Vasodilators

Vascular tone, ventricular loading, and the body's response

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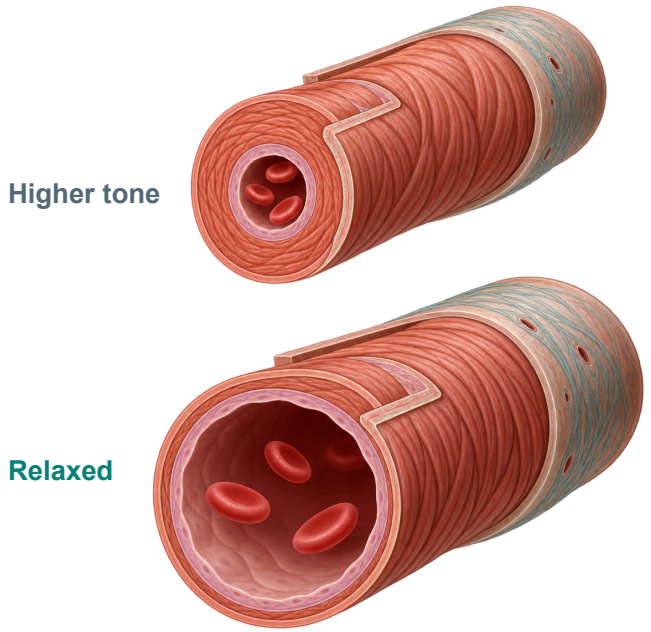


KEY RELATIONSHIP From a change in vascular tone to a predictable physiological response.

Notes

Save a copy to highlight, write, or type notes. Use the page links for animations and explanations.

TARGET → ACTION → TISSUE EFFECT → BODY RESPONSE → USES AND OUTCOMES → SAFETY → PHARMACOKINETICS

Follow one causal chain

1 Target

Where does it act?

2 Action

What does it do there?

3 Tissue effect

What changes directly?

4 Body response

How does the body respond?

5 Uses and outcomes

Who benefits, and how?

6 Safety

What could go wrong?

7 Pharmacokinetics

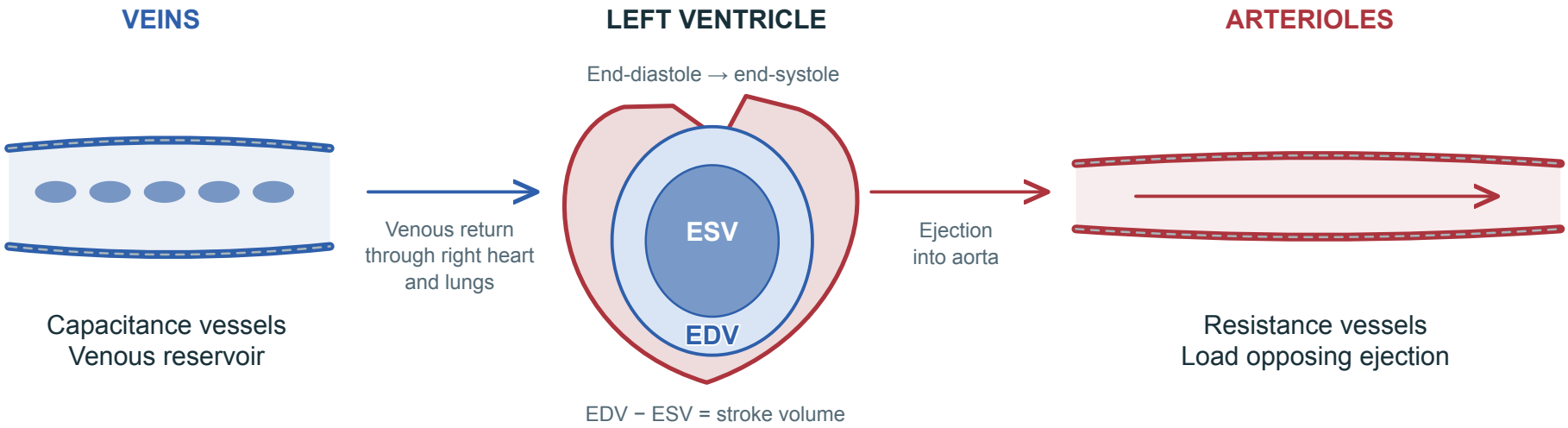
How does exposure change the response?

KEY RELATIONSHIP The vessel changes first. Compensation and exposure determine the net response.

Notes

TISSUE EFFECT

The ventricle fills, then ejects



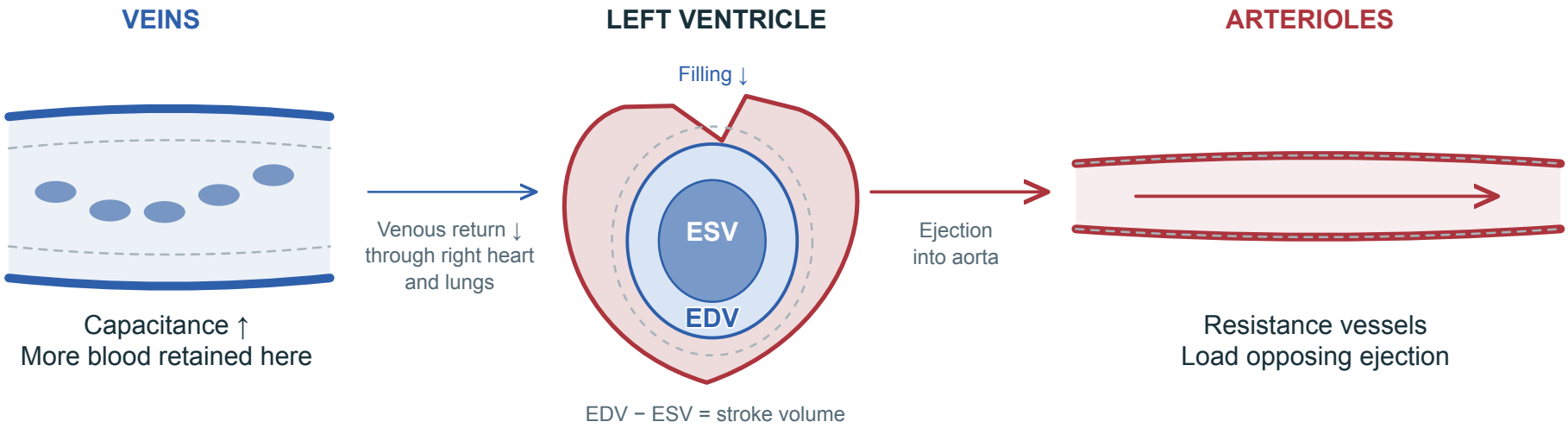
KEY RELATIONSHIP

Stroke volume is the difference between end-diastolic and end-systolic volume.

Notes

TISSUE EFFECT

A larger venous reservoir leaves less blood for filling

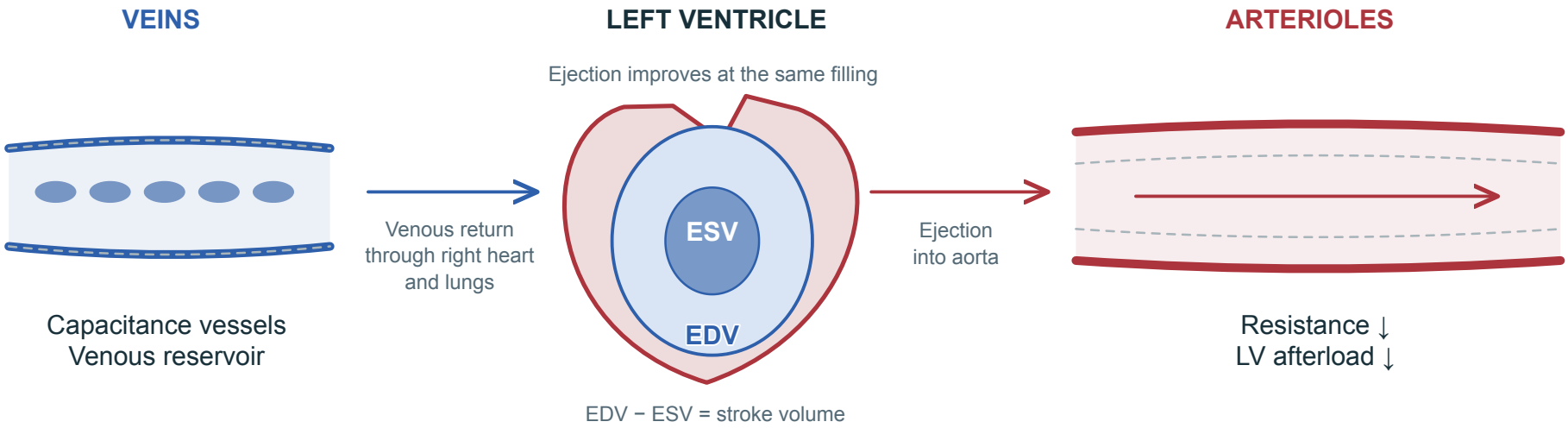


KEY RELATIONSHIP Venous capacitance ↑ → venous return ↓ → ventricular preload ↓.

Notes

TISSUE EFFECT

Lower ejection resistance can increase stroke volume



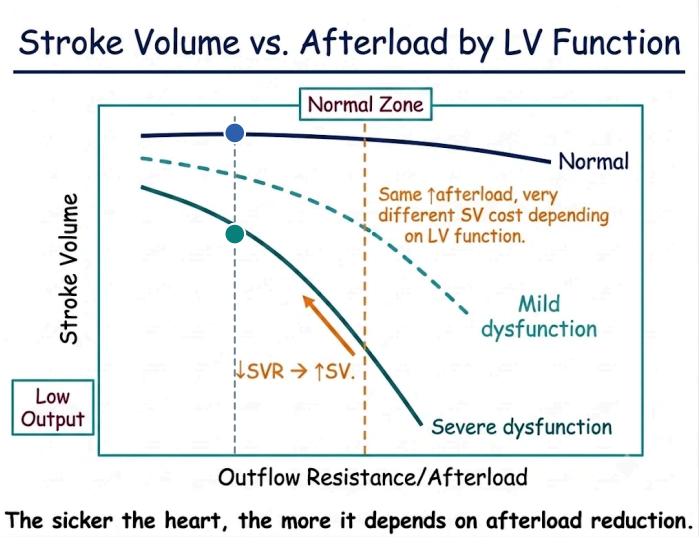
KEY RELATIONSHIP

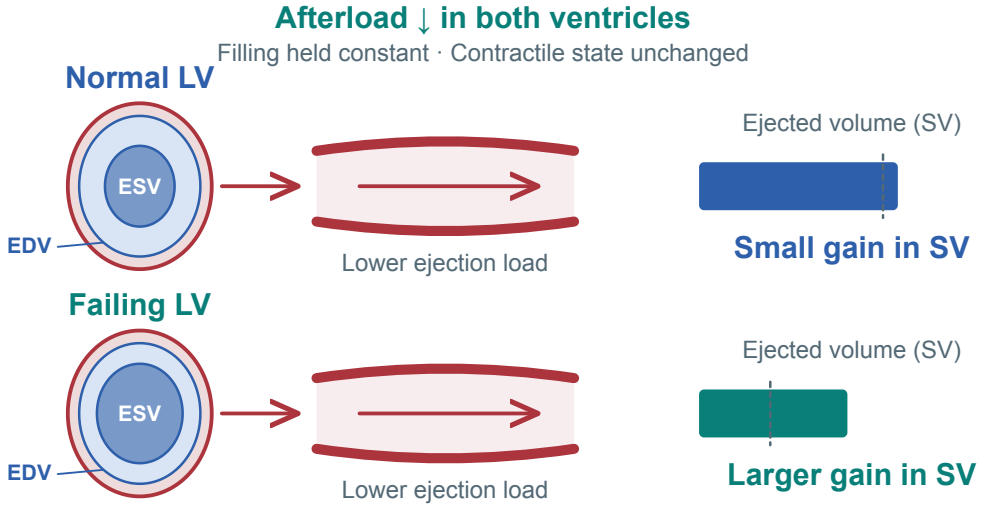
Arteriolar resistance ↓ → LV afterload ↓ → less blood left after ejection.

Notes

TISSUE EFFECT

A failing ventricle may gain more from afterload reduction





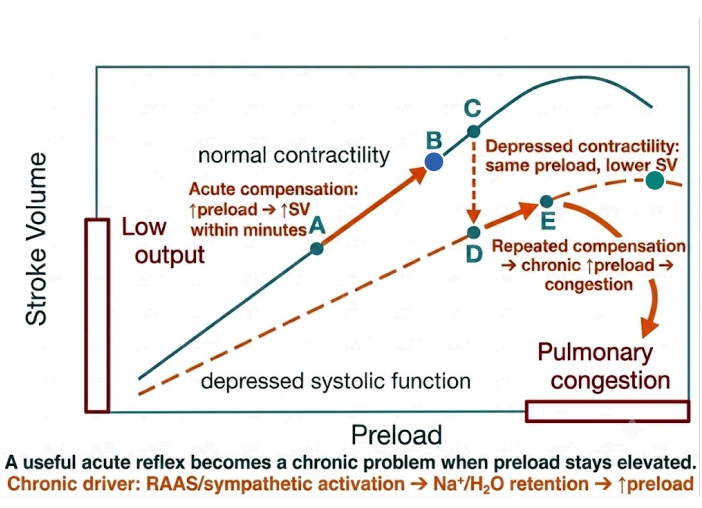
KEY RELATIONSHIP

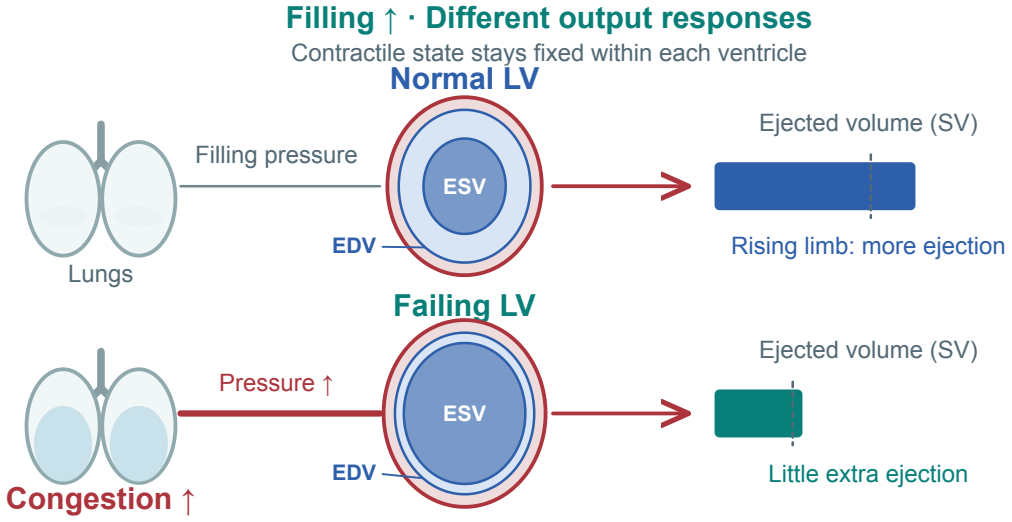
An increase in stroke volume can reflect easier ejection without a direct inotropic action.

Notes

TISSUE EFFECT

More filling is not always more useful output





KEY RELATIONSHIP

At high filling pressure, a failing ventricle may gain little output while congestion worsens.

Notes

TISSUE EFFECT → BODY RESPONSE

A lower pressure can coexist with better forward flow

$$MAP \approx CO \times SVR$$

$$CO = HR \times SV$$

Stroke volume (SV) = EDV − ESV

Direct loading effect

Arteriolar dilation lowers resistance.
Easier ejection can increase stroke volume.

Whole-body response

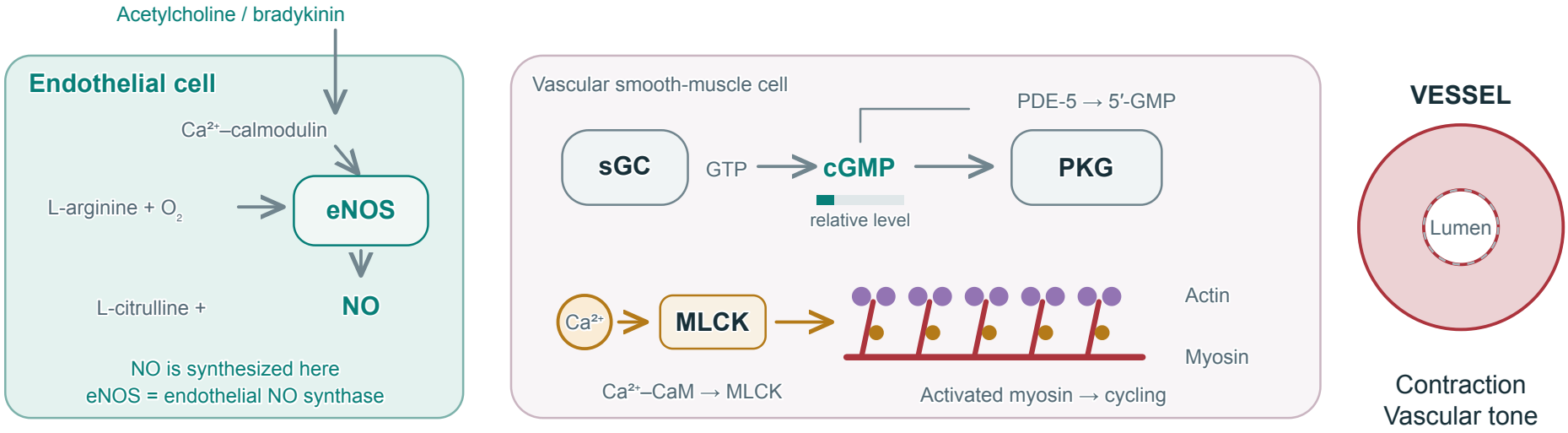
Reflexes change heart rate.
Renal responses change blood volume.

KEY RELATIONSHIP MAP may fall as SVR falls, even if stroke volume and cardiac output improve.

Notes

ACTION → TISSUE EFFECT

Ca^{2+} activates myosin; relaxation reverses that activation

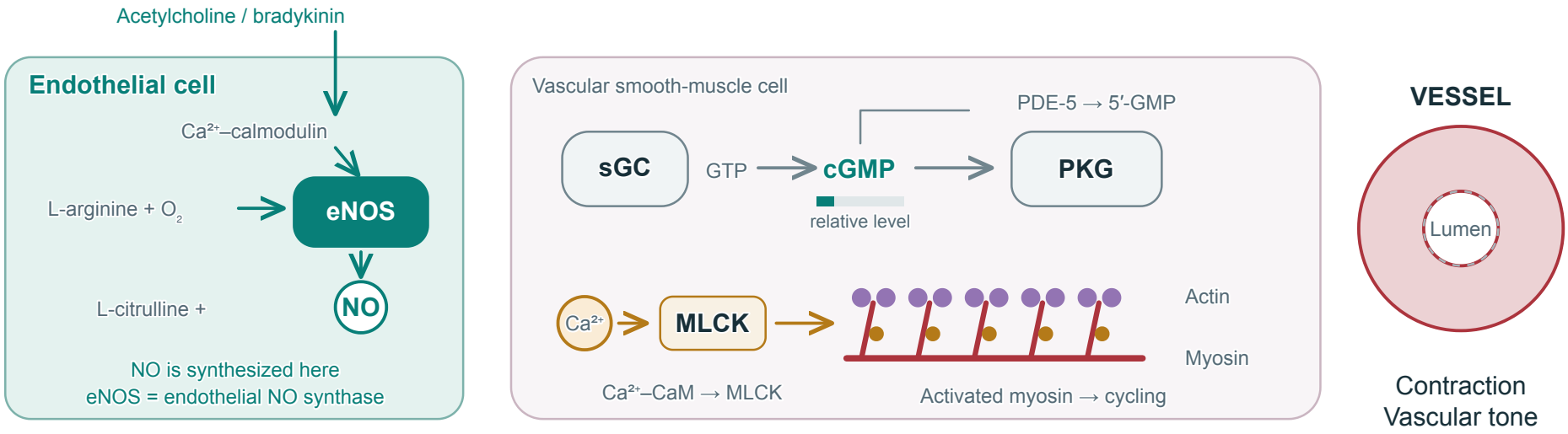


KEY RELATIONSHIP Ca^{2+}–calmodulin → myosin light-chain kinase (MLCK) → myosin phosphorylation → contraction.

Notes

TARGET → ACTION

The endothelial cell makes NO from L-arginine

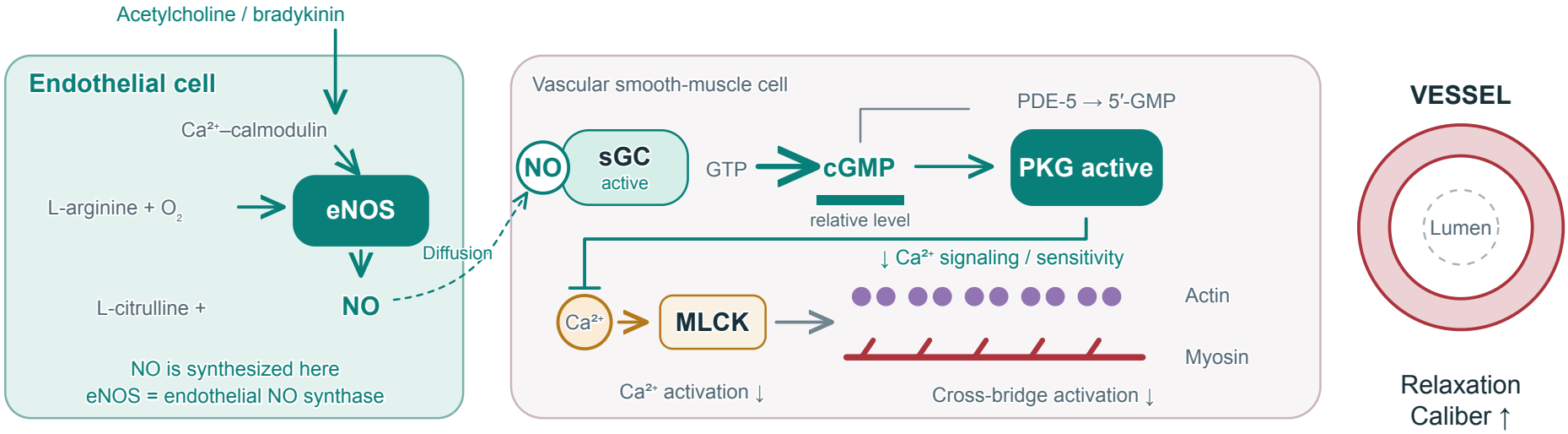


KEY RELATIONSHIP Acetylcholine / bradykinin → eNOS activation; L-arginine + O_2 → NO + L-citrulline.

Notes

TARGET → ACTION → TISSUE EFFECT

Follow NO from its endothelial source to relaxation

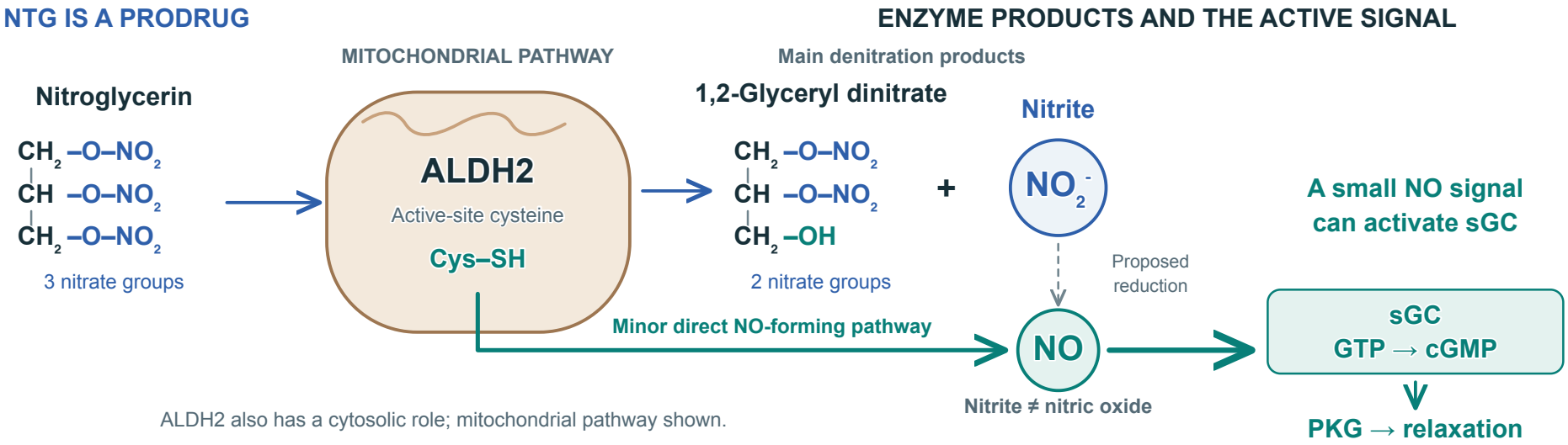


KEY RELATIONSHIP cGMP activates PKG → Ca²⁺ signaling / sensitivity ↓ → myosin dephosphorylation → relaxation.

Notes

TARGET → ACTION → PHARMACOKINETICS

Nitroglycerin must be bioactivated before it signals

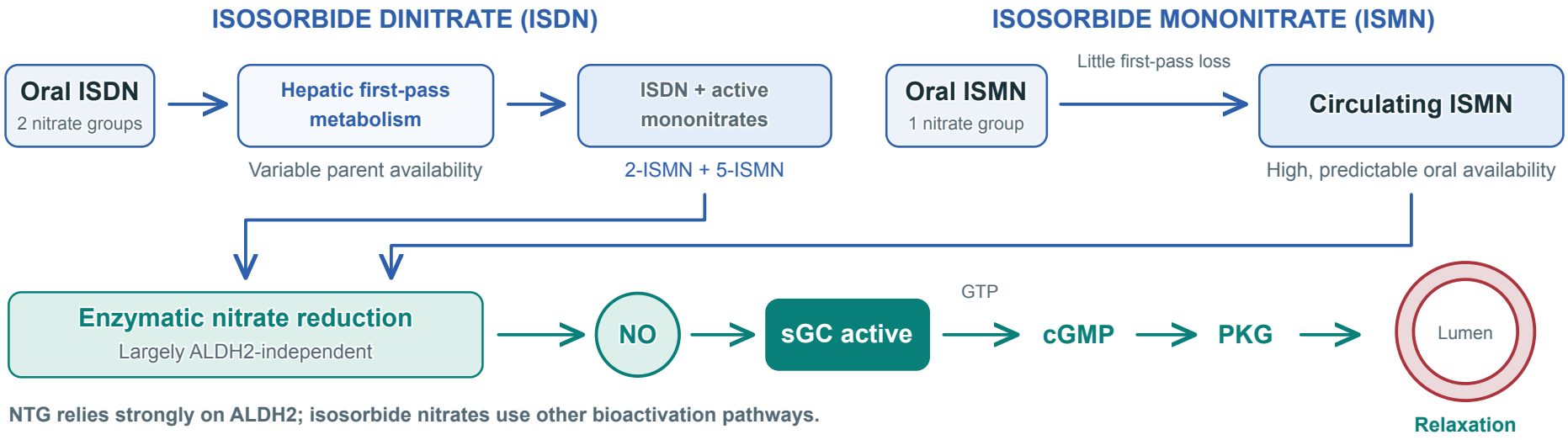


KEY RELATIONSHIP NTG is the prodrug; ALDH2 helps generate the NO signal that activates sGC.

Notes

ACTION → TISSUE EFFECT → PHARMACOKINETICS

Isosorbide nitrates reach the same NO–cGMP pathway



NTG relies strongly on ALDH2; isosorbide nitrates use other bioactivation pathways.

KEY RELATIONSHIP ISDN forms active mononitrates; ISMN has predictable oral availability. Both still require bioactivation.

Notes

USES AND OUTCOMES

Nitrates: therapeutic uses

Clinical setting	Therapeutic role
Angina: stable or vasospastic	Sublingual NTG for acute relief; longer-acting nitrates for prevention
Acute coronary syndromes	Sublingual or IV NTG for persistent ischemic symptoms when BP permits
Acute HF / pulmonary edema	IV NTG to reduce filling pressures and congestion when BP is adequate
Selected acute BP control	IV NTG with ischemia, pulmonary edema, or perioperative hypertension
Chronic HFrEF: selected patients	Isosorbide dinitrate (ISDN) + hydralazine for symptom and outcome benefit

KEY RELATIONSHIP

Nitrates relieve ischemia and congestion; selected HFrEF patients benefit from ISDN + hydralazine.

Notes

USES AND OUTCOMES → PHARMACOKINETICS

Match nitrate formulation to the clinical need

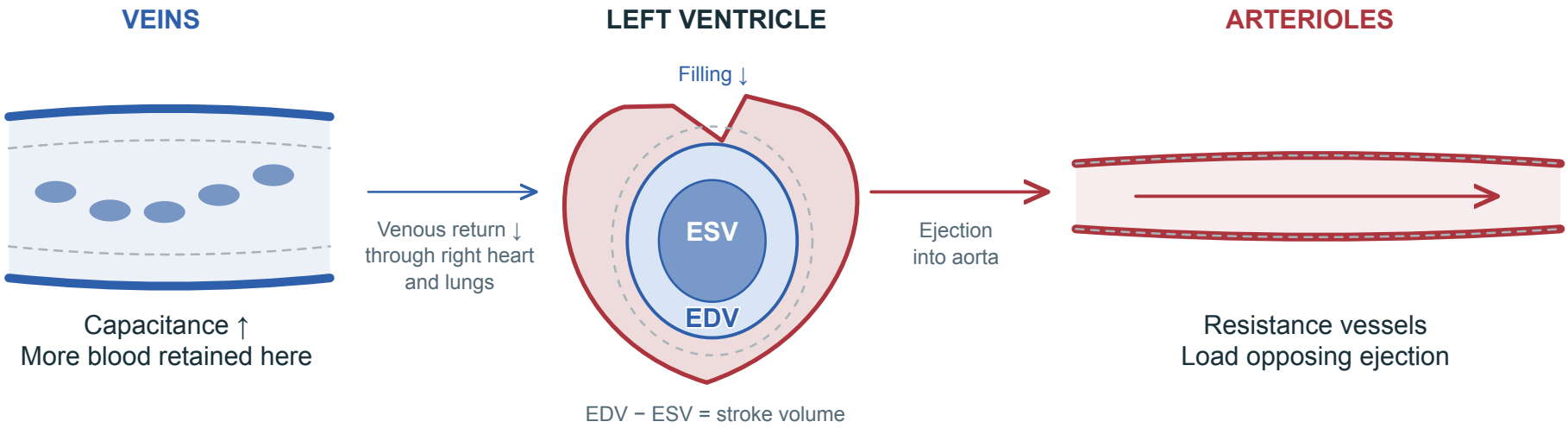
Clinical need	Formulation	Exposure and implication
Acute angina relief	Sublingual NTG tablet / spray	Acts within minutes; avoids initial hepatic first pass
Sustained prevention	Transdermal NTG; oral ISDN / ISMN	Slower or prolonged delivery; not a substitute for rescue
Rapid monitored adjustment	IV NTG infusion	Selected acute ischemia, congestion or BP control

KEY RELATIONSHIP Match the formulation’s onset, duration, and adjustability to rescue, prevention, or IV titration.

Notes

TARGET → ACTION → TISSUE EFFECT → USES AND OUTCOMES

Nitrates relieve angina mainly by lowering preload

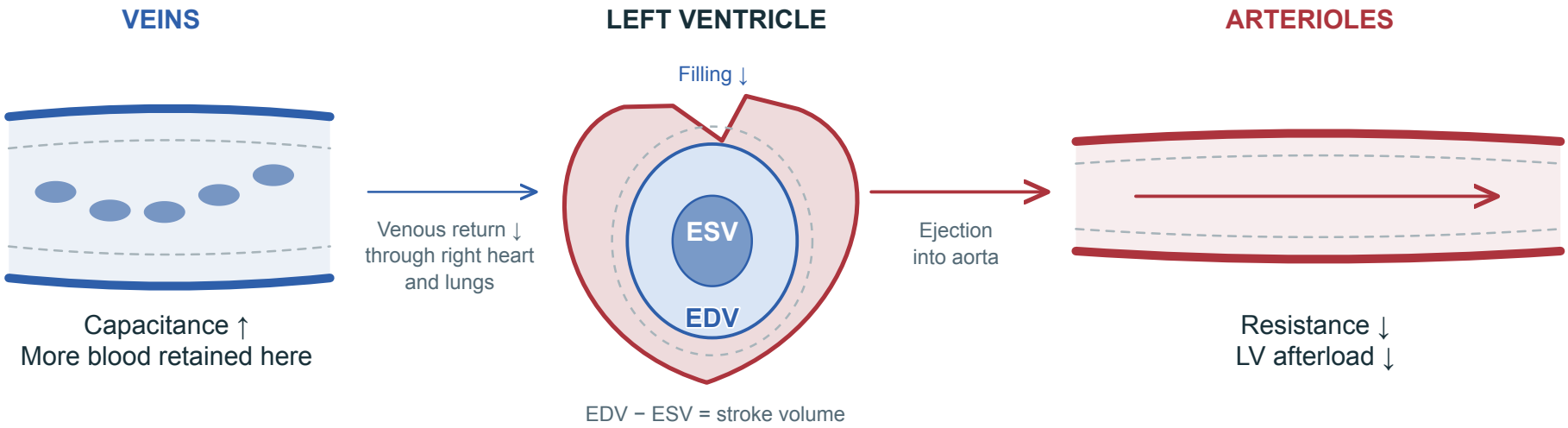


KEY RELATIONSHIP Bioactivation → NO–sGC–cGMP → venous dilation → preload and myocardial O_2 demand ↓.

Notes

TISSUE EFFECT → BODY RESPONSE

Higher nitrate exposure adds arterial unloading



KEY RELATIONSHIP Venous effects predominate at usual exposure; increasing exposure can also lower SVR and afterload.

Notes

TISSUE EFFECT → USES AND OUTCOMES

Nitrates for ischemic heart disease: start with oxygen balance

O_2 DEMAND

Heart rate

Contractility

Wall stress: preload + afterload

Resting work
Lower oxygen requirement

Balance at rest

Supply meets resting demand

O_2 SUPPLY

Coronary

Flow × arterial O_2 content

Flow reserve · perfusion pressure

Diastolic time · vessel patency

Flow matches resting work
Reserve is available

Nitrates reduce demand mainly through preload; coronary spasm relief is a separate supply benefit.

KEY RELATIONSHIP Normal coronary flow can meet resting demand and increase when cardiac work rises.

Notes

TISSUE EFFECT → BODY RESPONSE

Normal exertion raises demand and recruits coronary flow

O_2 DEMAND

Heart rate

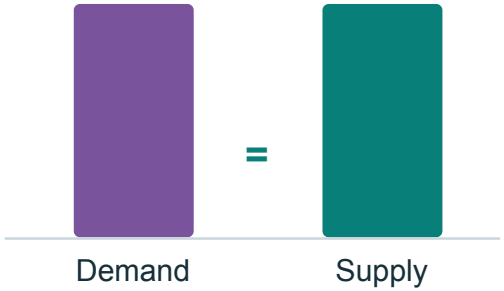
Contractility

Wall stress: preload + afterload

Exertion raises cardiac work

HR + contractility ↑

Normal exertion



O_2 SUPPLY

Coronary

Flow × arterial O_2 content

Flow reserve · perfusion pressure

Diastolic time · vessel patency

Metabolic vasodilation

Flow rises to meet demand

Normal response: supply catches up to demand

Nitrates reduce demand mainly through preload; coronary spasm relief is a separate supply benefit.

KEY RELATIONSHIP

In a normal circulation, metabolic vasodilation increases flow to match the heart’s work.

Notes

TISSUE EFFECT → USES AND OUTCOMES

A fixed stenosis limits the increase in oxygen supply

O_2 DEMAND

Heart rate

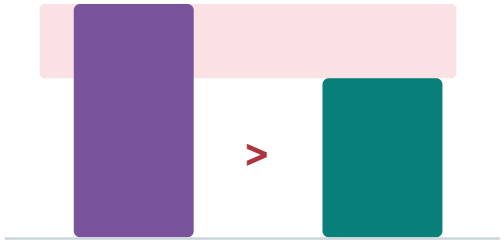
Contractility

Wall stress: preload + afterload

Exertion raises cardiac work

HR + contractility ↑

Exertion + fixed stenosis



Demand Supply

O_2 deficit → ischemia

O_2 SUPPLY

Coronary

Flow × arterial O_2 content

Flow reserve · perfusion pressure

Diastolic time · vessel patency

Limited flow reserve

Supply cannot meet exertion

Nitrates reduce demand mainly through preload; coronary spasm relief is a separate supply benefit.

KEY RELATIONSHIP

Supply may be adequate at rest but insufficient for exertional demand.

Notes

TISSUE EFFECT → USES AND OUTCOMES

Nitrates reduce demand mainly by lowering preload

O_2 DEMAND

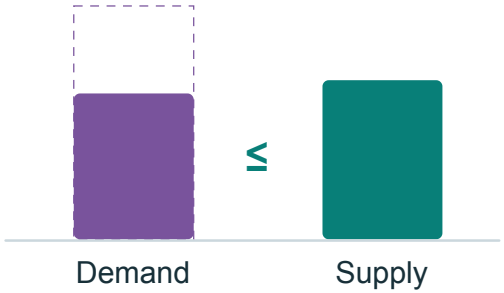
Heart rate

Contractility

Wall stress: preload + afterload

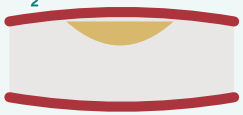
Venodilation → preload ↓
LV radius / wall stress ↓
No direct slowing of HR

Stenosis + nitrate



Lower demand fits the available supply

O_2 SUPPLY



Coronary

Flow × arterial O_2 content

Flow reserve · perfusion pressure

Diastolic time · vessel patency

Epicardial dilation / spasm relief
Fixed plaque remains

Nitrates reduce demand mainly through preload; coronary spasm relief is a separate supply benefit.

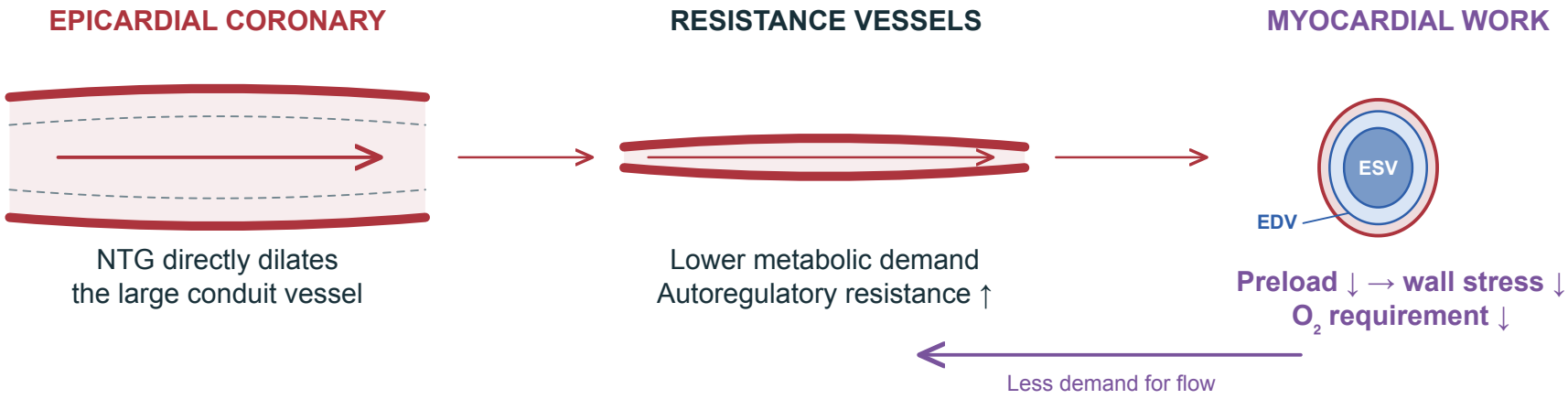
KEY RELATIONSHIP

Venodilation → less LV filling and wall stress → lower myocardial O_2 demand.

Notes

TISSUE EFFECT → USES AND OUTCOMES

Epicardial dilation can coexist with lower absolute flow



Observed: vessel volume ↑ · microvascular resistance +8.0% · absolute flow −13.3%

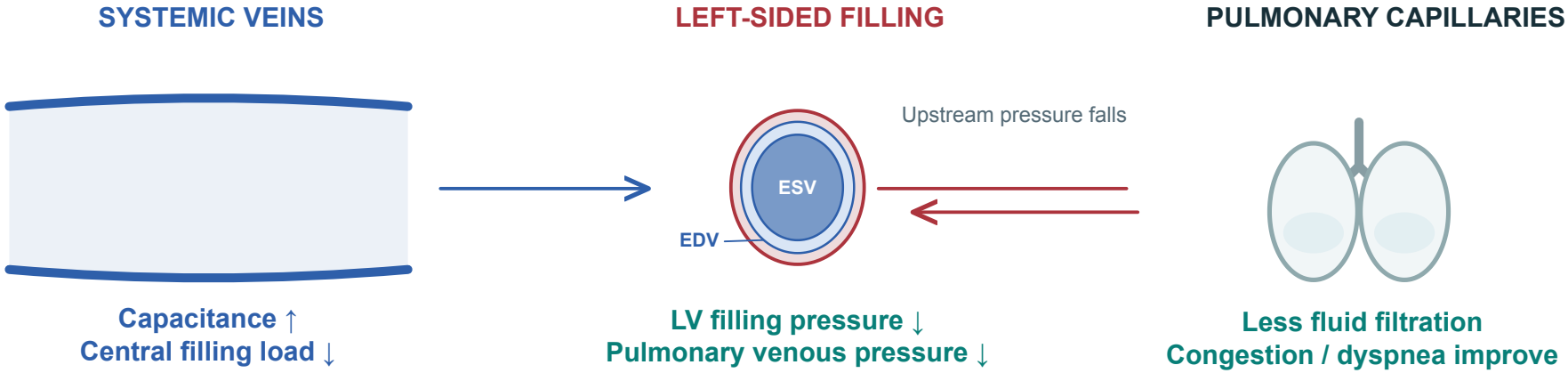
KEY RELATIONSHIP

Preload and O_2 demand fall; demand-driven autoregulation can reduce the flow required.

Notes

TISSUE EFFECT → USES AND OUTCOMES → SAFETY

Lower filling pressure can rapidly relieve pulmonary edema



Rapid pressure relief; adjunct to decongestion when BP permits—not direct removal of fluid.

KEY RELATIONSHIP

Venous unloading lowers pulmonary capillary pressure; greater exposure also reduces afterload.

Notes

BODY RESPONSE → SAFETY

Nitrate adverse effects follow vasodilation and exposure

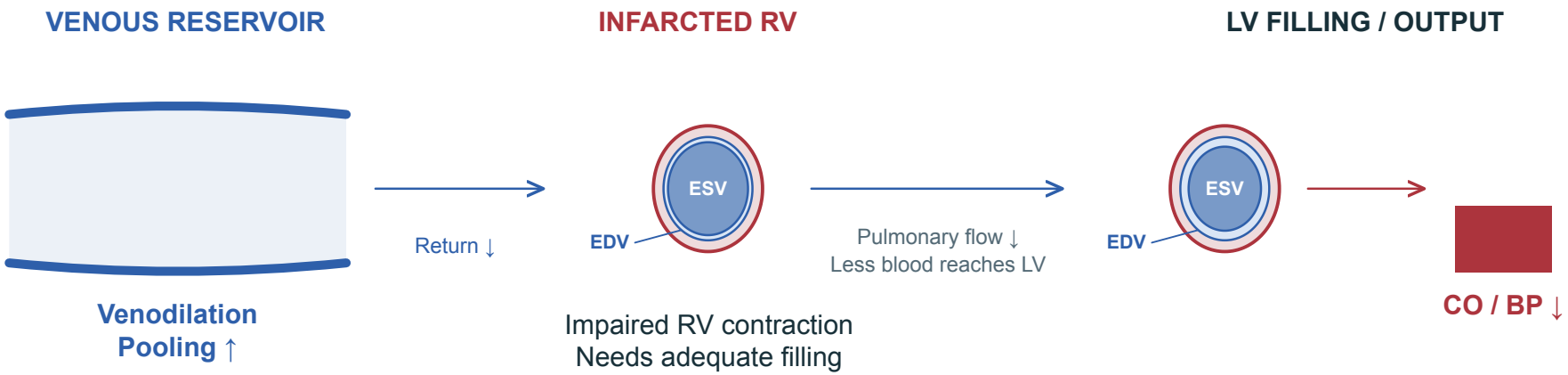
Adverse effect / setting	Why it happens	Teaching implication
Headache / flushing	Vascular dilation	Common dose-limiting symptoms
Orthostasis / syncope	Venous pooling and reduced pressure	Greater risk with volume depletion
Reflex tachycardia	Baroreflex response to falling BP	May offset the O_2-demand benefit
Severe hypotension	RV infarction / preload dependence; PDE-5 or riociguat interaction	Avoid these unsafe settings
Methemoglobinemia (rare)	High exposure can impair hemoglobin O_2 carriage	A distinct toxicity, beyond vasodilation

KEY RELATIONSHIP Headache, flushing, hypotension and reflex tachycardia are extensions of the mechanism.

Notes

TISSUE EFFECT → BODY RESPONSE → SAFETY

Why nitrates are avoided in right ventricular infarction



RV infarction + reduced venous return → less LV filling → potentially profound hypotension.

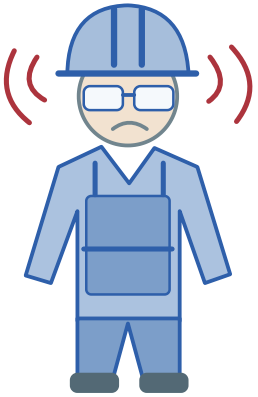
KEY RELATIONSHIP

An injured RV may depend on filling pressure to maintain pulmonary flow and LV preload.

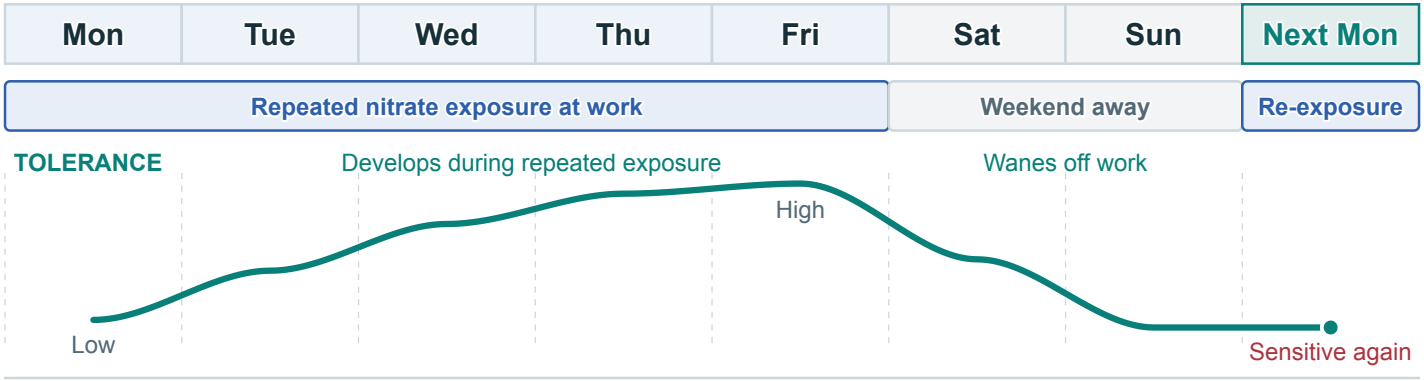
Notes

BODY RESPONSE → SAFETY → PHARMACOKINETICS

Dynamite factory workers and “Monday disease”



Dynamite factory worker
NTG absorbed at work



MONDAY
Headache, dizziness
± reflex tachycardia

DURING THE WEEK
Symptoms fade
despite continued exposure

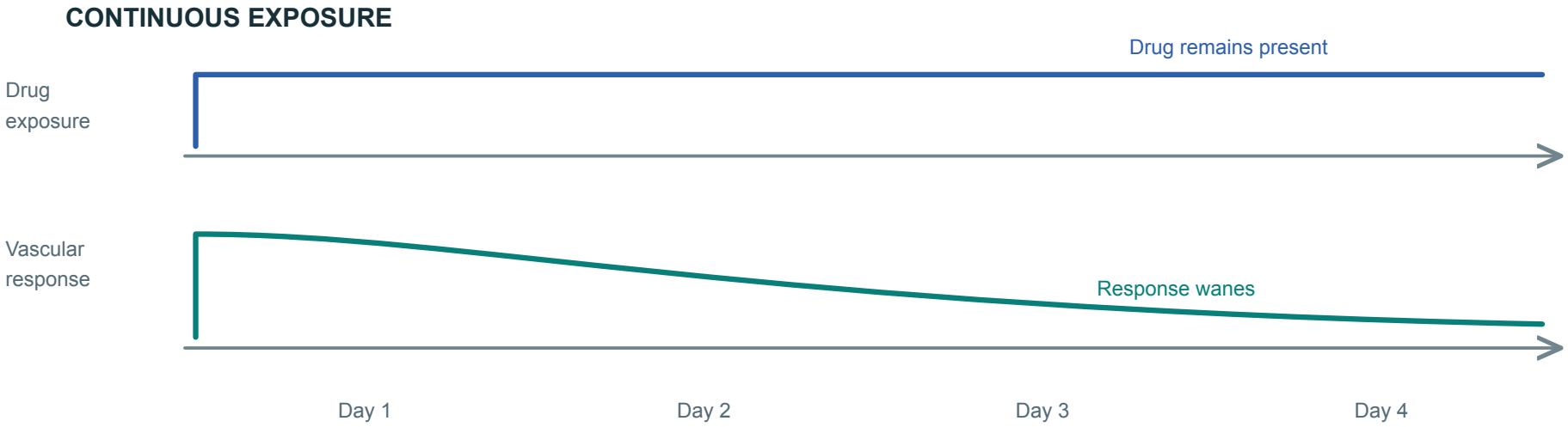
NEXT MONDAY
Symptoms return
when exposure resumes

KEY RELATIONSHIP Tolerance = less response to the same exposure; time away allows sensitivity to return.

Notes

BODY RESPONSE → SAFETY → PHARMACOKINETICS

A constant nitrate exposure does not guarantee a constant response

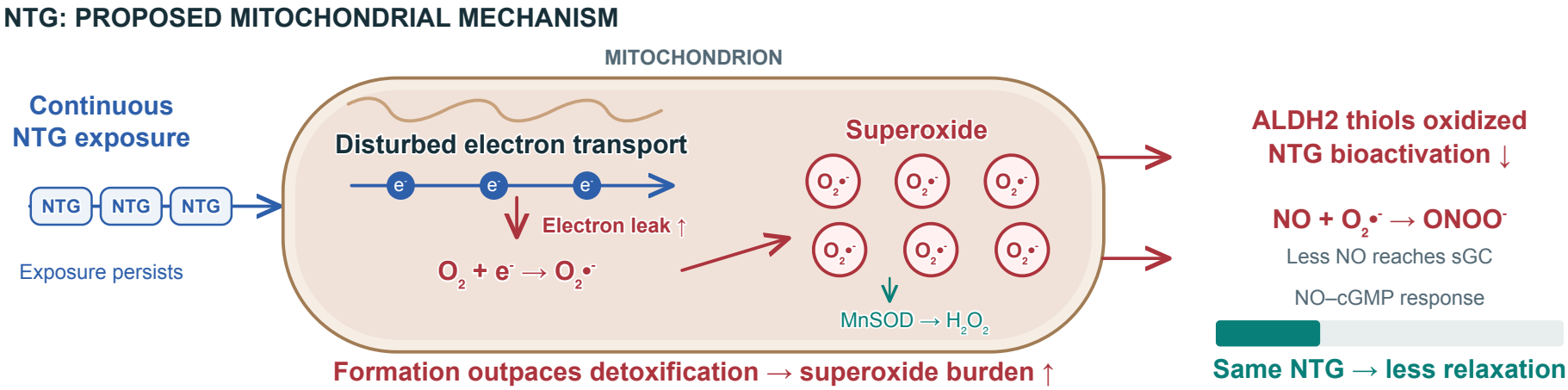


KEY RELATIONSHIP Tolerance reflects reduced responsiveness plus counter-regulatory mechanisms.

Notes

ACTION → BODY RESPONSE → SAFETY → PHARMACOKINETICS

NTG tolerance: a proposed mitochondrial mechanism



ISDN / ISMN: largely ALDH2-independent, yet tolerance can still occur.

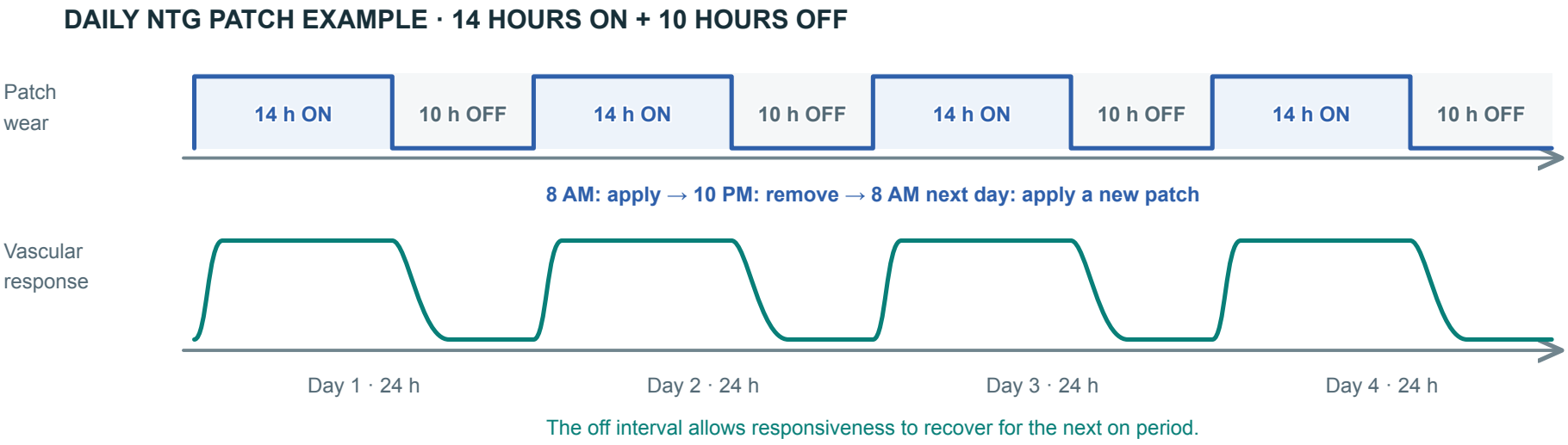
Other contributors: altered vascular responsiveness + compensatory Na^+ / water retention.

KEY RELATIONSHIP Tolerance can reflect impaired bioactivation, altered vascular signaling, and the body's compensation for vasodilation.

Notes

SAFETY → PHARMACOKINETICS

NTG patches: 12–14 hours on, 10–12 hours off

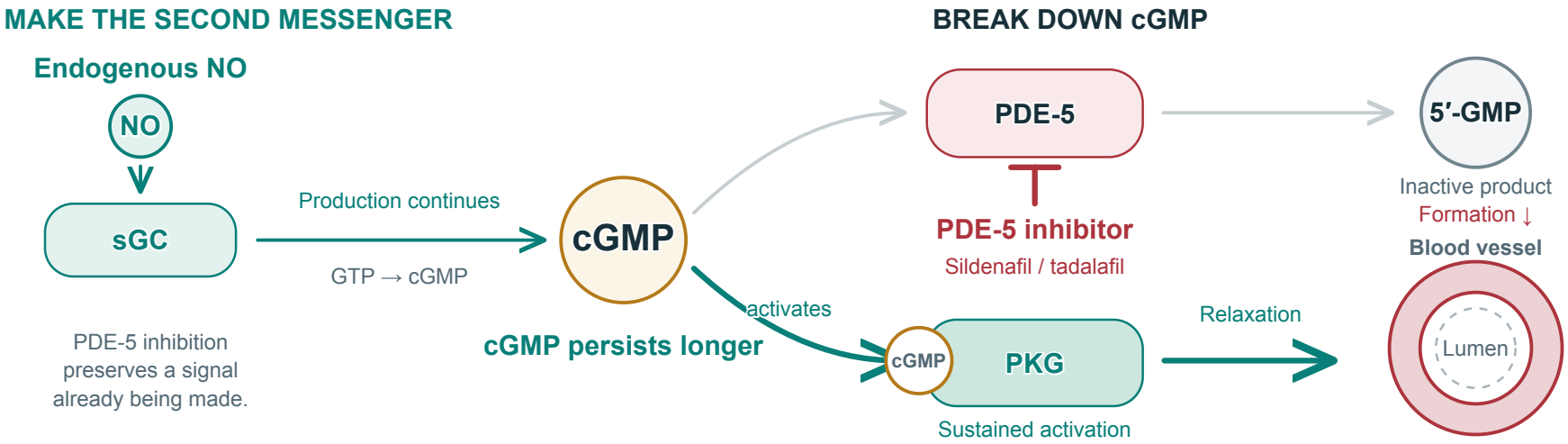


KEY RELATIONSHIP Schedule the off interval when angina is least likely; oral nitrate schedules are formulation-specific.

Notes

TARGET → ACTION

PDE-5 inhibitors preserve cGMP signaling



Slower cGMP breakdown prolongs PKG signaling and smooth-muscle relaxation.

KEY RELATIONSHIP

Sildenafil / tadalafil: PDE-5 inhibition → cGMP breakdown ↓; selected uses include ED and PAH.

Notes

USES AND OUTCOMES → SAFETY

PDE-5 inhibitors: drugs, uses and adverse effects

Drugs and therapeutic uses

Drug	Uses
Sildenafil	ED · PAH
Tadalafil	ED · PAH · BPH symptoms
Vardenafil	ED
Avanafil	ED

ED: erectile dysfunction
PAH: pulmonary arterial hypertension
BPH: benign prostatic hyperplasia

Adverse effects

Common: headache, flushing, nasal congestion, dyspepsia

BP lowering: dizziness / symptomatic hypotension

Sildenafil: transient color-vision changes

Tadalafil: back pain / myalgia

Vardenafil: QT prolongation precaution

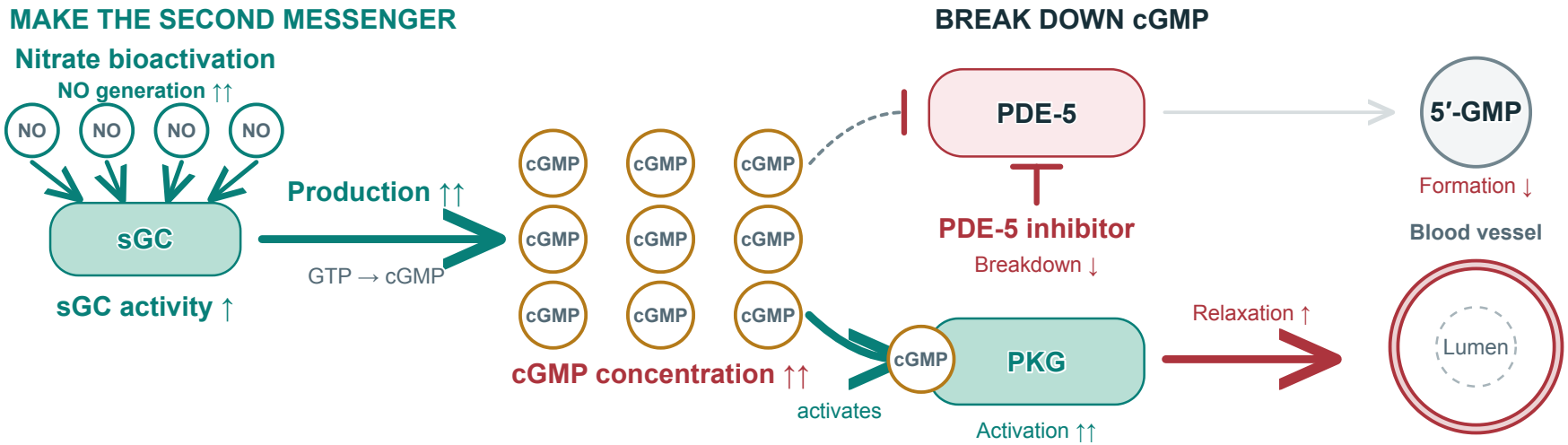
Rare, serious: priapism; sudden vision or hearing loss reported

KEY RELATIONSHIP All four treat ED; sildenafil and tadalafil also treat PAH, and tadalafil treats BPH symptoms.

Notes

ACTION → TISSUE EFFECT → SAFETY

Do not combine nitrates with PDE-5 inhibitors

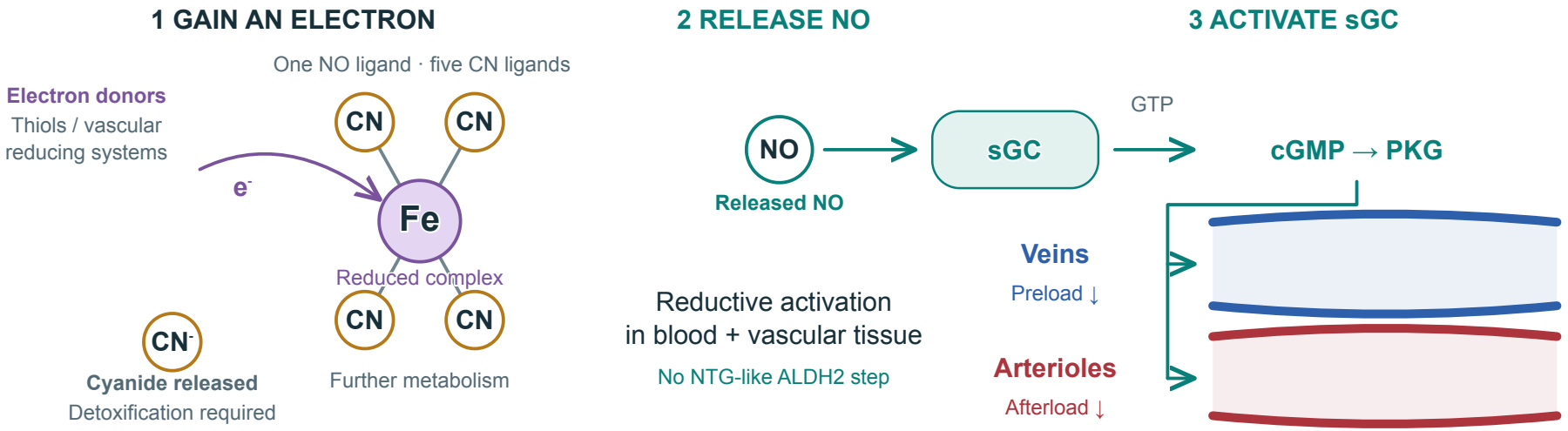


KEY RELATIONSHIP Nitrate-derived NO ↑ → cGMP production ↑; PDE-5 inhibition → breakdown ↓. Together: cGMP rises much higher.

Notes

TARGET → ACTION → TISSUE EFFECT → PHARMACOKINETICS

How nitroprusside releases its NO ligand



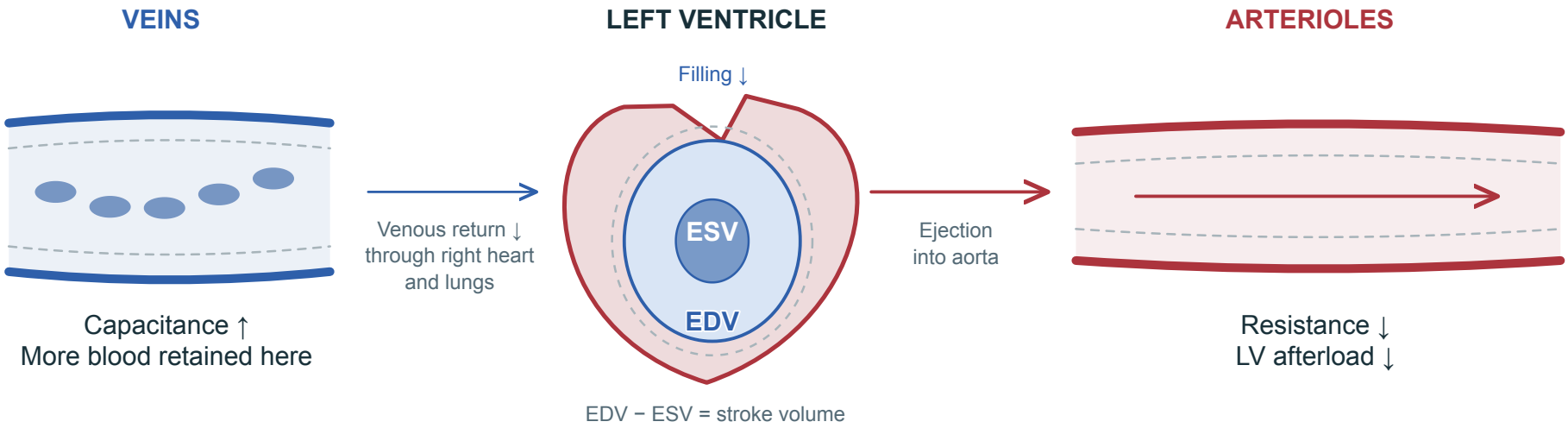
Released NO activates the shared pathway; veins and arterioles both relax.

KEY RELATIONSHIP Electron gain → cyanide loss → NO release → sGC–cGMP–PKG → preload and afterload ↓.

Notes

TISSUE EFFECT → BODY RESPONSE → USES AND OUTCOMES

Reduce filling pressure and ejection resistance together

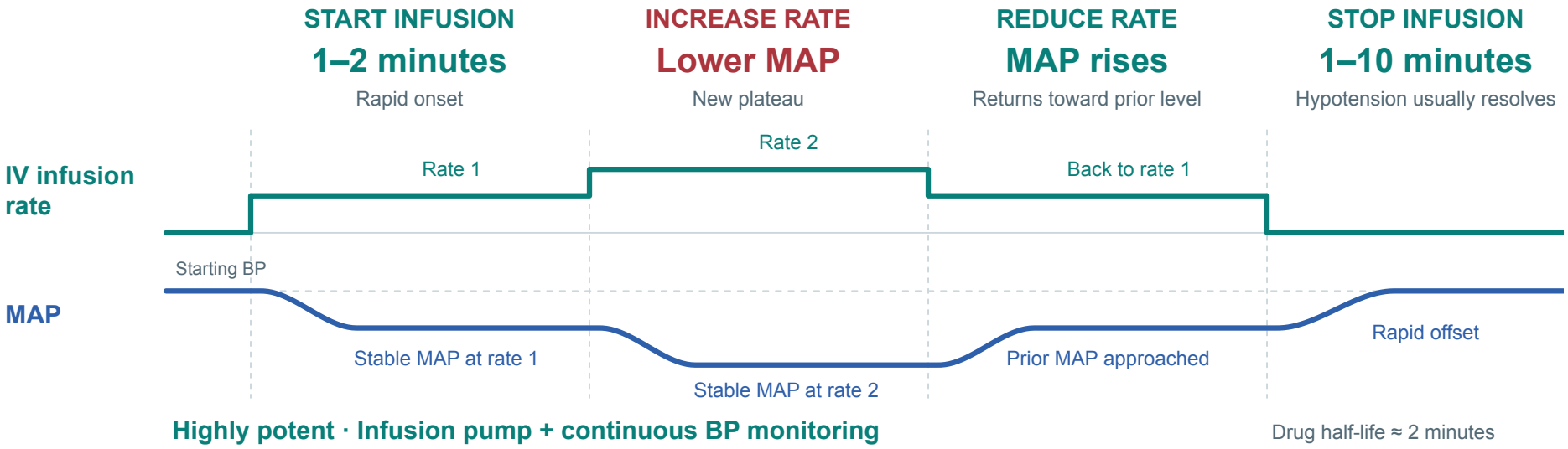


KEY RELATIONSHIP Preload ↓ + afterload ↓: stroke volume may improve when the ventricle is afterload-sensitive.

Notes

USES AND OUTCOMES → SAFETY → PHARMACOKINETICS

Nitroprusside: BP rapidly follows changes in infusion rate

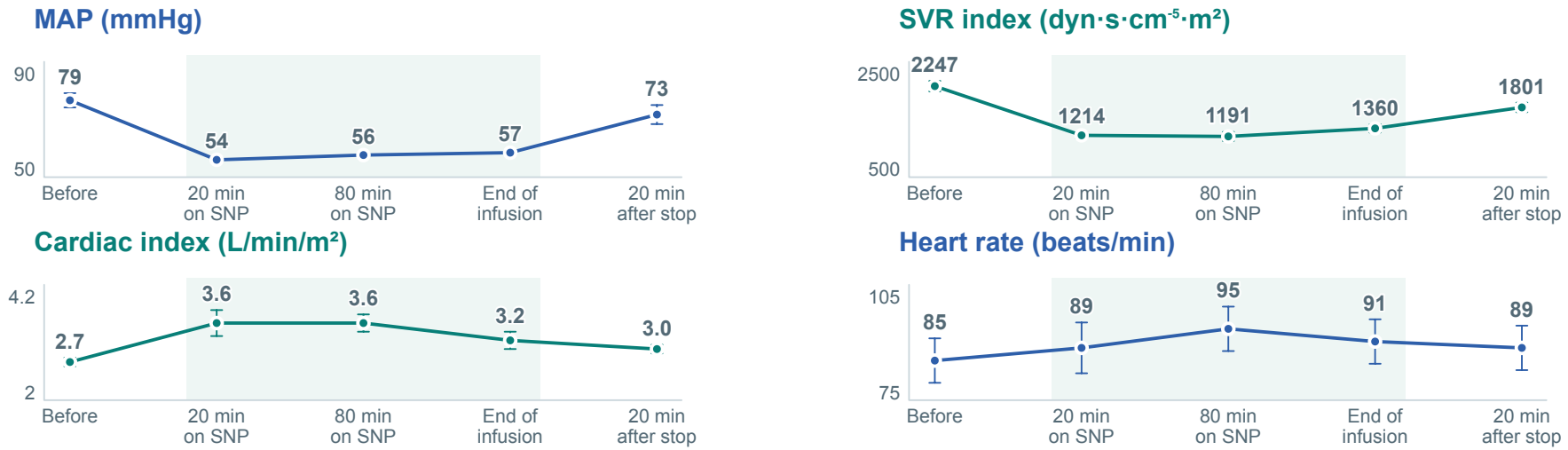


KEY RELATIONSHIP At a constant rate, BP approaches a plateau; changing the rate changes the effect.

Notes

TISSUE EFFECT → BODY RESPONSE

Lower BP can coexist with higher cardiac output



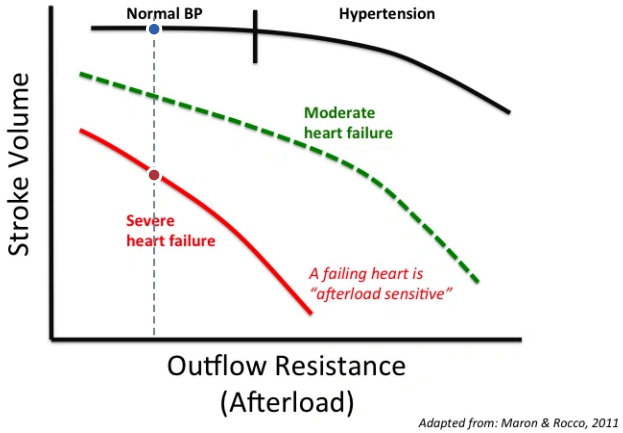
Perioperative observations during spinal surgery under anesthesia

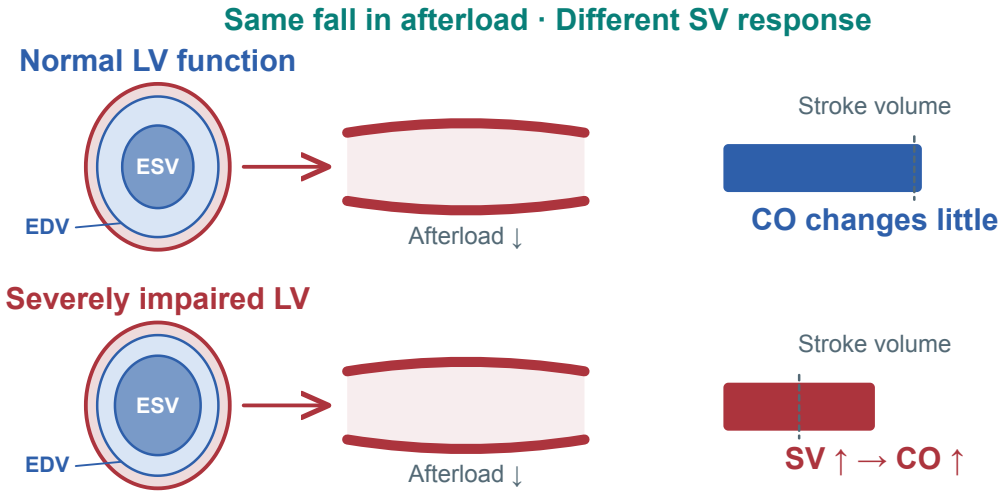
KEY RELATIONSHIP SVR ↓ and MAP ↓, while cardiac index ↑ with a comparatively small change in heart rate.

Notes

TISSUE EFFECT → BODY RESPONSE → USES AND OUTCOMES

The hemodynamic response depends on the starting ventricle





Normal LV: mainly BP ↓ · Failing LV: a larger gain in forward flow

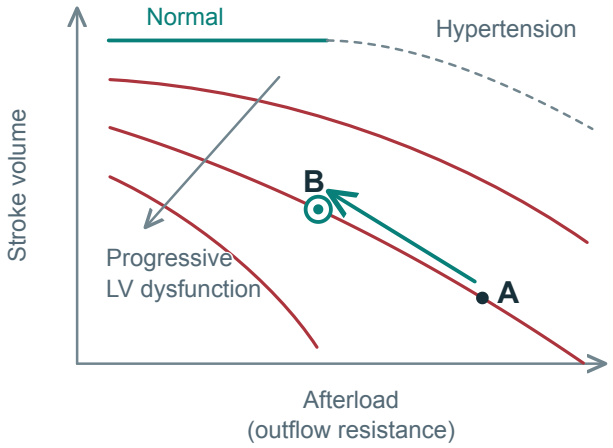
KEY RELATIONSHIP Normal LV: mainly BP ↓. Severely impaired LV: afterload reduction can substantially increase SV and CO.

Notes

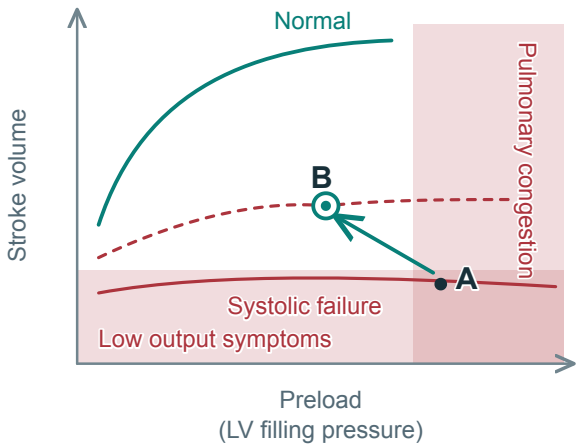
TISSUE EFFECT → BODY RESPONSE → USES AND OUTCOMES

Nitroprusside can reduce pulmonary congestion and increase forward flow

Afterload and stroke volume



Filling pressure and output



Venous dilation + improved LV emptying

LV filling pressure ↓

Pulmonary venous pressure ↓

Less pulmonary congestion

Arteriolar dilation

Afterload ↓ → ejection ↑

Stroke volume / CO ↑

More forward flow

KEY RELATIONSHIP Lower filling pressure relieves pulmonary congestion; lower afterload improves forward flow.

Notes

TISSUE EFFECT → USES AND OUTCOMES → SAFETY → PHARMACOKINETICS

Nitroprusside is effective when both loads need rapid control

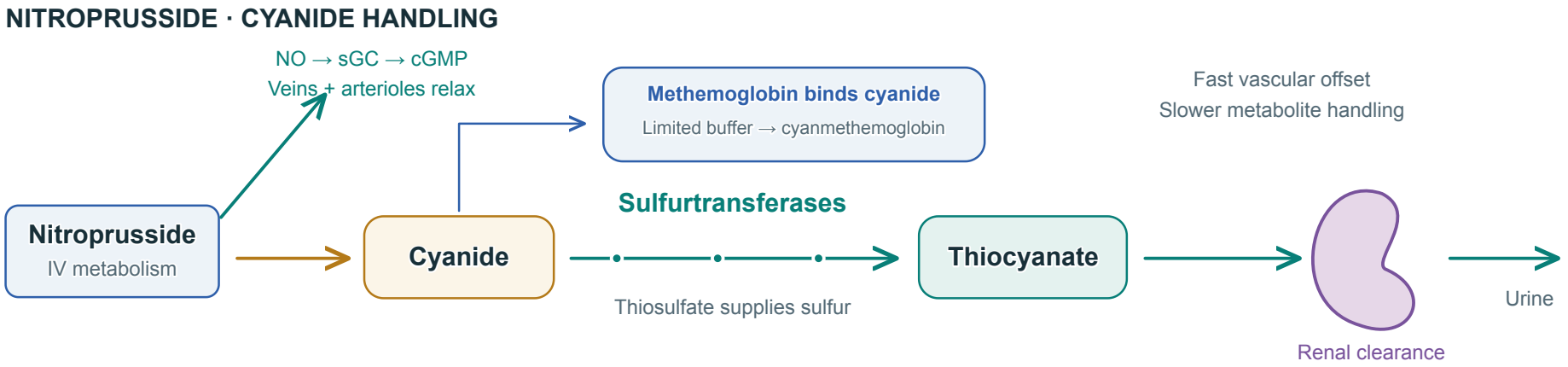
Clinical setting	Why it can help	Why use is limited
Selected hypertensive emergencies	Very rapid BP reduction with infusion titration	Continuous BP monitoring; overshoot can cause ischemia
Acute HF with high SVR and adequate BP	Afterload + filling pressure ↓; forward SV may rise	Avoid low-SVR / hypotensive HF; no proven survival benefit
Controlled surgical hypotension	Rapid adjustment of vascular tone	Requires tightly monitored anesthesia / infusion care
Aortic dissection, if an additional vasodilator is needed	Lowers arterial pressure after impulse control	Control HR / contractile impulse first; avoid reflex shear

KEY RELATIONSHIP Rapid, adjustable unloading is useful only while organ perfusion and toxicity remain controlled.

Notes

SAFETY → PHARMACOKINETICS

Cyanide detoxification precedes renal elimination



Buffering, detoxification and renal elimination are distinct processes.

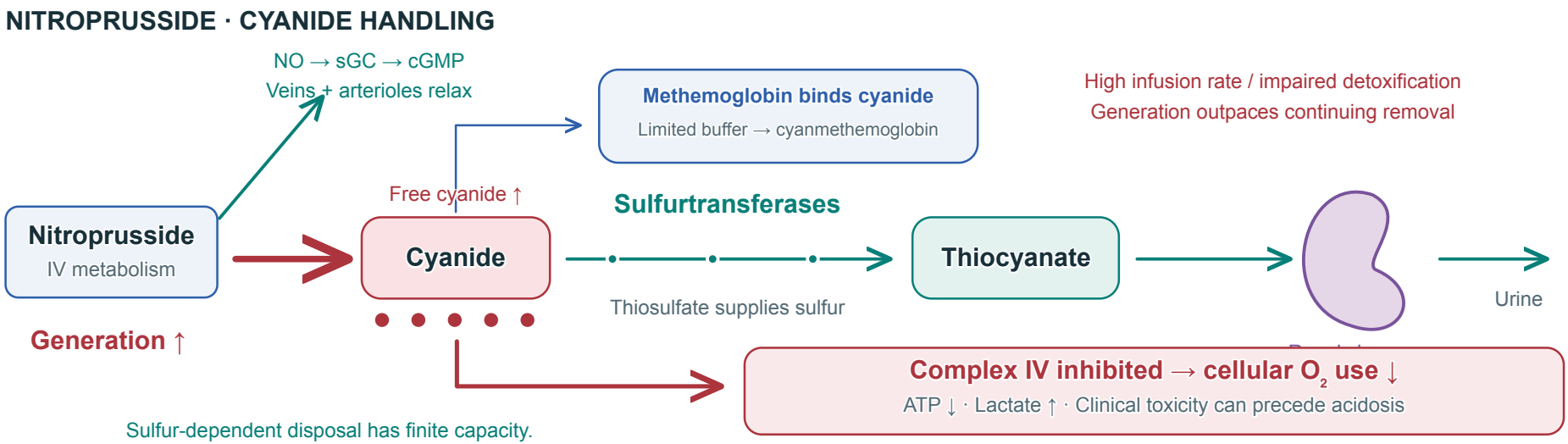
KEY RELATIONSHIP

Cyanide → sulfur-dependent conversion → thiocyanate → renal clearance.

Notes

SAFETY → PHARMACOKINETICS

Cyanide accumulates when generation outruns detoxification

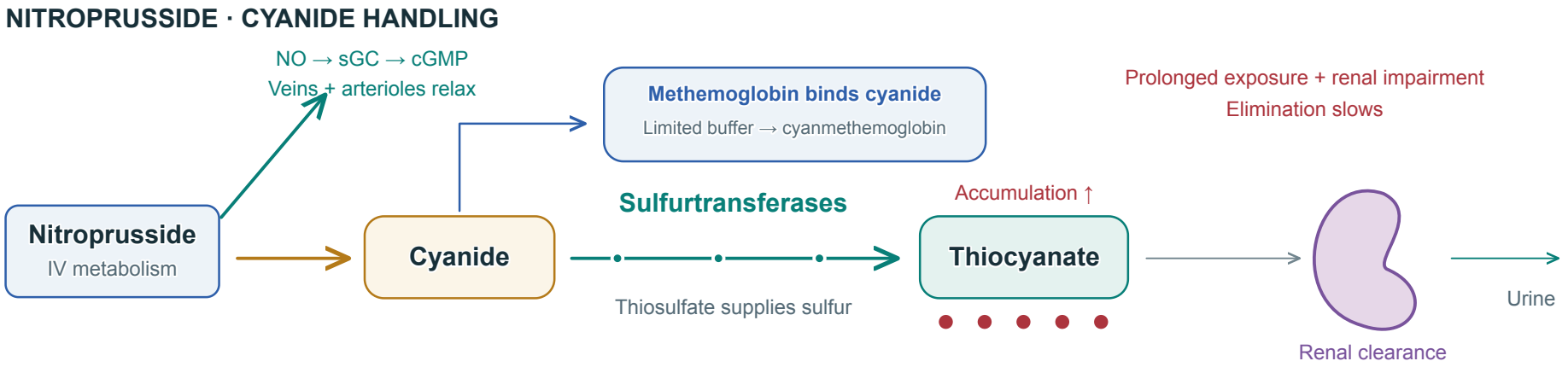


KEY RELATIONSHIP Excess cyanide inhibits mitochondrial complex IV → impaired O_2 use → ATP depletion and lactic acidosis.

Notes

SAFETY → PHARMACOKINETICS

Thiocyanate can accumulate even when cyanide is being converted



Cyanide conversion continues; retained thiocyanate causes neurologic toxicity.

KEY RELATIONSHIP Prolonged exposure + impaired renal elimination → delayed neurologic toxicity.

Notes

SAFETY → PHARMACOKINETICS

Distinguish nitroprusside’s toxicities and vascular adverse effects

Problem	Mechanism	Risk / recognition
Cyanide	Blocks complex IV → cellular O_2 utilization fails	High infusion rate / limited detoxification; confusion, deterioration, lactate ↑
Thiocyanate	Renally cleared metabolite accumulates	Prolonged exposure / CKD; tinnitus, confusion, neurologic toxicity
Methemoglobinemia	Hemoglobin iron oxidized → effective O_2 carriage ↓	High cumulative exposure; cyanosis despite adequate arterial oxygen tension
Excess vasodilation	Perfusion pressure falls	Immediate dose-related hypotension; continuously monitor BP
Increased intracranial pressure (ICP)	Cerebral vasodilation → intracranial blood volume ↑	Cerebral perfusion may fall; particular concern when ICP is already elevated

KEY RELATIONSHIP Separate impaired O_2 use, impaired O_2 carriage, metabolite neurotoxicity, and compromised perfusion.

Notes

SAFETY → PHARMACOKINETICS

Suspected cyanide toxicity requires action before confirmatory testing

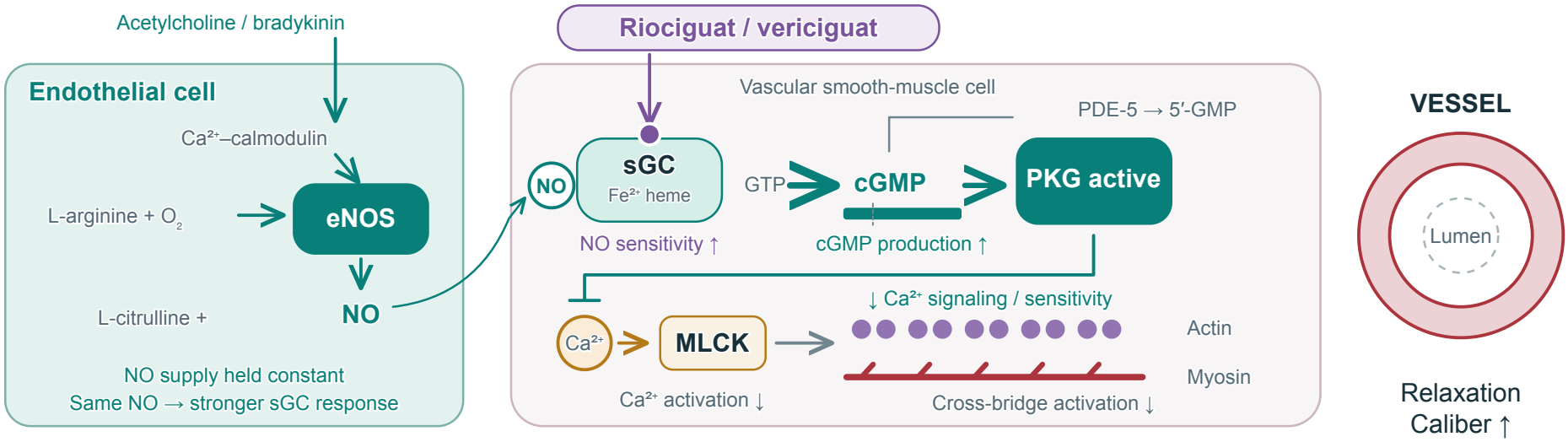
Clinical clue / action	Mechanism or implication
Escalating infusion requirement; new confusion or deterioration	Cyanide may be accumulating; lactic acidosis can appear late
Hydroxocobalamin	Binds cyanide → cyanocobalamin; a specific cyanide antidote
Sodium thiosulfate	Supplies sulfur for cyanide → thiocyanate conversion
Nitrite-based antidote strategy	Creates methemoglobin to bind cyanide; can worsen hypotension / O_2 carriage
Severe thiocyanate toxicity	Different problem: hemodialysis can remove thiocyanate, not cyanide effectively

KEY RELATIONSHIP Stop nitroprusside; support oxygenation and perfusion and obtain urgent toxicology guidance.

Notes

TARGET → ACTION → TISSUE EFFECT

The same NO signal produces more cGMP

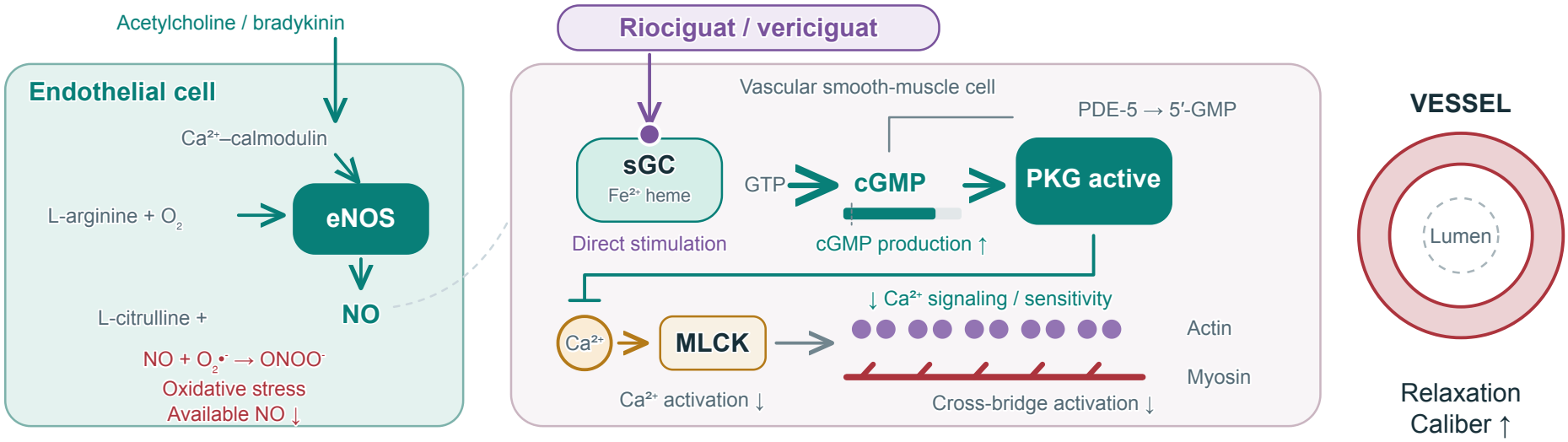


KEY RELATIONSHIP Riociguat and vericiguat enhance sGC sensitivity to NO and directly stimulate the enzyme.

Notes

TARGET → ACTION → TISSUE EFFECT

Direct sGC stimulation increases cGMP when NO is scarce



Stimulators act on reduced-heme sGC; activators target oxidized or heme-free sGC.

KEY RELATIONSHIP Low available NO → weak cGMP signaling; direct stimulation can recover output from reduced-heme sGC.

Notes

USES AND OUTCOMES → SAFETY

A shared target does not imply a shared indication

Agent	Therapeutic use	Important safety / outcome points
Riociguat	Pulmonary arterial hypertension (WHO Group 1).	**Only FDA-approved pulmonary vasodilator for CTEPH.**
	Chronic thromboembolic pulmonary hypertension (CTEPH; WHO group 4): inoperable or persistent / recurrent after surgery.	Hypotension; pregnancy contraindication; avoid nitrates and PDE-5 inhibitors
Vericiguat	Symptomatic chronic HF, EF <45%, after recent HF hospitalization or outpatient IV diuretics.	Hypotension, anemia; pregnancy contraindication; PDE-5 combination not recommended.
	Add-on to guideline-directed medical therapy (GDMT).	**VICTORIA:** reduced the CV-death / HF-hospitalization composite when added to GDMT.

KEY RELATIONSHIP

Riociguat and vericiguat have different evidence-based clinical roles.

Notes

TARGET → ACTION → USES AND OUTCOMES

The Nesiritide Story: A Lesson in Surrogates vs Outcomes

Recombinant BNP → NPR-A / membrane guanylyl cyclase → cGMP → vasodilation

2000	**Nesiritide Study Group** 127 patients	6-hour placebo-controlled trial in acute decompensated HF. **PCWP fell and dyspnea improved.**
2001	**FDA approval** August 10	Short-term IV treatment of acute decompensated HF with dyspnea at rest or minimal activity.
2002	**VMAC published** 489 treated patients	Nesiritide vs IV nitroglycerin vs placebo. At 3 h: PCWP ≈2 mmHg lower than NTG; **no better dyspnea than NTG.**
2003	**Rapid expansion** Through 2004	Medicare billing begins; chronic-HF infusion clinics expand. **2004 U.S. hospital / clinic spending: nearly $400 million.**

KEY RELATIONSHIP

Lower filling pressure and early symptom relief encouraged use before long-term benefit was established.

Notes

USES AND OUTCOMES → SAFETY

Nesiritide's Fall from Grace

2005 — **Safety meta-analyses**

Renal worsening: RR 1.54 (+54%); 5 trials, n = 1,269.
30-day mortality: RR 1.74 (+74%); 3 trials, n = 862.
Mortality signal uncertain: 95% CI 0.97–3.12; P = .059.

2006 — **Medicare changes coverage**

March 2

Chronic-HF treatment no longer covered in any setting.
The acute decompensated-HF indication is unchanged.

2011 — **ASCEND-HF**

7,141 randomized patients

Nesiritide vs placebo: **no 30-day death / HF-readmission benefit.**
Small dyspnea change missed the prespecified significance threshold.
More hypotension; no significant renal or mortality harm.

Today — **U.S. market status**

Natrecor is discontinued.
FDA did not attribute discontinuation to safety or effectiveness.

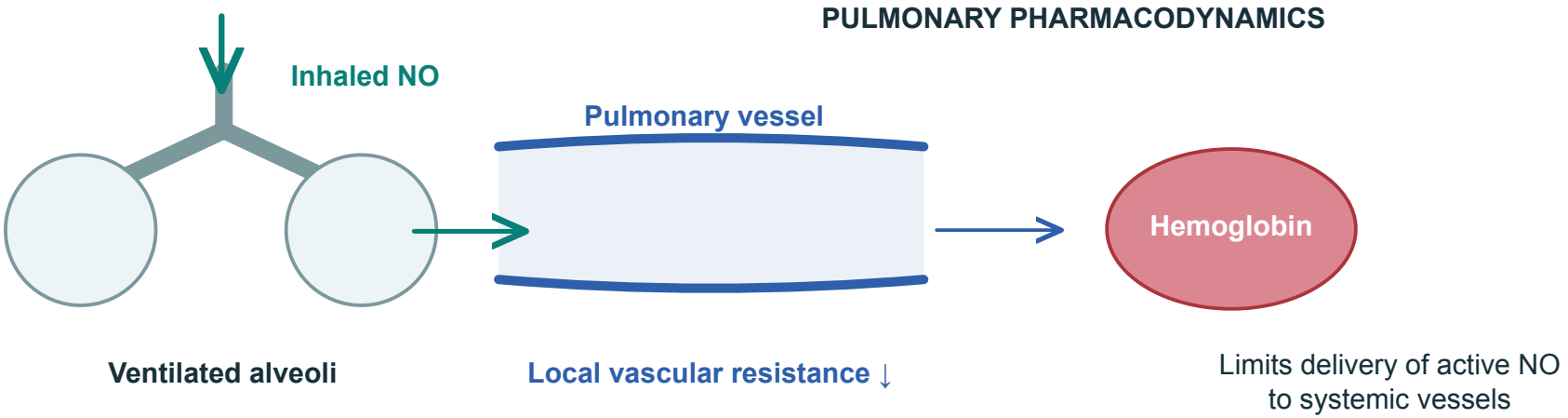
KEY RELATIONSHIP

Improving a surrogate does not establish better outcomes; an early safety signal also needs confirmation.

Notes

TARGET → ACTION → TISSUE EFFECT → BODY RESPONSE

Inhaled NO reaches ventilated lung regions



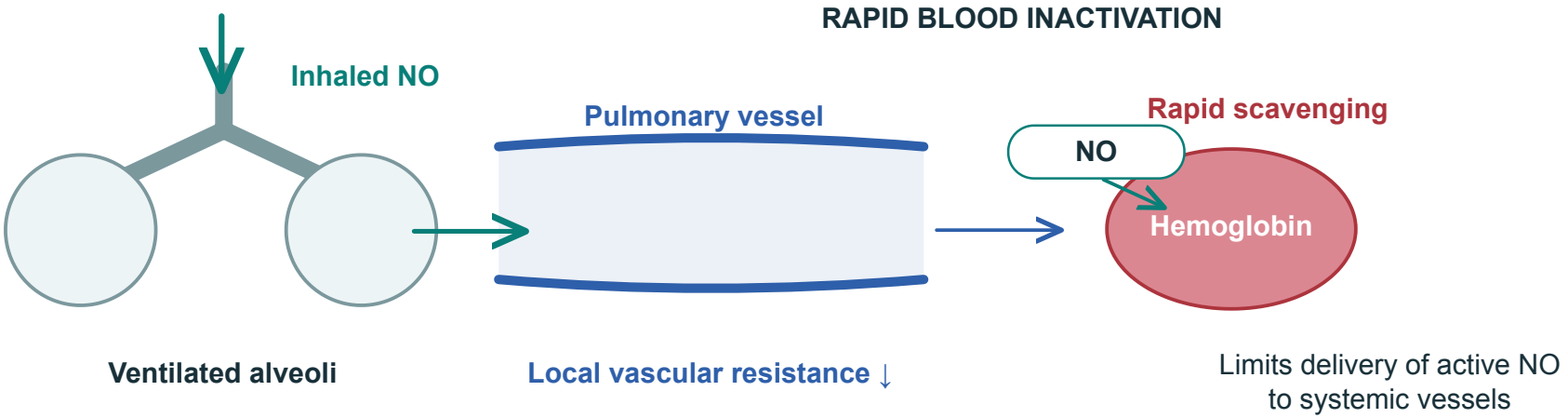
PD: NO → sGC → cGMP → pulmonary relaxation; perfusion favors ventilated alveoli

KEY RELATIONSHIP NO → sGC → cGMP: pulmonary resistance and RV afterload fall; ventilation–perfusion matching can improve.

Notes

TISSUE EFFECT → SAFETY → PHARMACOKINETICS

Hemoglobin limits active NO reaching systemic vessels



PK: inhalation → hemoglobin reaction → methemoglobin + nitrate; nitrate → urine

KEY RELATIONSHIP Rapid onset and short-lived action require continuous inhalation; hemoglobin scavenging limits systemic vasodilation.

Notes

BODY RESPONSE → USES AND OUTCOMES

Inhaled NO: neonatal treatment and selected adult rescue

Approved neonatal use

- **Term / near-term neonates (>34 weeks)** with hypoxic respiratory failure and pulmonary hypertension.
- Includes **persistent pulmonary hypertension of the newborn (PPHN)**.
- Improves oxygenation and reduces the need for **ECMO**, alongside ventilatory support.

Selected adult uses · off-label

- Acute pulmonary hypertension / **RV failure**, including perioperative support.
- Temporary rescue for **refractory hypoxemia**.
- **ARDS:** oxygenation may improve transiently; no established survival benefit. Not routine treatment.

KEY RELATIONSHIP Lower pulmonary resistance can improve oxygenation and unload the RV; clinical benefit depends on the setting.

Notes

SAFETY → PHARMACOKINETICS

Pulmonary selectivity does not eliminate toxicity

Exposure-related adverse effects

- **Methemoglobinemia:** oxidized hemoglobin carries less O_2 → check blood methemoglobin.
- **NO_2 formation:** NO reacts with O_2 → airway / lung injury; monitor inspired NO and NO_2.
- **Hypotension;** pulmonary edema can worsen with **LV dysfunction**.

Withdrawal and patient selection

- **Abrupt withdrawal:** rebound pulmonary hypertension and hypoxemia → wean gradually.
- **Contraindicated** in neonates who depend on right-to-left shunting for systemic blood flow.
- Monitor oxygenation and hemodynamics; maintain a reliable gas supply.

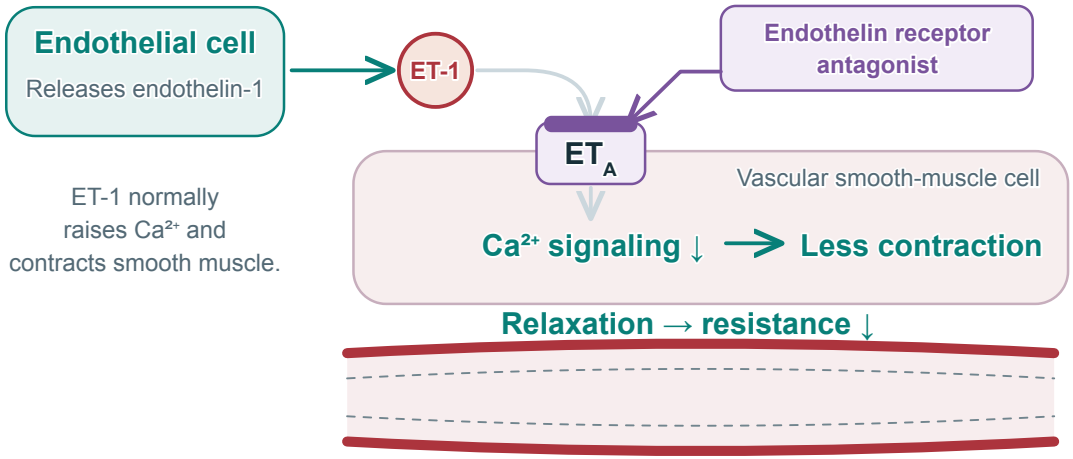
KEY RELATIONSHIP Monitor oxygenation, methemoglobin and delivered gases; wean gradually to avoid rebound pulmonary hypertension.

Notes

TARGET → ACTION → TISSUE EFFECT → USES AND OUTCOMES → SAFETY

Endothelin receptor antagonists reduce vasoconstrictor tone

Endothelin-1 is a local vasoconstrictor



ET-1 normally raises Ca^{2+} and contracts smooth muscle.

Oral antagonists

Pulmonary arterial hypertension (PAH)

Ambrisentan — ET_A selective

Bosentan / macitentan — ET_A + ET_B

Pulmonary resistance ↓ → right-ventricular load ↓

Systemic hypertension: aprocitentan

Add-on when other drugs do not control BP

Important adverse effects

Embryo-fetal toxicity — avoid in pregnancy

Edema / fluid retention; anemia

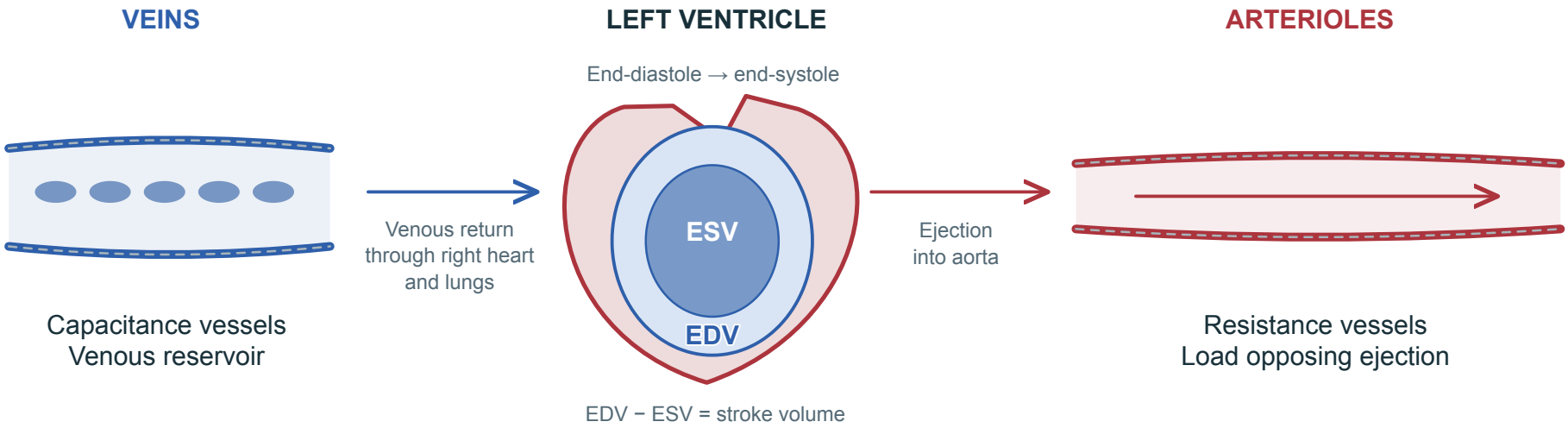
Bosentan: liver toxicity → monthly liver tests

KEY RELATIONSHIP Block endothelin signaling → less smooth-muscle contraction → lower vascular resistance.

Notes

TARGET → ACTION

Hydralazine: a direct arteriolar vasodilator

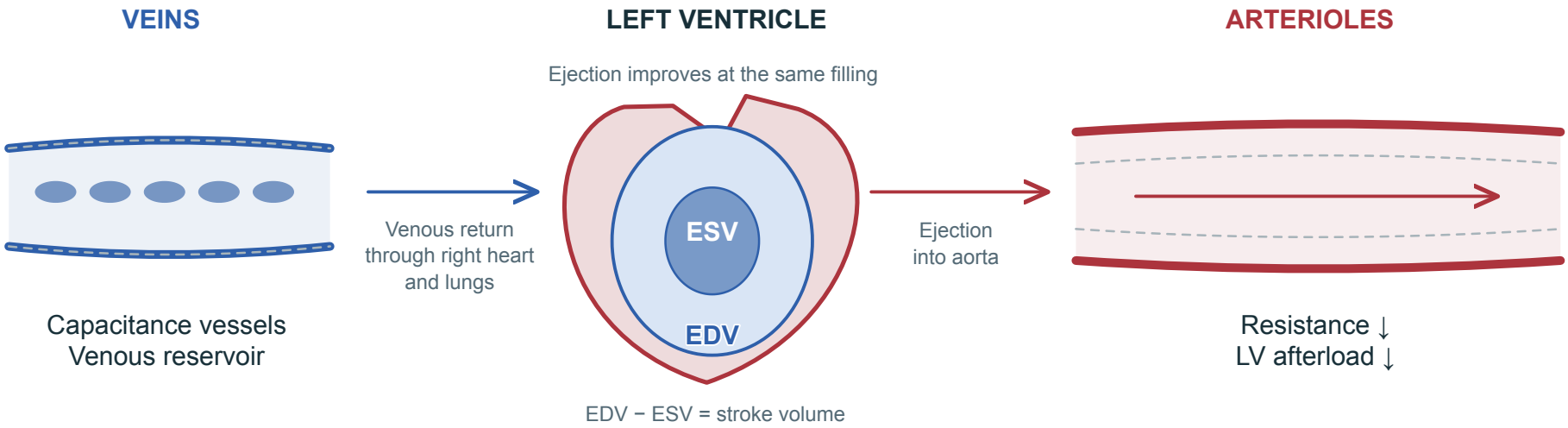


KEY RELATIONSHIP Hydralazine’s arteriolar effect is established; a single precise molecular target is not.

Notes

TISSUE EFFECT

Arterioles relax while the venous reservoir is relatively spared

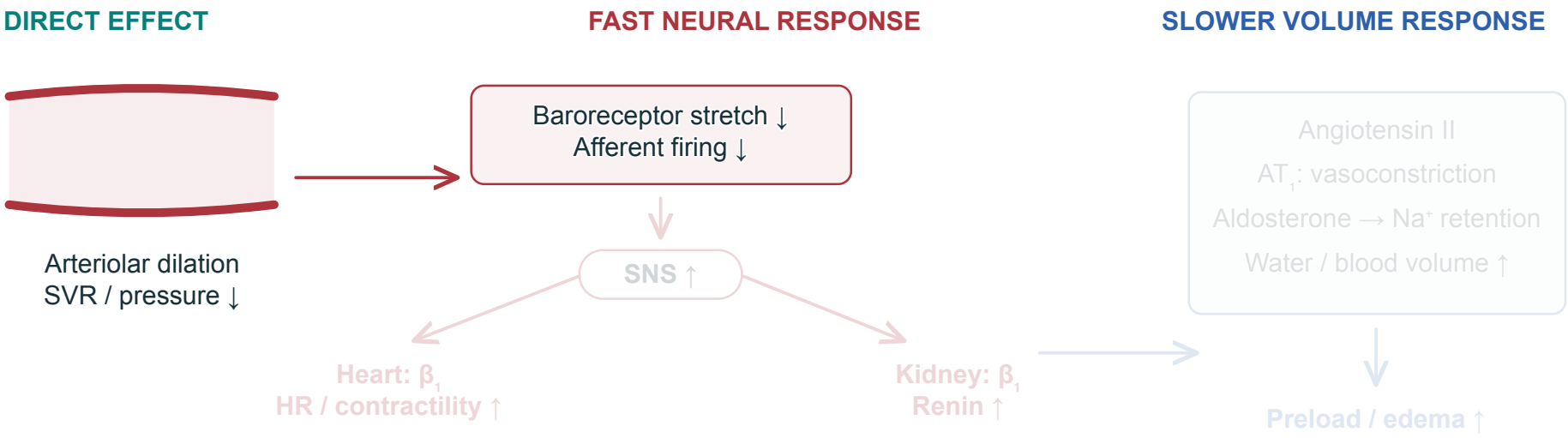


KEY RELATIONSHIP SVR / afterload ↓; preload does not fall directly as it does with a venodilator.

Notes

TISSUE EFFECT → BODY RESPONSE

The drug lowers pressure before compensation develops



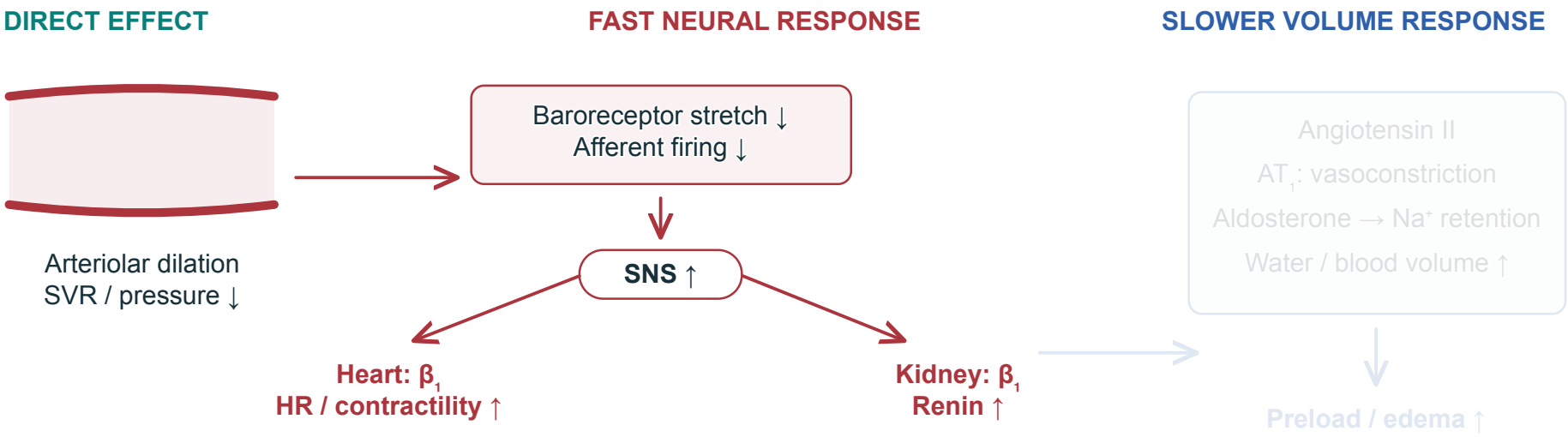
Follow the timing: direct vascular change → fast neural response → slower renal / volume response

KEY RELATIONSHIP Arteriolar relaxation reduces SVR; reduced stretch is the trigger for the reflex.

Notes

BODY RESPONSE → SAFETY

Less baroreceptor firing increases sympathetic output



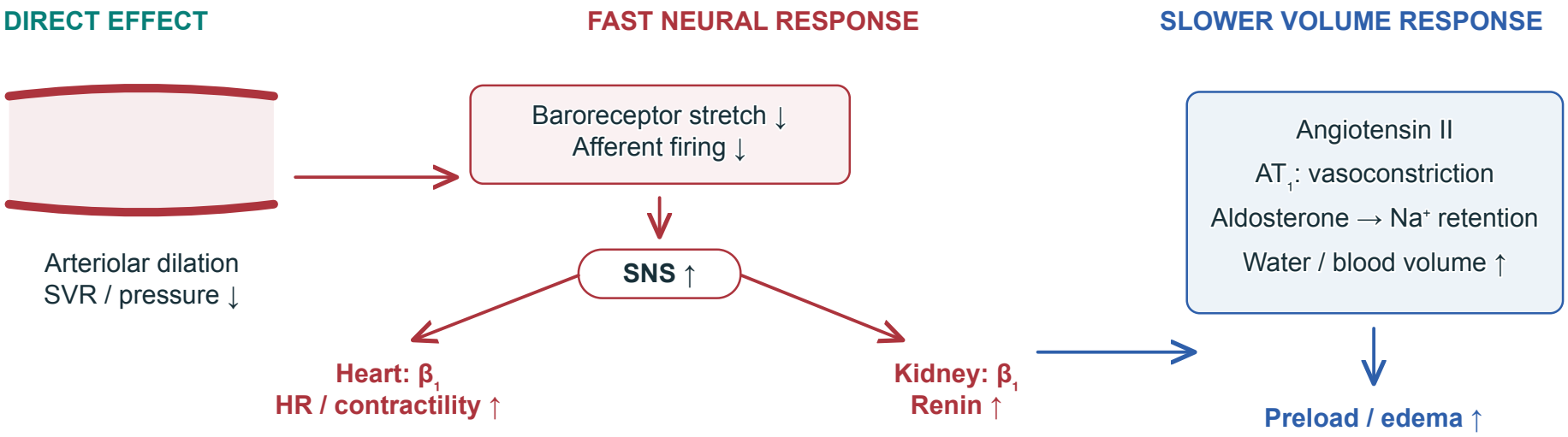
Heart and juxtaglomerular β_1 responses are both part of compensation

KEY RELATIONSHIP β_1 stimulation raises heart rate / contractility and stimulates renin release.

Notes

BODY RESPONSE → SAFETY

Renal and hormonal responses restore volume and resistance



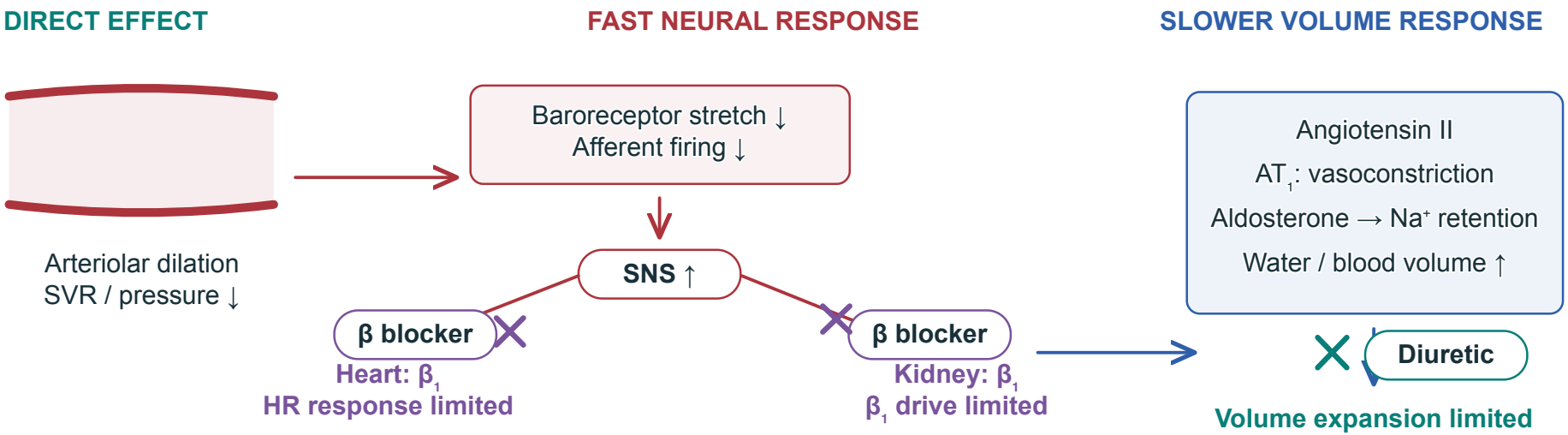
Vasoconstrictor feedback and volume retention are related but distinct responses

KEY RELATIONSHIP Angiotensin II opposes dilation; sodium / water retention raises preload and promotes edema.

Notes

BODY RESPONSE → USES AND OUTCOMES → SAFETY

Match the companion drug to the response



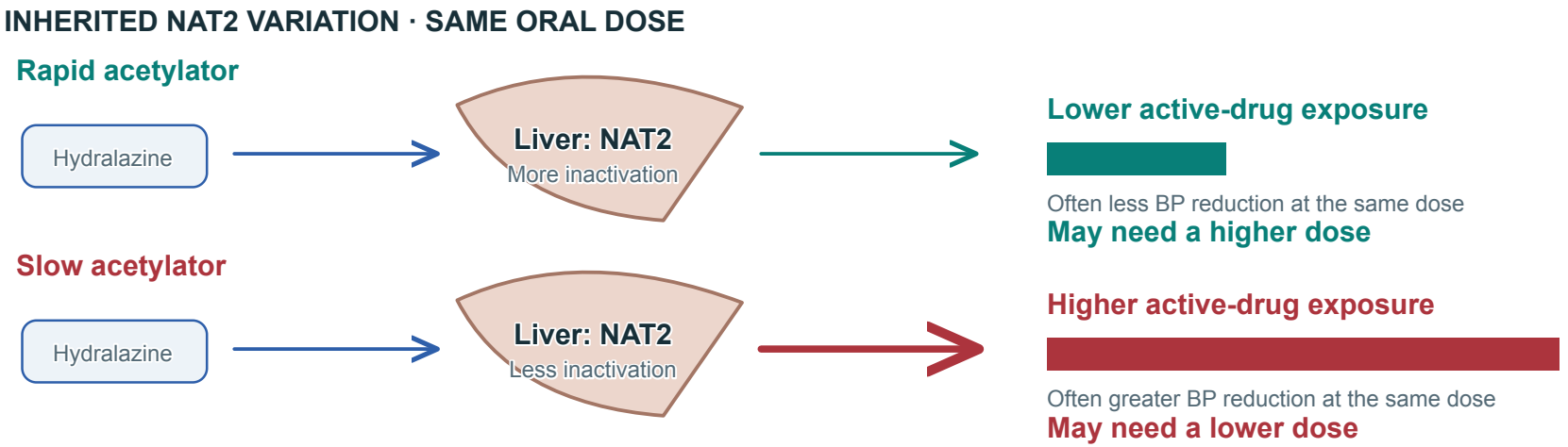
Especially important with oral minoxidil; fenoldopam is an exception to routine β-blocker pairing

KEY RELATIONSHIP A β blocker limits adrenergic effects; a diuretic limits sodium / water retention.

Notes

PHARMACOKINETICS

Hydralazine: inherited NAT2 differences alter response and dose needs



Schematic comparison of rapid and slow acetylators; intermediate phenotypes also occur. Bar lengths are not a fixed exposure ratio.

KEY RELATIONSHIP NAT2 genotype → acetylation rate → oral drug exposure → BP response and dose requirement.

Notes

BODY RESPONSE → SAFETY → PHARMACOKINETICS

Separate reflex effects from hydralazine-specific toxicity

Pattern	Mechanistic connection	Teaching clue
Tachycardia / angina	Reflex SNS activation	Myocardial O_2 demand can rise
Edema / fluid retention	Renal and hormonal compensation	Direct arterial dilation does not prevent volume expansion
Drug-induced lupus	Immune-mediated; risk rises with dose, duration and slower acetylation	Joint pain, fever, serositis; ANA / anti-histone antibodies
Peripheral neuropathy	Possible vitamin B_6 antagonism → impaired nerve function	Numbness / tingling; add pyridoxine (B_6) if symptoms develop

KEY RELATIONSHIP Tachycardia and edema follow compensation; lupus and neuropathy are drug-specific toxicities.

Notes

USES AND OUTCOMES → SAFETY

Hydralazine is used in selected hypertension and HFrEF settings

Selected hypertension settings

- **Oral:** control reflex tachycardia and fluid retention.
- **IV — hypertensive emergencies**, especially severe hypertension in preeclampsia.
- **Generally not first-line outside pregnancy:** bolus dosing, unpredictable response, and prolonged duration of action.

Selected HFrEF

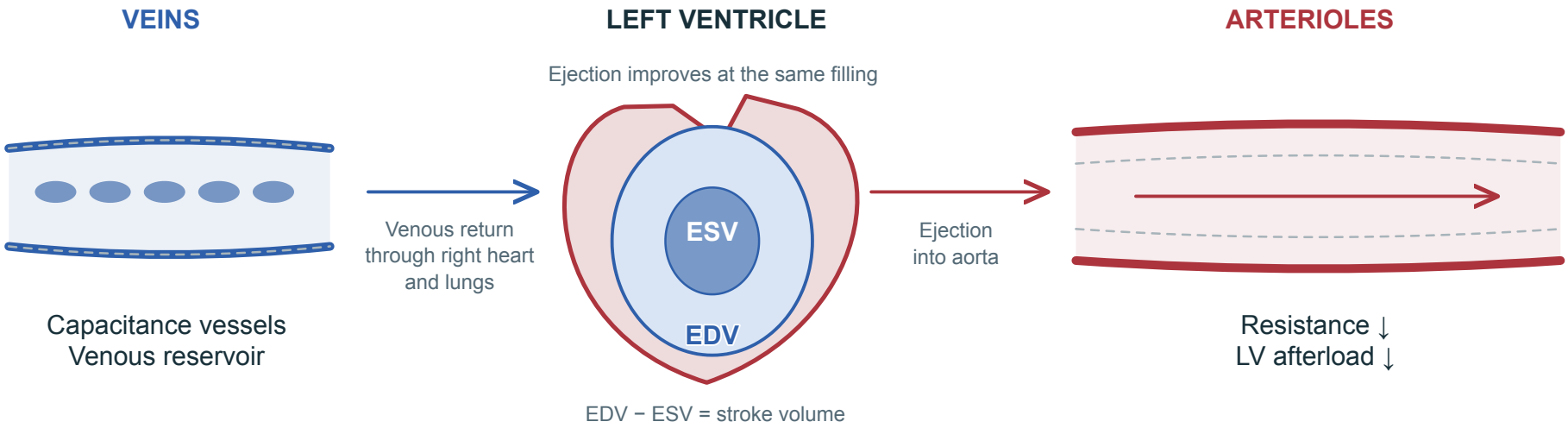
- Use with ISDN for complementary arterial and venous unloading.
- Apply the evidence to the indicated clinical population.

KEY RELATIONSHIP In HFrEF, its role is with isosorbide dinitrate; in hypertension, anticipate compensation.

Notes

TISSUE EFFECT

Hydralazine reduces the ejection load



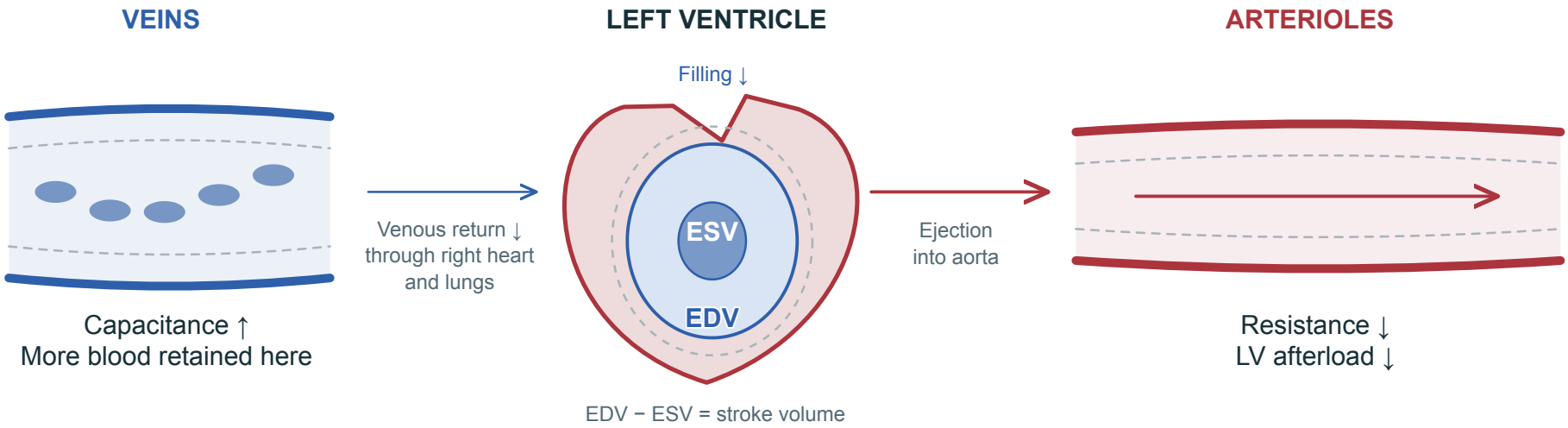
KEY RELATIONSHIP

Arterial relaxation → afterload ↓.

Notes

TISSUE EFFECT → USES AND OUTCOMES

ISDN adds venous unloading to the arterial effect

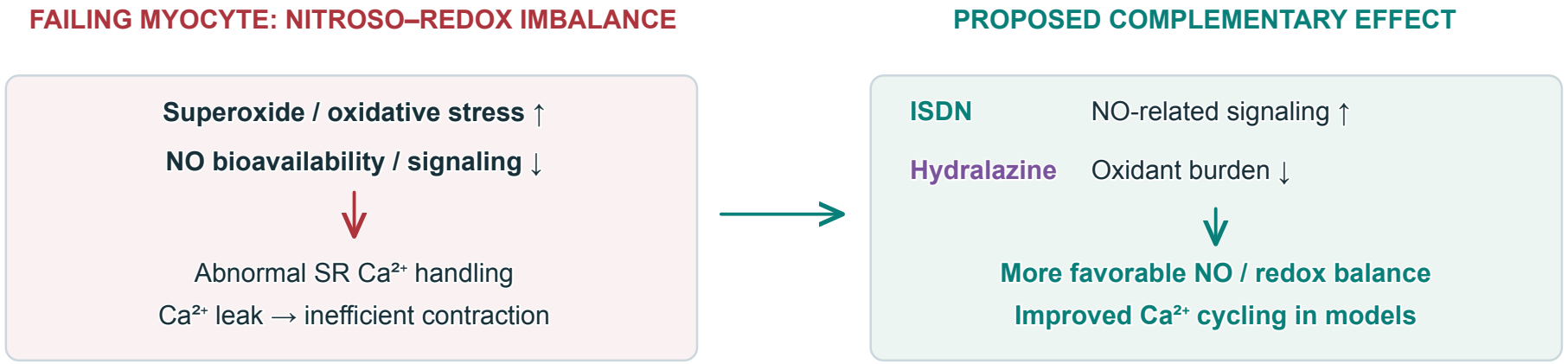


KEY RELATIONSHIP Complementary venous and arterial actions reduce filling load and ejection load together.

Notes

ACTION → TISSUE EFFECT → USES AND OUTCOMES

Hydralazine / ISDN may also improve nitroso–redox balance



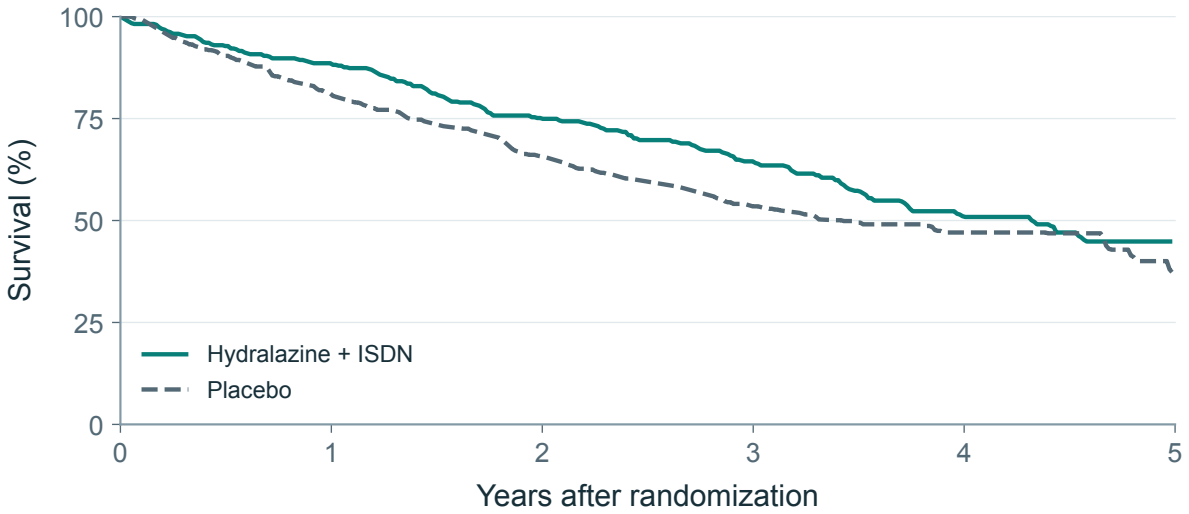
A mechanistic hypothesis beyond unloading; clinical outcome benefit is established by trials.

KEY RELATIONSHIP ISDN supports NO signaling; hydralazine may limit oxidative NO loss and abnormal Ca^{2+} cycling.

Notes

USES AND OUTCOMES

V-HeFT I: does combined vasodilation improve survival?



1986 · V-HeFT I

Added to digoxin and diuretics

Mortality at 2 years

25.6%
Hydralazine + ISDN

34.3%
Placebo

Prespecified 2-year test: P < .028

Whole-curve log-rank P = .093.
The time horizon and analysis matter.

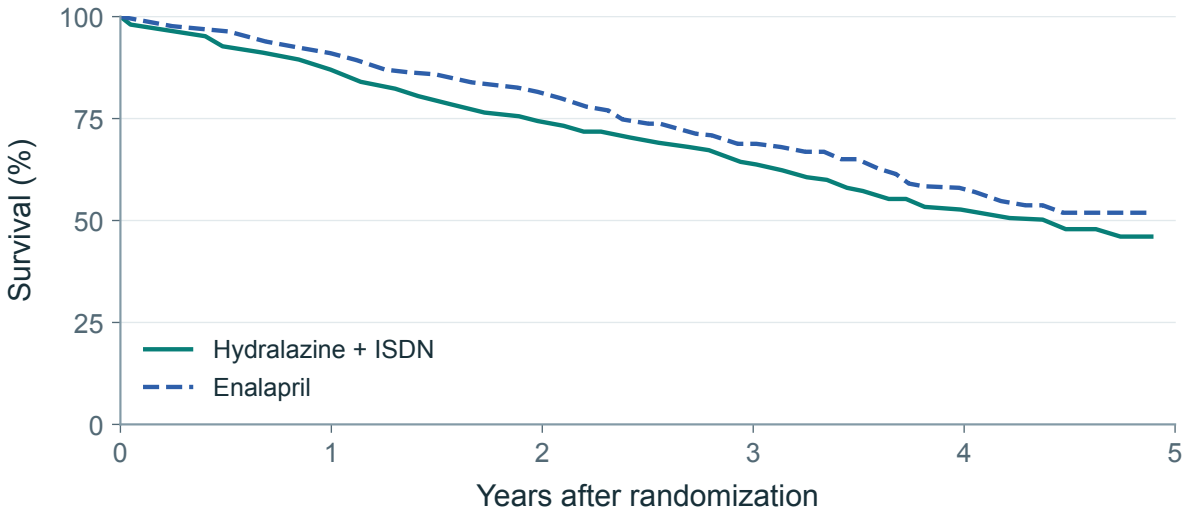
Approximate redraws of published survival curves; no patient-level reanalysis. Exact trial statistics are reported separately.

KEY RELATIONSHIP Hydralazine–ISDN improved survival in the prespecified 2-year comparison with placebo.

Notes

USES AND OUTCOMES

V-HeFT II: enalapril versus hydralazine–ISDN



1991 · 804 men

A direct comparison on digoxin and diuretics

Mortality at 2 years

18%
Enalapril

25%
Hydralazine + ISDN

2-year comparison: P = .016

Entire follow-up: P = .08.
This trial tested alternative regimens.

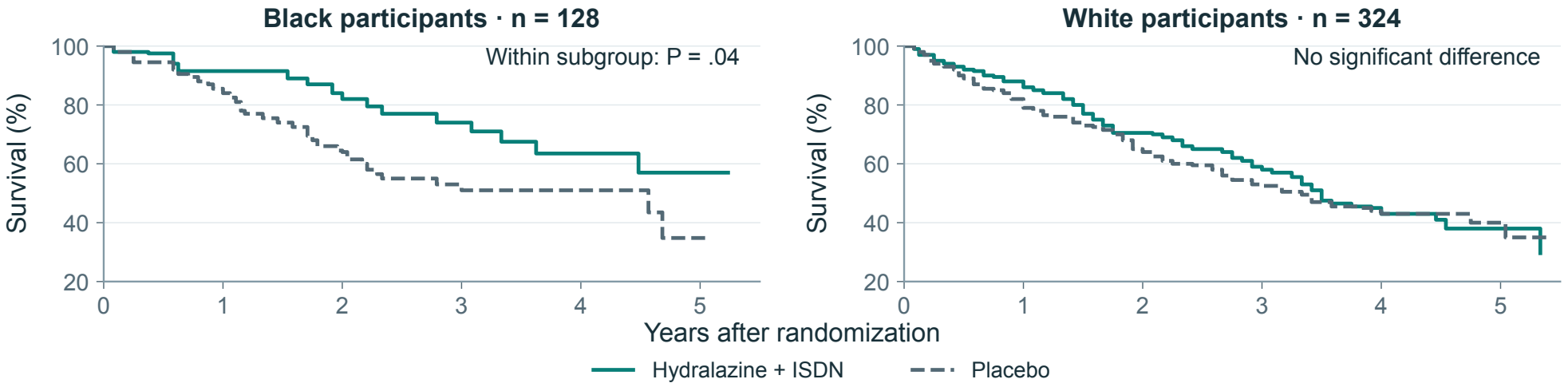
Approximate redraws of published survival curves; no patient-level reanalysis. Exact trial statistics are reported separately.

KEY RELATIONSHIP Enalapril improved 2-year survival compared with hydralazine–ISDN on the background therapy of that era.

Notes

USES AND OUTCOMES

V-HeFT I: a retrospective signal in Black participants



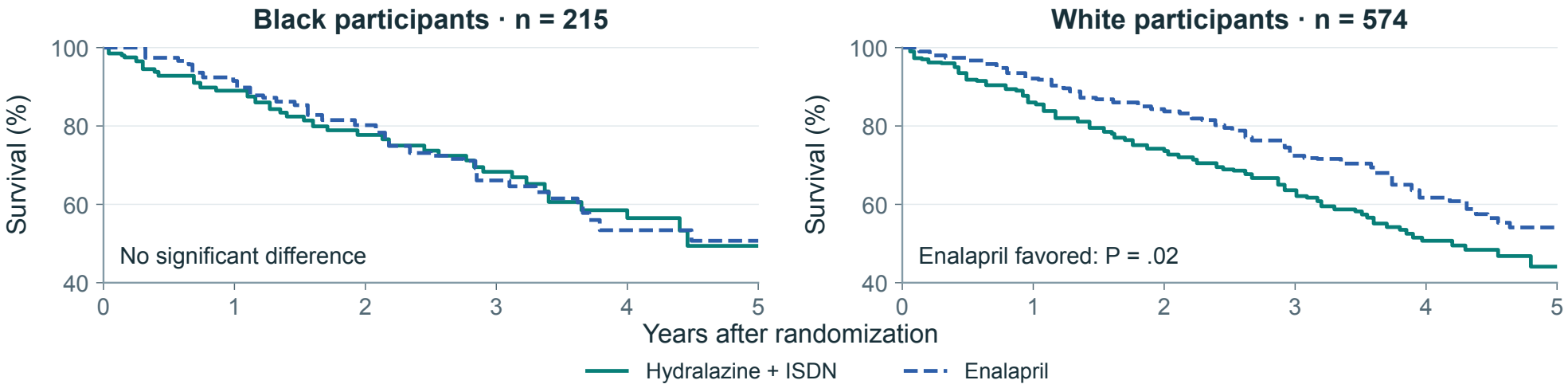
Retrospective analysis · Identical axes (20–100% survival) · Hydralazine–ISDN versus placebo · Approximate curve tracings

KEY RELATIONSHIP The subgroup signal helped generate a hypothesis; it did not establish that race determines an individual response.

Notes

USES AND OUTCOMES

V-HeFT II: subgroup results prompted a new question



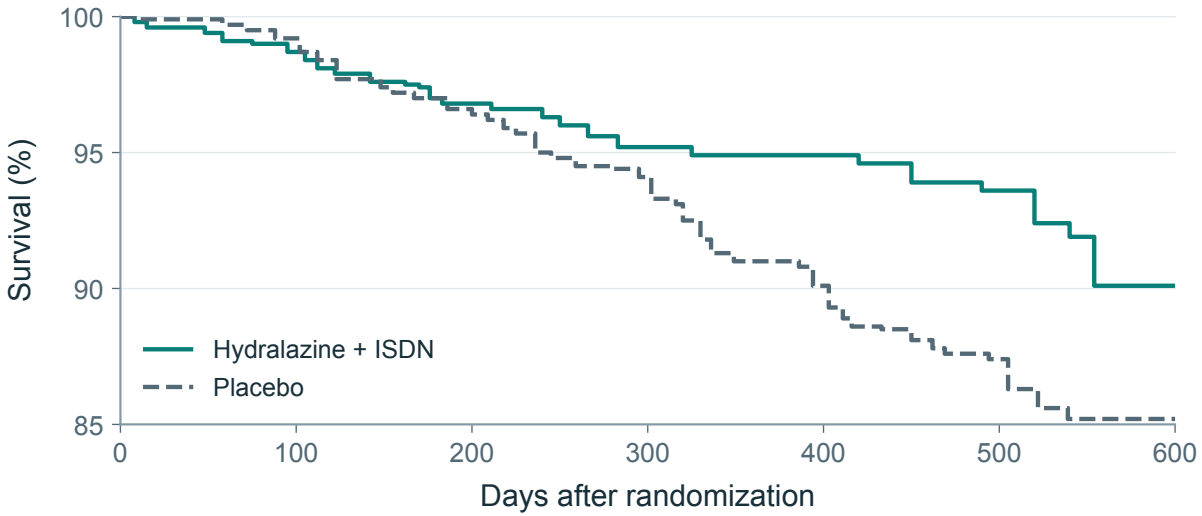
Retrospective analysis · Identical axes (40–100% survival) · Treatment-by-race interaction P = .09 · Approximate curve tracings

KEY RELATIONSHIP A significant result in one subgroup and a nonsignificant result in another do not prove that treatment effects differ.

Notes

USES AND OUTCOMES

A-HeFT: prospective evidence for add-on hydralazine–ISDN



2004 · 1,050 self-identified Black patients

NYHA III–IV HF
Added to background therapy

Deaths during the trial

6.2% Hydralazine + ISDN

10.2% Placebo

Mortality HR 0.57 · P = .01

Stopped early for benefit.
Fewer first HF hospitalizations.

Kaplan–Meier survival · Expanded axis (85–100%) · Approximate redraw of the U.S. label figure; exact results from Taylor et al. (2004)

KEY RELATIONSHIP

A-HeFT established add-on benefit in its enrolled population; it did not compare treatment effects across racial groups.

Notes

USES AND OUTCOMES → SAFETY

Use the combination in the clinical setting supported by evidence

Add to optimal HFrEF therapy

- Recommended for self-identified **Black patients with NYHA III–IV HFrEF** symptoms despite optimal therapy.
- **A-HeFT:** improved survival and reduced HF hospitalization.
- The combination supplements foundational RAASi treatment.

When renin–angiotensin drugs cannot be used

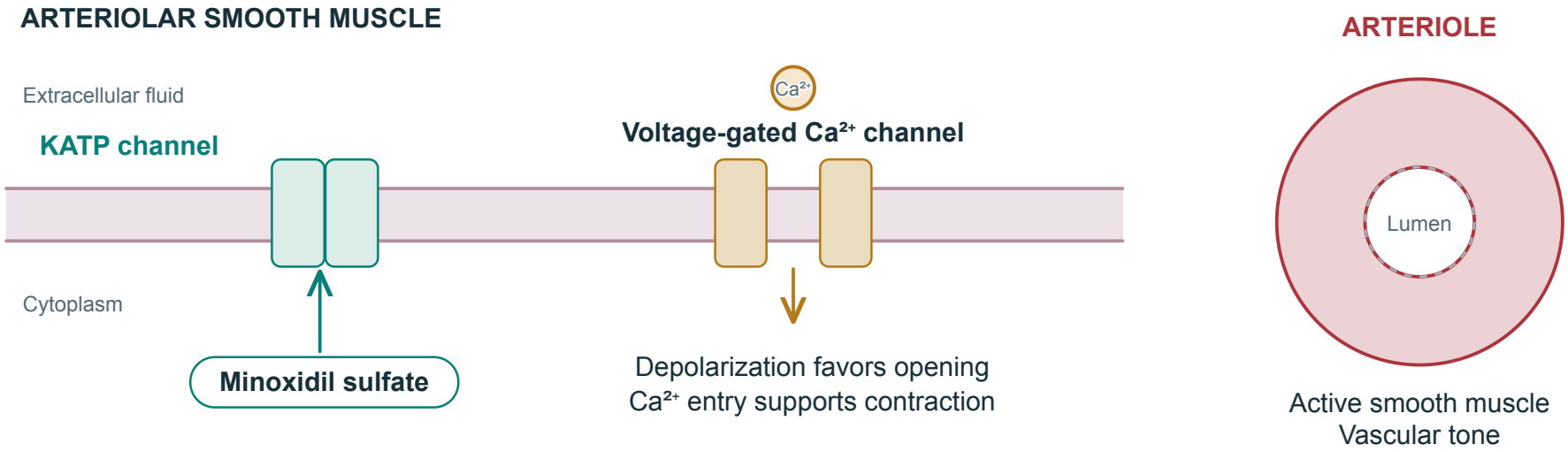
- May be considered in symptomatic HFrEF when **ARNI, ACE inhibitor or ARB** therapy is not usable.
- Evidence for this alternative role is less direct.
- Account for BP, adverse effects and a multidose regimen.

KEY RELATIONSHIP V-HeFT compared regimens; A-HeFT tested add-on treatment. The comparisons answer different clinical questions.

Notes

TARGET → TISSUE EFFECT

Voltage-dependent Ca^{2+} entry supports contraction



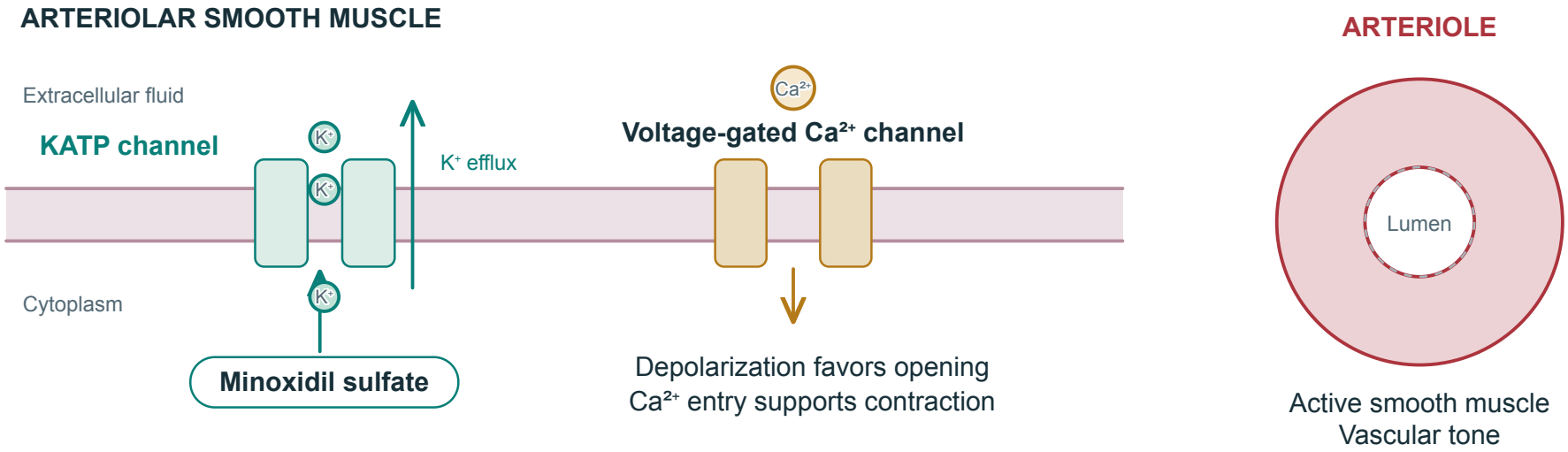
KATP = ATP-sensitive potassium channel; calcium-channel opening depends on membrane voltage

KEY RELATIONSHIP Membrane potential helps determine how much Ca^{2+} enters the smooth-muscle cell.

Notes

TARGET → ACTION → PHARMACOKINETICS

Active minoxidil sulfate increases K^+ conductance



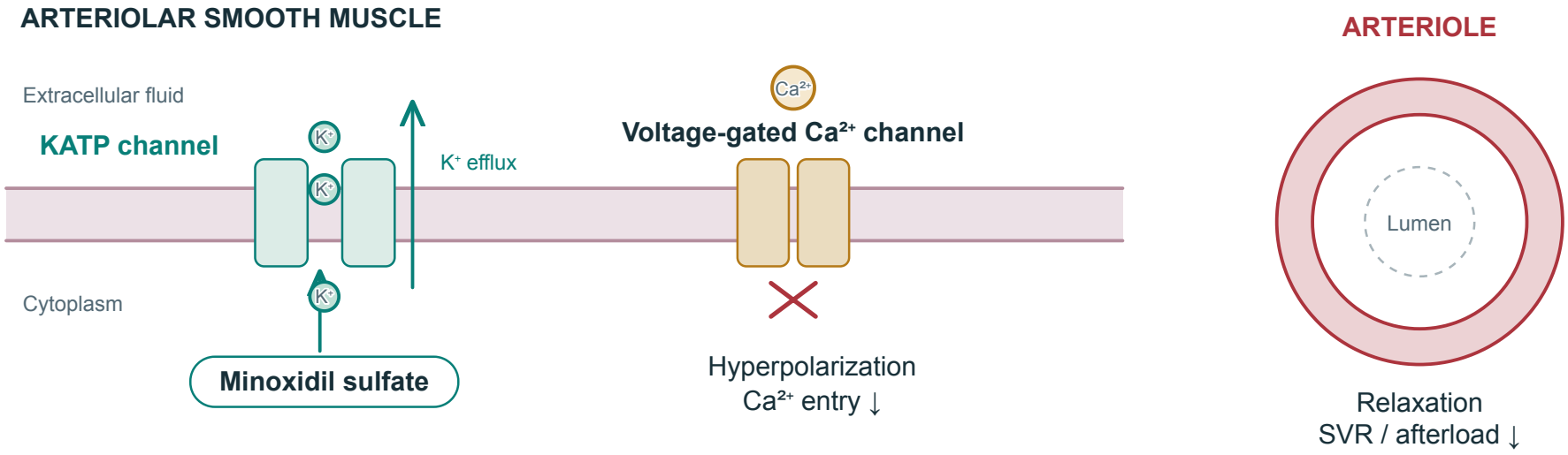
Movement of labeled K^+ shows efflux; it is not a calibrated count of ions

KEY RELATIONSHIP K^+ efflux through opened KATP channels drives membrane hyperpolarization.

Notes

ACTION → TISSUE EFFECT

Hyperpolarization reduces voltage-dependent Ca^{2+} entry



Follow the order: KATP opening → hyperpolarization → Ca^{2+} entry ↓ → relaxation

KEY RELATIONSHIP Less Ca^{2+} entry → less contractile activation → arteriolar relaxation.

Notes

TISSUE EFFECT → BODY RESPONSE

Minoxidil also dilates renal resistance vessels

RENAL RESISTANCE VESSELS

Direct renal arteriolar dilation
Renal vascular resistance ↓

RBF / GFR preserved

THE VOLUME RESPONSE STILL MATTERS

Systemic BP falls → SNS / renin ↑

Salt and water retention

Edema / volume expansion

Renal vasodilation does not make minoxidil a diuretic or eliminate fluid-retention risk.

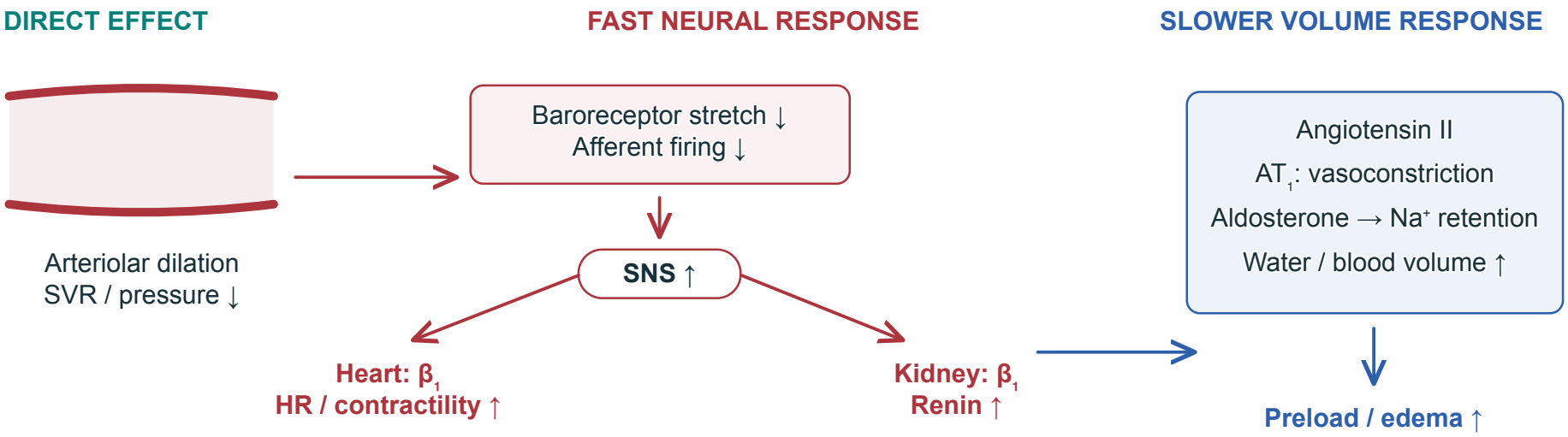
KEY RELATIONSHIP

Renal resistance falls, yet renin activation and salt / water retention still require treatment.

Notes

BODY RESPONSE → USES AND OUTCOMES → SAFETY

Oral minoxidil provokes marked tachycardia and fluid retention



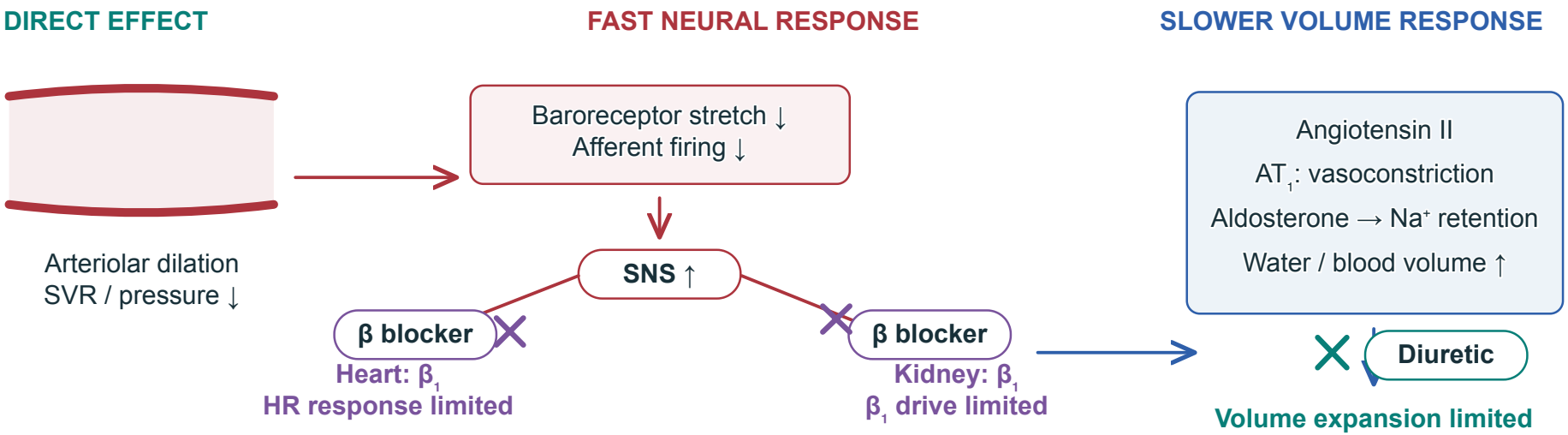
Direct effect: arterial unloading · Compensatory effect: cardiac stimulation and volume expansion

KEY RELATIONSHIP The compensatory response is central to minoxidil's clinical use, not a minor footnote.

Notes

BODY RESPONSE → USES AND OUTCOMES → SAFETY

Usually pair oral minoxidil with a β blocker and an effective diuretic



β blockade addresses adrenergic drive; the diuretic addresses retained sodium and water

KEY RELATIONSHIP Control the reflex response while watching for pericardial effusion and worsening angina.

Notes

USES AND OUTCOMES → SAFETY → PHARMACOKINETICS

Oral minoxidil is reserved for hypertension resistant to three drugs

Before oral minoxidil:
Inadequate response to maximum therapeutic doses of
a diuretic + two other antihypertensives

Boxed warning

Pericardial effusion → possible tamponade.
Angina may worsen.

Companion therapy

Usually a β blocker / sympathetic suppressant plus an effective, often loop, diuretic.

KEY RELATIONSHIP The boxed warning includes pericardial effusion that may progress to tamponade.

Notes

USES AND OUTCOMES → SAFETY → PHARMACOKINETICS

The same drug can have very different systemic exposure

Route / role	Exposure goal	Important consequence
Oral, reserved hypertension therapy	Systemic arteriolar effect	Requires attention to reflex tachycardia, fluid retention and pericardial toxicity
Topical scalp use	Local hair-growth effect with much lower systemic exposure	Absorption depends on formulation, dose and skin condition
Characteristic adverse effect	Hypertrichosis 	Distinct from hemodynamic toxicity; also explains the hair-growth application

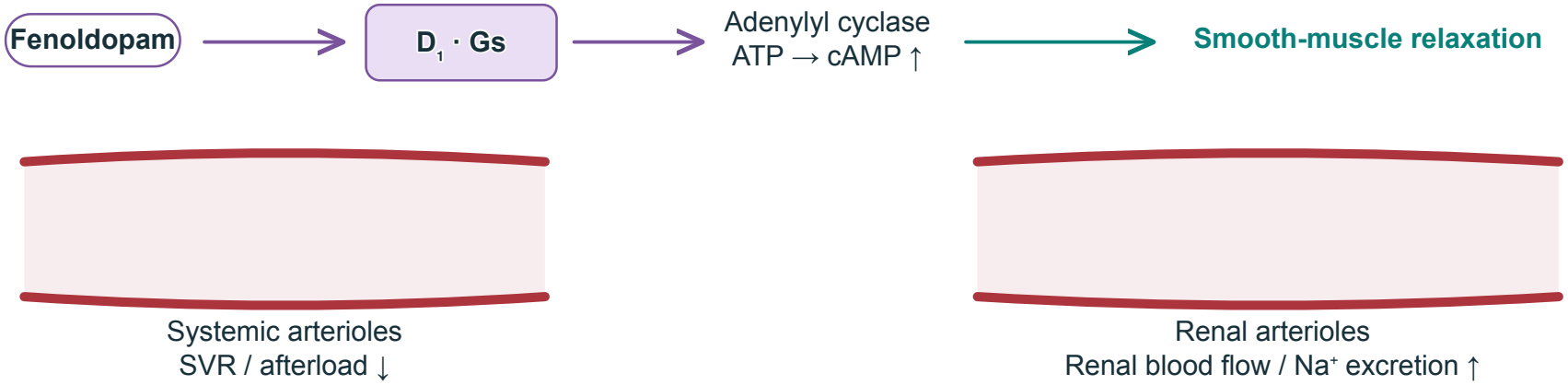
KEY RELATIONSHIP Systemic antihypertensive use and topical scalp use should not be taught as equivalent regimens.

Notes

TARGET → ACTION → TISSUE EFFECT

D_1-like receptor activation relaxes systemic and renal vessels

D_1-LIKE RECEPTOR → cAMP



Different second messenger: fenoldopam raises cAMP, not cGMP

KEY RELATIONSHIP D_1 / Gs → adenylyl cyclase → cAMP ↑ → vascular relaxation.

Notes

TARGET → ACTION → TISSUE EFFECT → USES AND OUTCOMES

Fenoldopam is a vasodilator, not a dopamine-like pressor

	Fenoldopam	Dopamine
Receptor pattern	D_1-like agonist; no meaningful β_1 / α_1 agonism	Dopaminergic + β_1 + α_1 effects; dose-dependent overlap
Heart	No direct β_1 inotropic effect; reflex tachycardia can occur	β_1 stimulation increases contractility / cardiac drive
Vessels / kidneys	Arteriolar dilation; renal blood flow and Na^+ excretion ↑	Higher exposure recruits α_1 vasoconstriction
Clinical direction	Lower severe BP by titrated IV infusion	Support hemodynamics in selected shock settings

KEY RELATIONSHIP D_1-like selectivity explains renal / systemic dilation without dopamine's β_1 and α_1 actions.

Notes

USES AND OUTCOMES → SAFETY → PHARMACOKINETICS

A short IV effect supports titration in severe hypertension

Use and exposure

- Short-term IV treatment of severe hypertension.
- Rapidly titratable exposure.
- Renal flow / natriuresis are physiological effects.

Safety distinctions

- Hypotension, reflex tachycardia, hypokalemia.
- Increased intraocular pressure is relevant in glaucoma.
- Do not automatically add a β blocker: combined use may exaggerate hypotension.

KEY RELATIONSHIP Renal vasodilation does not by itself establish protection from kidney failure.

Notes

TARGET → ACTION → TISSUE EFFECT → BODY RESPONSE → SAFETY → PHARMACOKINETICS

The tissue effect converges; the molecular actions differ

Drug	Target → action	Body response / safety distinction
Hydralazine	Arteriolar relaxation; precise molecular target uncertain	Reflex tachycardia / retention; NAT2 exposure and lupus
Minoxidil	Active sulfate opens KATP → hyperpolarization → Ca^{2+} entry ↓	Strong compensation; usual β blocker + diuretic; pericardial effusion
Fenoldopam	D_1 / Gs → cAMP ↑	Renal vascular / sodium effects; hypokalemia; increased intraocular pressure (eye pressure); avoid automatic β-blocker pairing

KEY RELATIONSHIP Hydralazine, minoxidil and fenoldopam all lower resistance, but their targets and safety distinctions differ.

Notes

TARGET → ACTION → TISSUE EFFECT → BODY RESPONSE → USES AND OUTCOMES → SAFETY → PHARMACOKINETICS

Start with the vessel, then predict the ventricle

Drug / pattern	Direct change	Central teaching consequence
Usual organic nitrate exposure	Predominantly venous dilation	Preload / wall stress / myocardial O_2 demand ↓
Nitroprusside	Venous + arterial dilation	Both loads ↓; net output depends on the starting ventricle
Hydralazine / minoxidil	Predominantly arteriolar dilation	Afterload ↓, followed by sympathetic and renal compensation
PDE-5 inhibition	cGMP breakdown ↓	Signal persistence; dangerous amplification with nitrates

KEY RELATIONSHIP Venous dilation changes filling; arterial dilation changes ejection; compensation modifies both.

Notes

ACTION → TISSUE EFFECT → BODY RESPONSE → SAFETY → PHARMACOKINETICS

Can you reconstruct the mechanism without the drug list?

Three causal predictions

- Why does a nitrate relieve ordinary angina?
- Why is nitrate + PDE-5 inhibition dangerous?
- Why does oral minoxidil usually need two companion drugs?

Two exposure predictions

- Why can a constant nitrate dose lose effect?
- Why does CKD change nitroprusside toxicity even when the BP response looks controlled?

KEY RELATIONSHIP A useful answer connects the steps rather than stopping at the second messenger.

Notes

Questions

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MED 9408 · Vasodilators

Companion modules

cGMP vasodilator pharmacology ↗

Direct arterial vasodilators ↗

KEY RELATIONSHIP Revisit the same seven-step relationships in the companion modules.

Notes