347.7C**

Prevention & Treatment: Frusemide

Renal Replacement Therapy



Mortality

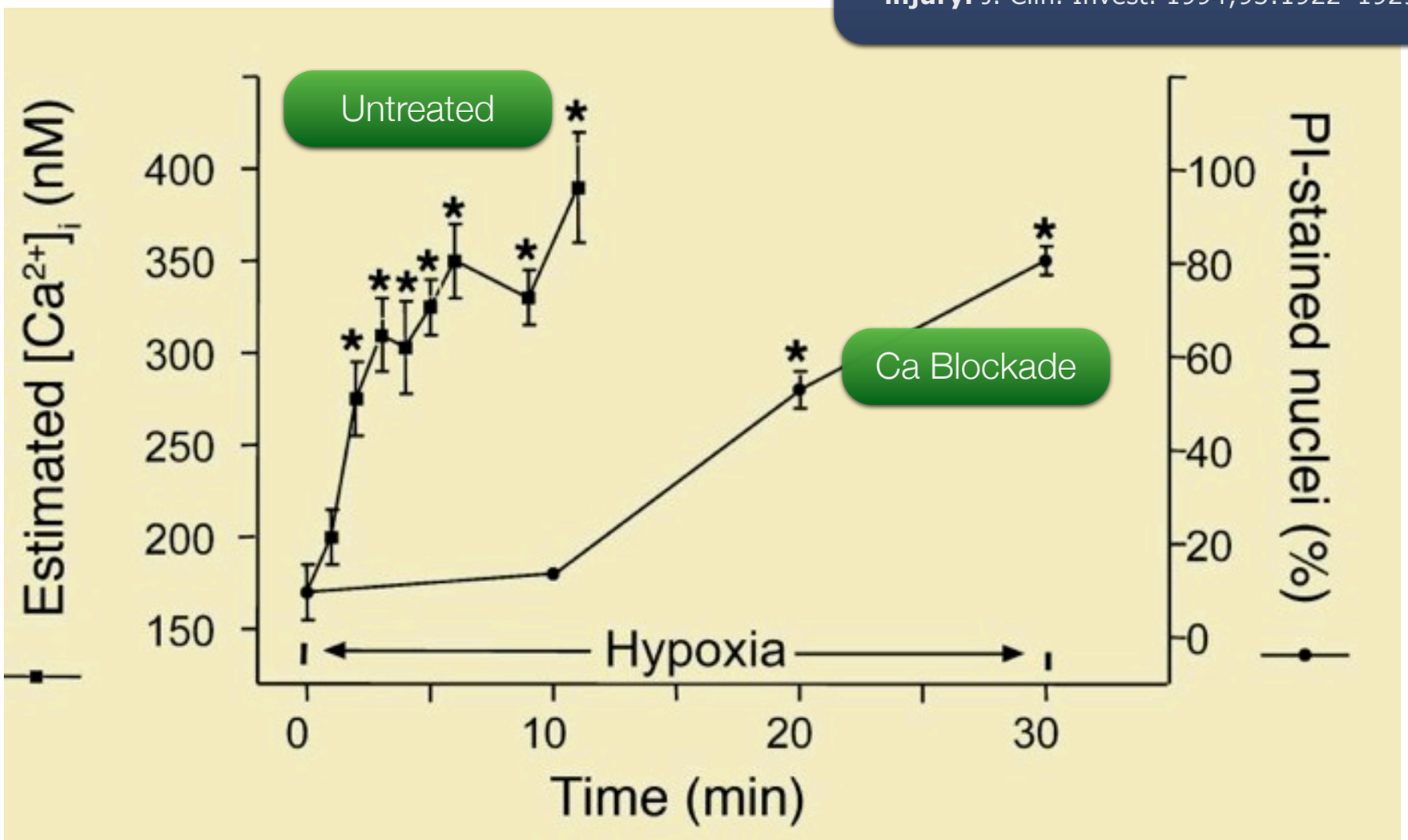


Prevention

Treatment

Prevention: Ca Channel Blockers

Kribben, A, et al. **Evidence for role of cytosolic free calcium in hypoxia-induced proximal tubule injury.** J. Clin. Invest. 1994;93:1922–1929



Prevention: Ca Channel Blockers

- n = 210
- Better serum creatinine at 3 months and 12 months post for patients receiving live or cadaveric kidney transplant
- Poor quality evidence.
- Adverse effects not reported.
- Other, trials (cumulatively larger) limited to cadaveric transplants have failed to find a benefit

V Riemsdijk, et al. **Isradipine results in a beter renal function after kidney transplant.** *Transplantation*. 2000;70:122–126

Treatment: Dopamine/ Fenoldopam

- Based on the vasomotor nephropathy model
- Correct aberrant vascular responses and improve renal blood supply
- Good in-vitro evidence to show improved RBF & GFR

Treatment: Dopamine/ Fenoldopam

- 58 RCT
- n = 2149
- No difference from placebo in mortality or renal replacement therapy

Kellum J A, Decker J M: **The use of dopamine in acute renal failure: a meta-analysis.** *Crit Care Med* 2001;29:1526-1531

- This review did not list adverse effects but we know dopamine can cause:
  - Extravasation necrosis
  - Arythmias
  - Headaches

Treatment: Dialysis Dose

- The biggest RCT
- n = 425
- CVVHF
- 20 / 30 / 45 (ml/Kg/hour)
- Low dose substantially inferior to higher two cohorts
- Three-way comparison:
  - RR = 1.88 (1.14 - 1.67)
  - NNT = 7 (4 - 16)

Ronco C, Bellomo R, Homel et al. **Effects of different doses in continious veno-veno heamofiltration on outcomes of renal failure.** *Lancet 200;356:26-30*

Interventions: Summary

Prevention

Cause Prevention

Loop Diuretics

Osmotic Diuretics

Ca Channel Blockers

N-Acetylcysteine

Theophyllines

Treatment

Loop Diuretics

Natriuretic Peptides

Dopamine

Dialysis Mode

Dialysis Dosing

Interventions: Summary

	Prevention	Treatment
Cause Prevention	✔ ✔	Loop Diuretics
Loop Diuretics		Natriuretic Peptides
Osmotic Diuretics		Dopamine
Ca Channel Blockers		Dialysis Mode
N-Acetylcysteine		Dialysis Dosing
Theophyllines		

Interventions: Summary

	Prevention	Treatment
Cause Prevention	✔ ✔	Loop Diuretics
Loop Diuretics	↔	Natriuretic Peptides
Osmotic Diuretics		Dopamine
Ca Channel Blockers		Dialysis Mode
N-Acetylcysteine		Dialysis Dosing
Theophyllines		

Interventions: Summary

	Prevention	Treatment
Cause Prevention	✔ ✔	Loop Diuretics
Loop Diuretics	↔	Natriuretic Peptides
Osmotic Diuretics	↔	Dopamine
Ca Channel Blockers		Dialysis Mode
N-Acetylcysteine		Dialysis Dosing
Theophyllines		

Interventions: Summary

	Prevention	Treatment
Cause Prevention	✔ ✔	Loop Diuretics
Loop Diuretics	↔	Natriuretic Peptides
Osmotic Diuretics	↔	Dopamine
Ca Channel Blockers	↔	Dialysis Mode
N-Acetylcysteine		Dialysis Dosing
Theophyllines		

Interventions: Summary

	Prevention	Treatment
Cause Prevention	✔ ✔	Loop Diuretics
Loop Diuretics	↔	Natriuretic Peptides
Osmotic Diuretics	↔	Dopamine
Ca Channel Blockers	↔	Dialysis Mode
N-Acetylcysteine	✔	Dialysis Dosing
Theophyllines		

Interventions: Summary

	Prevention	Treatment
Cause Prevention	✔ ✔	Loop Diuretics
Loop Diuretics	↔	Natriuretic Peptides
Osmotic Diuretics	↔	Dopamine
Ca Channel Blockers	↔	Dialysis Mode
N-Acetylcysteine	✔	Dialysis Dosing
Theophyllines	↔	

Interventions: Summary

	Prevention
Cause Prevention	✔ ✔
Loop Diuretics	↔
Osmotic Diuretics	↔
Ca Channel Blockers	↔
N-Acetylcysteine	✔
Theophyllines	↔

	Treatment
Loop Diuretics	↔
Natriuretic Peptides	
Dopamine	
Dialysis Mode	
Dialysis Dosing	

Interventions: Summary

	Prevention
Cause Prevention	✔ ✔
Loop Diuretics	↔
Osmotic Diuretics	↔
Ca Channel Blockers	↔
N-Acetylcysteine	✔
Theophyllines	↔

	Treatment
Loop Diuretics	↔
Natriuretic Peptides	↔
Dopamine	
Dialysis Mode	
Dialysis Dosing	

Interventions: Summary

	Prevention
Cause Prevention	✔ ✔
Loop Diuretics	↔
Osmotic Diuretics	↔
Ca Channel Blockers	↔
N-Acetylcysteine	✔
Theophyllines	↔

	Treatment
Loop Diuretics	↔
Natriuretic Peptides	↔
Dopamine	↔
Dialysis Mode	
Dialysis Dosing	

Interventions: Summary

	Prevention
Cause Prevention	✔ ✔
Loop Diuretics	↔
Osmotic Diuretics	↔
Ca Channel Blockers	↔
N-Acetylcysteine	✔
Theophyllines	↔

	Treatment
Loop Diuretics	↔
Natriuretic Peptides	↔
Dopamine	↔
Dialysis Mode	↔
Dialysis Dosing	

Interventions: Summary

	Prevention
Cause Prevention	✔ ✔
Loop Diuretics	↔
Osmotic Diuretics	↔
Ca Channel Blockers	↔
N-Acetylcysteine	✔
Theophyllines	↔

	Treatment
Loop Diuretics	↔
Natriuretic Peptides	↔
Dopamine	↔
Dialysis Mode	↔
Dialysis Dosing	✔ High dose

Questions

Key points

- RIFLE is the future of ARF research
- Preventing the causes of ARF is our best strategy
- Frusemide for fluid management only