

Pathophysiology and Progression to Heart Failure

From compensatory remodeling to myocardial dysfunction

Mechanisms • structural adaptation • decompensation • clinicopathologic correlation

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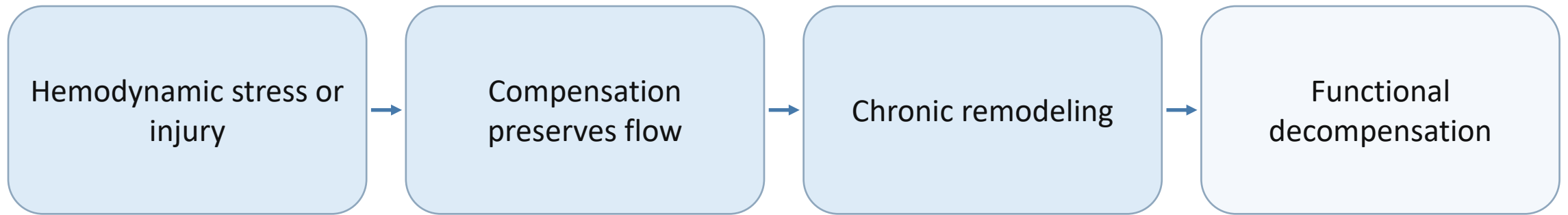
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Learning outcomes

- Explain why increased cardiac work induces myocyte hypertrophy and ventricular remodeling.
- Distinguish pressure-overload and volume-overload patterns at the sarcomere and organ levels.
- Trace ischemia, fibrosis, and molecular reprogramming toward systolic or diastolic failure.
- Differentiate physiologic exercise hypertrophy from persistent pathologic hypertrophy.

Heart failure is the endpoint of failed compensation



- Structural adaptation is initially useful, not intrinsically synonymous with failure.
- Persistence of the initiating stress can make the adaptive response harmful.

Heart failure: A functional definition

The heart cannot meet peripheral metabolic demands, or can do so only at elevated filling pressures.

- Reduced forward flow and elevated filling pressures are distinct, often coexisting problems.
- Anatomical enlargement alone does not establish heart failure.

Chronic stress and acute insults converge on failure

Chronic routes	Acute precipitants
Hypertension → persistent pressure work	Myocardial infarction → abrupt loss of contractile mass
Valve disease → sustained pressure or volume load	Abrupt valvular dysfunction
Ischemic heart disease → cumulative injury	Acute fluid overload

A failing circulation may emerge gradually or deteriorate abruptly.

Six cardiac pathophysiologic mechanisms

Pump failure

Impaired contraction or relaxation

Flow obstruction

Pressure load from stenosis or hypertension

Regurgitant flow

Volume burden from backward flow

Shunted flow

Inappropriate chamber/vessel flow

Conduction disorder

Ineffective coordinated pumping

Rupture

Loss of circulatory continuity

Pressure and volume loading are especially important routes into compensatory hypertrophy.

The compensation–decompensation distinction

Initially adaptive	Ultimately harmful if sustained
Augmented contraction and perfusion	Persistent metabolic demand
Salt/water conservation to support filling	Congestion and elevated filling pressure
Greater ventricular muscle mass	Supply–demand mismatch and fibrosis
Remodeling to accommodate load	Loss of contractile or filling reserve

The same response can change its effect over time.

Two functional dimensions of cardiac failure

Systolic dysfunction

Impaired ventricular emptying

Lower ejection fraction

Diastolic dysfunction

Impaired ventricular relaxation/filling

Elevated pressure despite preserved EF

These are physiological emphases, not completely separate diseases.

Ejection fraction describes ventricular emptying

$$\text{LVEF (\%)} = [(\text{EDV} - \text{ESV}) / \text{EDV}] \times 100$$

EDV: End-diastolic volume; ESV: End-systolic volume. EF is not a direct measure of perfusion.

- Textbook healthy reference: Approximately 50%–70%.
- A reduced value supports systolic dysfunction; Preserved EF does not exclude failure.

Textbook categories: Reduced versus preserved EF

HFrEF	HFpEF
LVEF $\leq 40\%$	LVEF $\geq 50\%$
Systolic dysfunction predominates	Diastolic dysfunction predominates
Ventricular emptying is impaired	Ventricular filling may require high pressure
Often linked to damage or dilation	Often linked to stiff, hypertrophied myocardium

The source section does not define the intermediate-EF category; No additional cutoff is implied.

Forward failure and backward failure

Forward consequence

Reduced cardiac output

↓ **Tissue perfusion**

Backward consequence

Venous blood pools upstream

Pulmonary or systemic edema

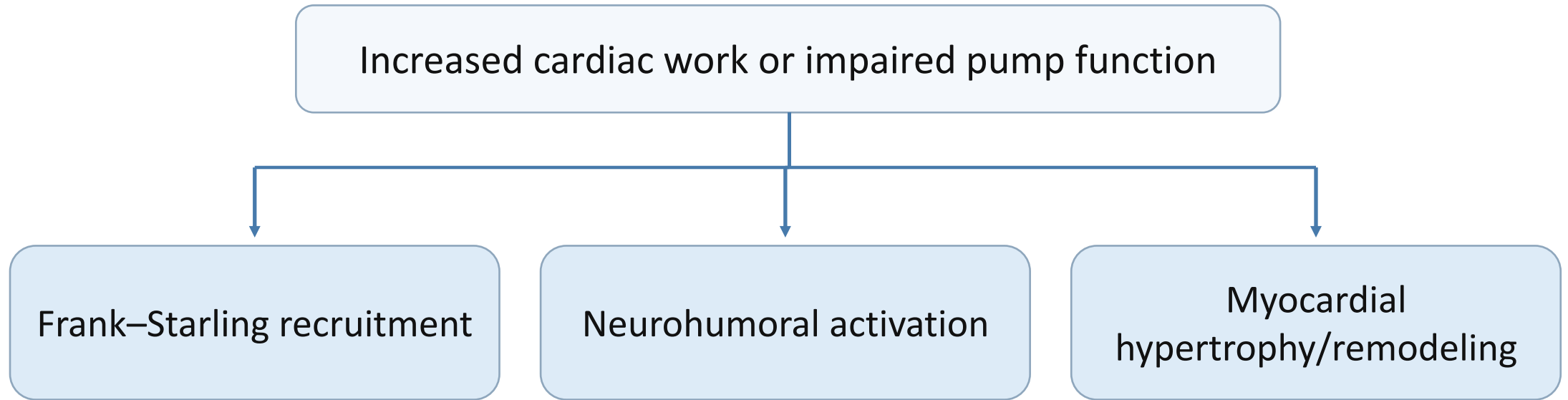
Both patterns may be present at different intensities in the same patient.

Ventricular remodeling is more than enlargement

Molecular, cellular, and structural alterations following injury or altered ventricular loading.

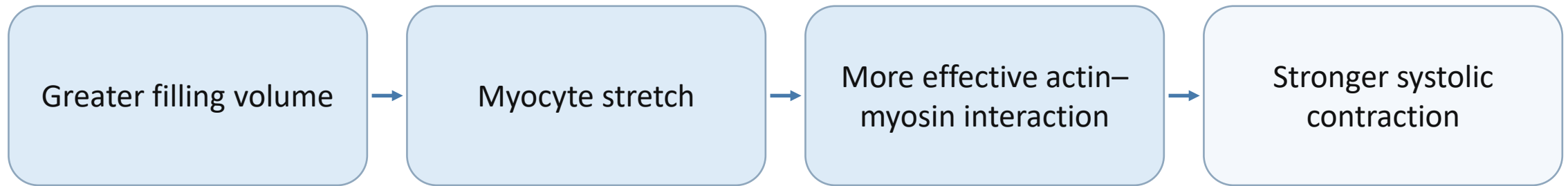
- Includes changes in myocyte size, chamber geometry, gene expression, and extracellular matrix.
- May initially preserve function but gradually reduce reserve.

Three coordinated compensatory mechanisms



- These responses support arterial pressure and tissue perfusion when work rises.
- They are limited in duration and may become contributors to progression.

Frank–Starling compensation: Filling recruits force

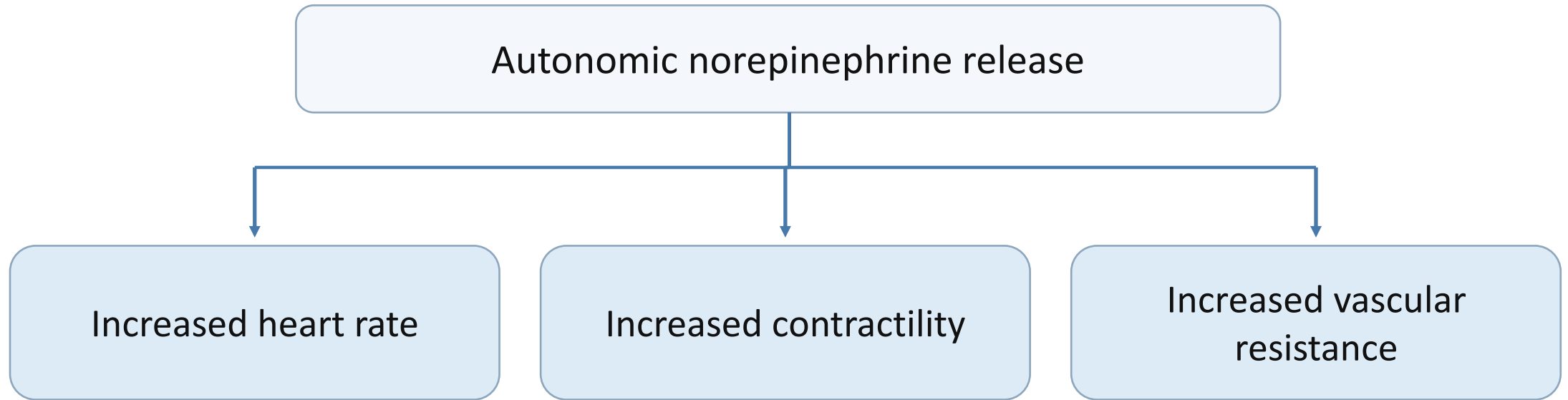


- Immediate adaptation uses existing myocardium rather than new muscle mass.
- Increased filling also raises the burden on a ventricle with limited reserve.

Frank–Starling reserve does not prevent progression

- More filling volume can initially strengthen systolic contraction.
- Structural remodeling may eventually compromise both contraction and relaxation.
- At decompensation, high filling pressures can coexist with inadequate output.
- The reserve mechanism explains compensation, not permanent correction of an injured heart.

Adrenergic activation: Immediate circulatory support



- These effects may initially maintain arterial pressure.
- Persistently increased heart rate and inotropy also increase oxygen consumption.

The adrenergic tradeoff

Short-term benefit

↑ Heart rate

↑ **Contractile force**

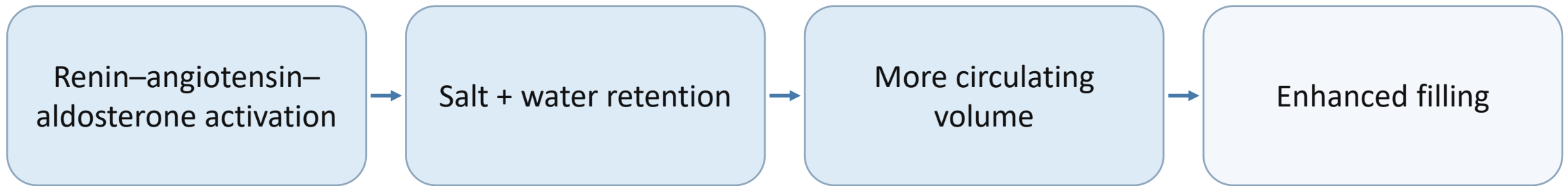
Long-term burden

↑ Metabolic requirement

Additional wall-work demand

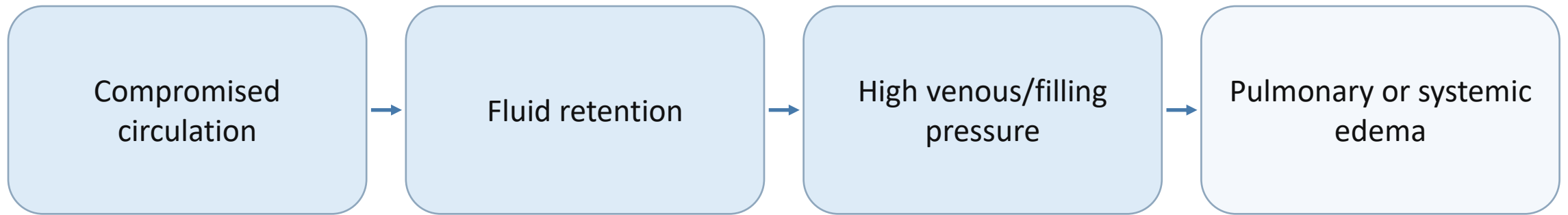
β -adrenergic signals among trophic stimuli for myocyte hypertrophy.

RAAS activation expands circulating volume



- RAAS also raises vascular tone.
- Expansion of volume can worsen congestion once filling capacity is limited.

RAAS compensation can increase backward pressure



- Volume conservation aids perfusion early in disease.
- Continued retention aggravates congestion in decompensated heart failure.

Atrial natriuretic peptide is counter-regulatory

RAAS response

Salt/water conservation

Increased vascular tone

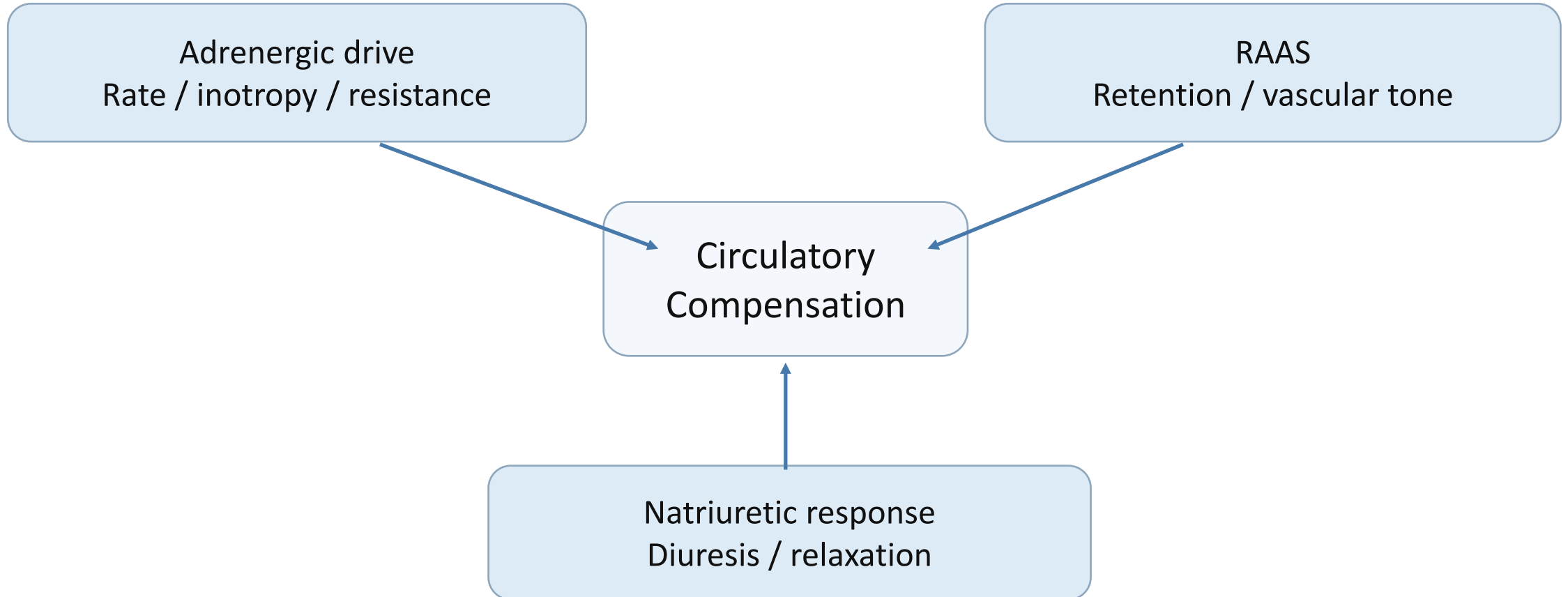
Atrial natriuretic peptide

Promotes diuresis

Relaxes vascular smooth muscle

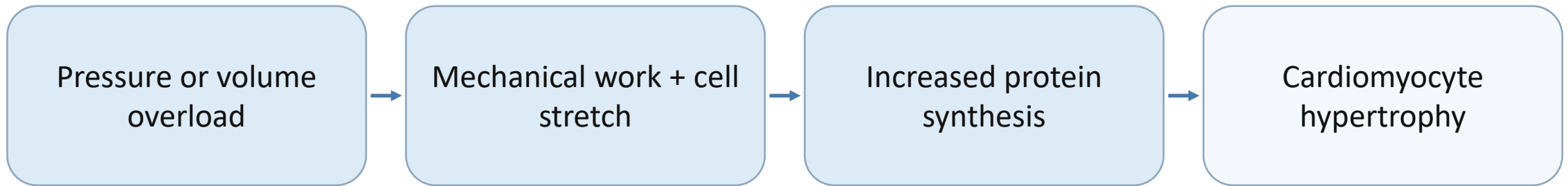
Competing neurohumoral responses regulate volume and pressure; Balance may still fail.

Neurohumoral activation is a balancing system



A systems response is useful acutely, but cannot eliminate ongoing myocardial injury.

Mechanical work activates myocyte growth



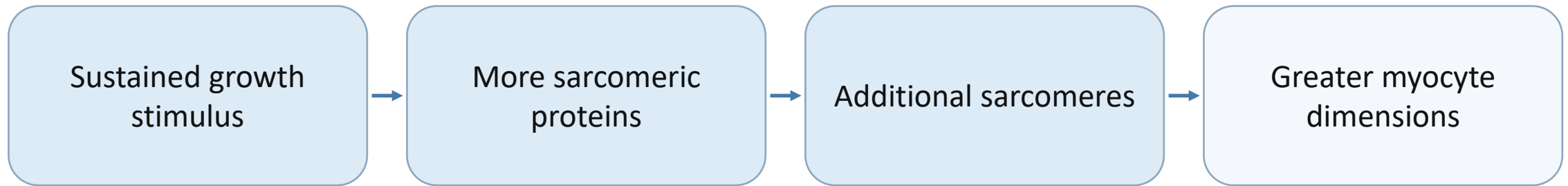
- Trophic signals, including β -adrenergic activation, may also initiate growth.
- Organ enlargement accumulates from growth of individual cardiac myocytes.

Cardiac hypertrophy is cellular enlargement

Greater myocyte size cumulatively increases cardiac mass and weight.

- The adaptive response requires synthesis of additional contractile proteins.
- Adult myocytes commonly respond by hypertrophy rather than a proportional rise in cell number.

New contractile machinery requires protein synthesis



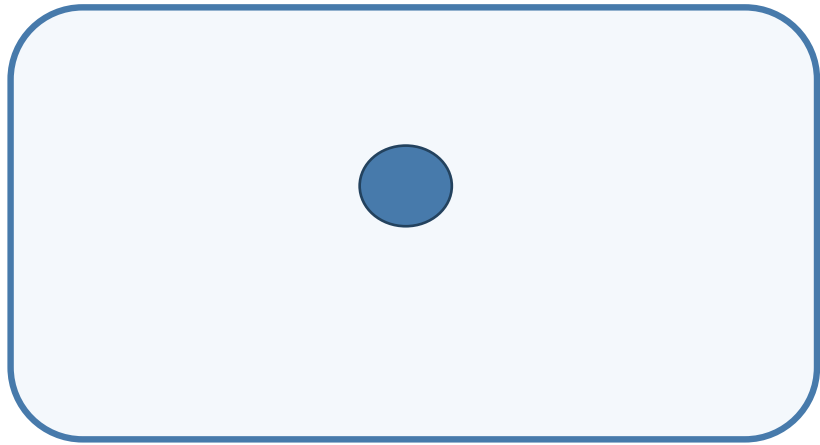
- The spatial arrangement of new sarcomeres determines the pattern of remodeling.
- Mitochondrial numbers also increase as the cell enlarges.

Mitochondria increase in hypertrophied cells

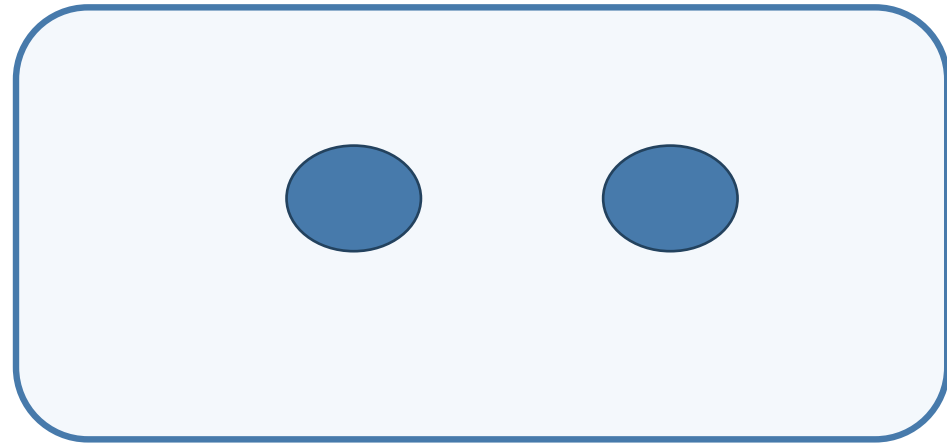
- Cardiac myocyte growth entails more than accumulation of contractile filaments.
- Additional mitochondria support the needs of an enlarged contractile cell.
- Despite greater cellular machinery, oxygen delivery may fail to scale with mass.
- This mismatch helps explain why marked hypertrophy can coexist with functional vulnerability.

Hypertrophic nuclei may enlarge or multiply

Schematic — not histologic microscopy



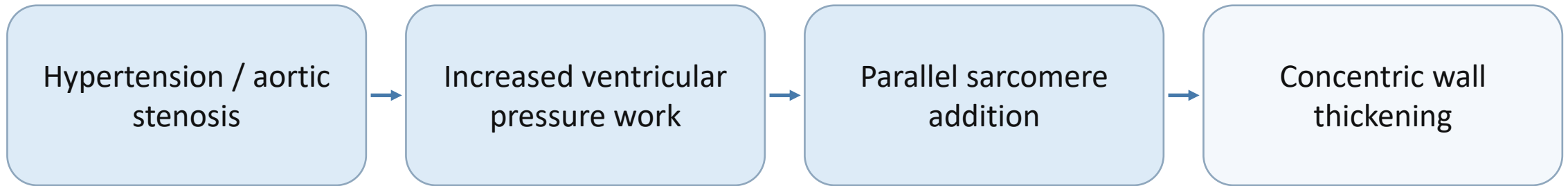
Baseline myocyte



Hypertrophied myocyte (schematic)

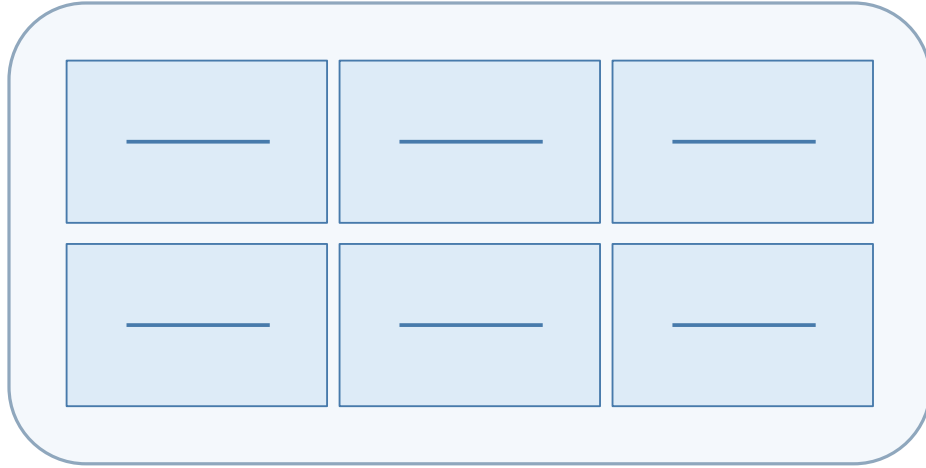
- Enlarged or multiple nuclei may accompany myocyte hypertrophy.
- DNA replication without cell division increases nuclear DNA ploidy.
- Microscopic nuclear enlargement is not, by itself, evidence of malignancy.

Pressure overload principally thickens myocardium



- The myocyte gains cross-sectional area.
- A characteristic response is increased wall thickness.

Parallel sarcomeres expand cell width



Baseline arrangement

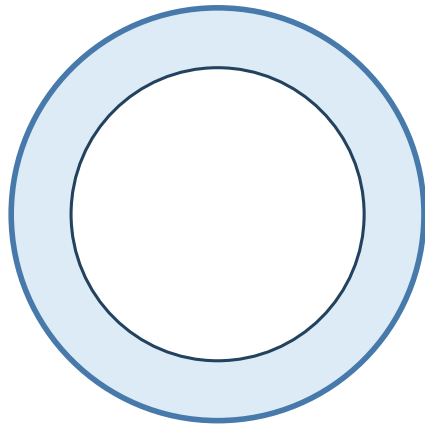


Parallel addition

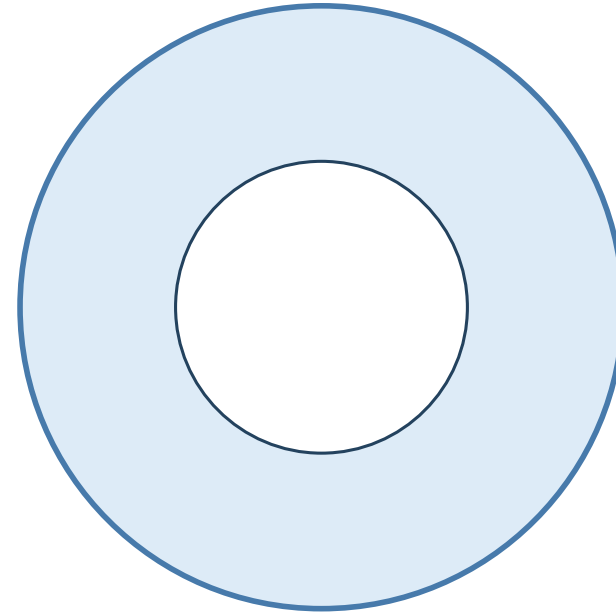
- New sarcomeres align predominantly beside existing sarcomeres.
- The resulting larger cell cross-section contributes to concentric hypertrophy.

Pressure overload: Concentric ventricular geometry

Original schematic ventricular cross-sections — not clinical images



Baseline



Pressure overload

- The ventricle accommodates sustained high pressure by increasing muscle thickness.
- Wall geometry alone does not establish preserved ventricular function.

Common pressure-overload settings

Systemic hypertension

Sustained systemic pressure burden

Aortic stenosis

Increased outflow resistance

Cardiac work

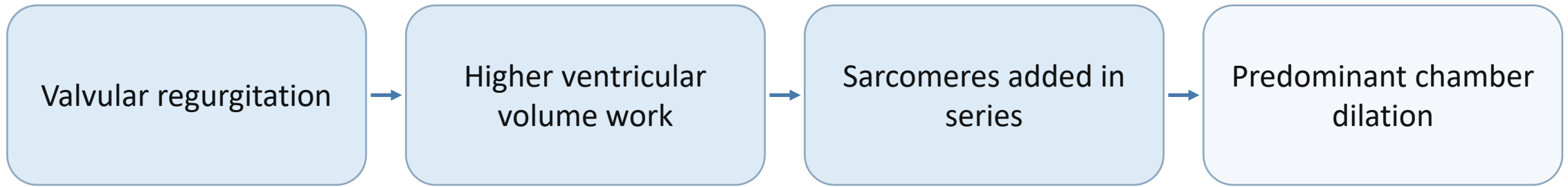
Higher load on ventricular myocytes

Typical response

Predominantly concentric hypertrophy

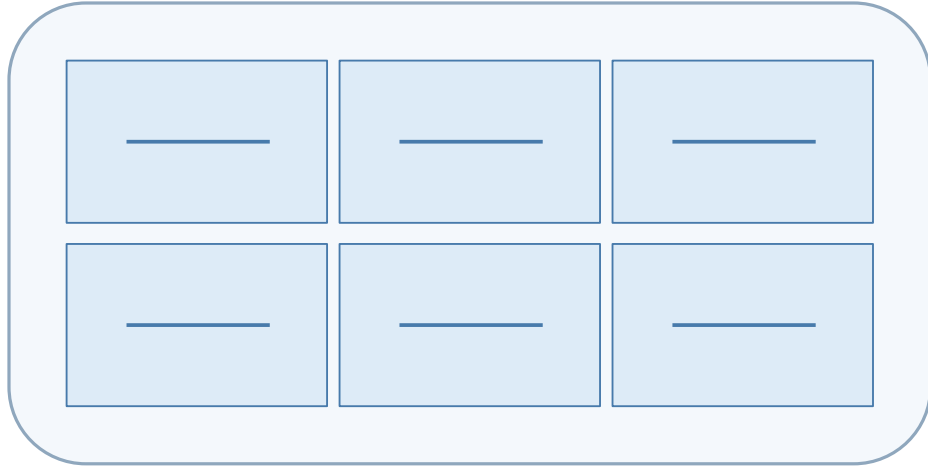
The cause and chamber loading must be identified, not inferred from wall thickness alone.

Volume overload chiefly dilates the chamber

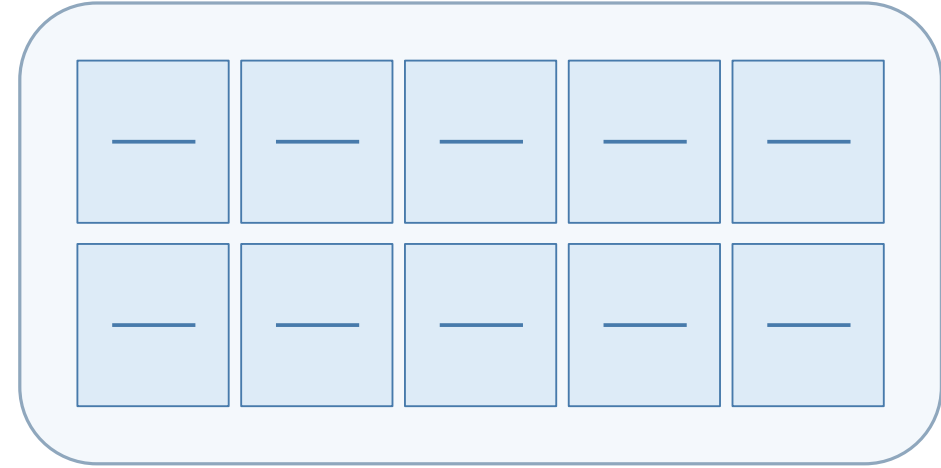


- The cell expands primarily along its long axis.
- In the enlarged chamber, wall thickness can be variable.

Series sarcomeres increase myocyte length



Baseline arrangement

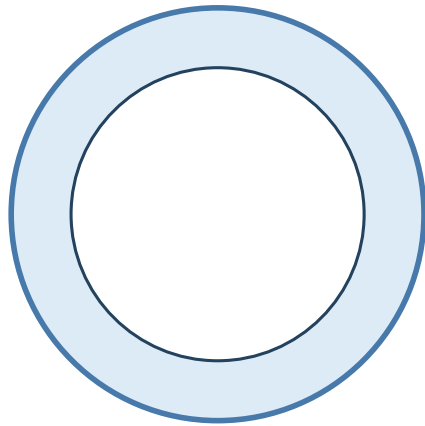


Series addition

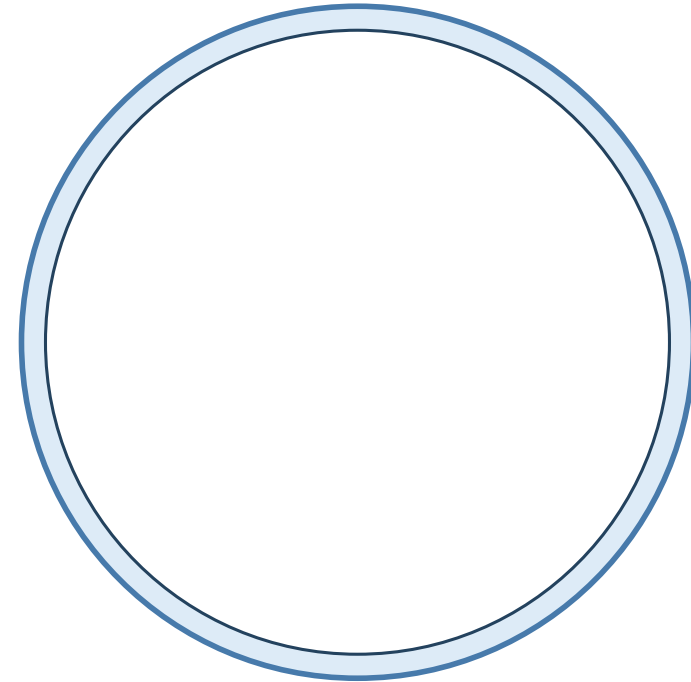
- Additional sarcomeres are arranged end-to-end with existing units.
- Myocyte lengthening contributes to ventricular dilation.

Volume overload: A dilated ventricular chamber

Original schematic ventricular cross-sections — not clinical images



Baseline



Volume overload

- Regurgitant loading favors increased cavity size.
- Cardiac mass can increase even if the wall does not appear thick.

Wall thickness is unreliable in a dilated heart

Why a dilated heart may look thin	What better captures hypertrophy
The chamber circumference is enlarged	Heart weight reflects overall muscle mass
Thickness can increase, remain normal, or decrease	Thickness alone can understate growth
Dilation can follow previous pressure hypertrophy	Interpret weight with chamber dimensions

Robbins explicitly favors heart weight over wall thickness in dilated hearts.

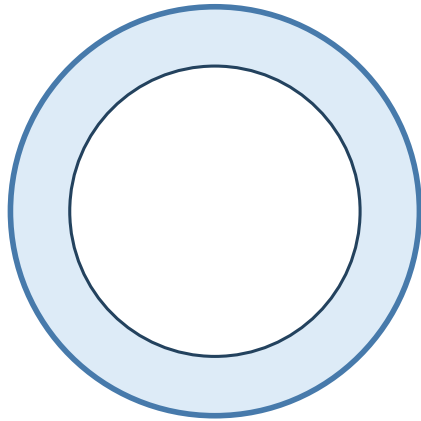
Pressure and volume overload: Side-by-side

Pressure overload	Volume overload
Hypertension; Aortic stenosis	Valvular regurgitation
Parallel sarcomere addition	Series sarcomere addition
Myocyte cross-sectional growth	Myocyte longitudinal growth
Concentric wall thickening	Predominant ventricular dilation
Wall thickness often rises	Wall thickness may be variable

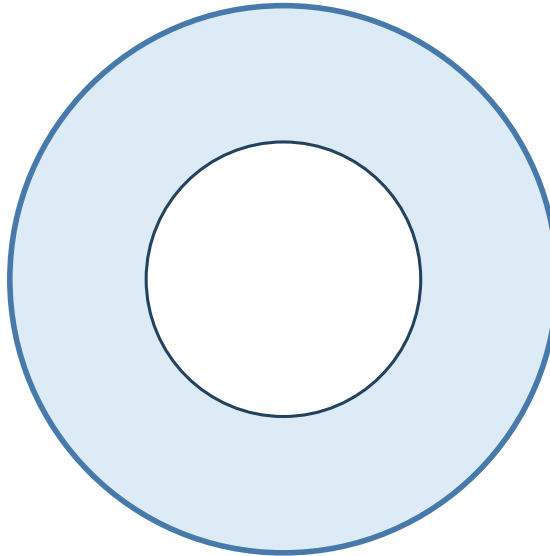
Both routes can produce increased heart mass and eventual dysfunction.

The heart can be both hypertrophied and dilated

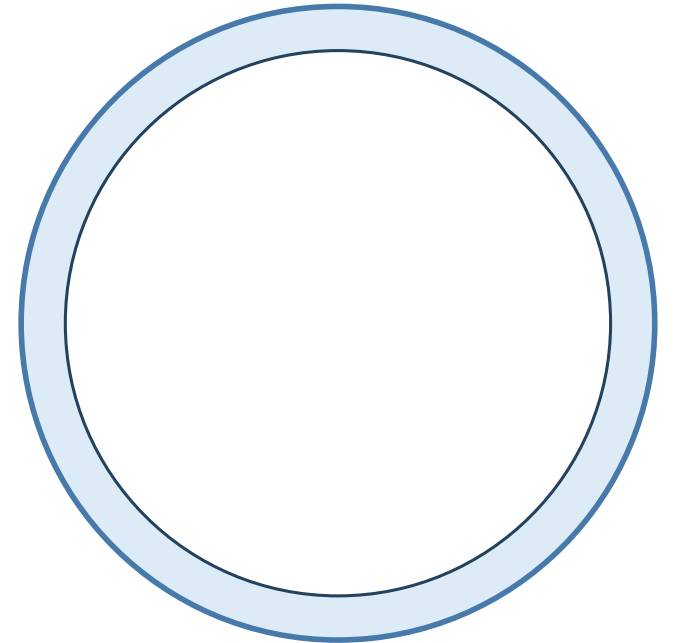
Original schematic ventricular cross-sections — not clinical images



Baseline



Concentric



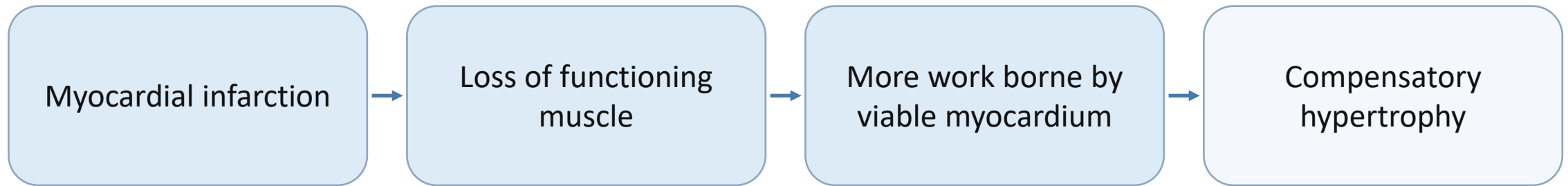
Hypertrophy + dilation

- An initially thick-walled ventricle may dilate with progressive failure.
- The dilated hypertrophied ventricle can appear deceptively normal in wall thickness.

Cardiac weight may rise strikingly

- Systemic hypertension, ischemic heart disease, aortic stenosis, mitral regurgitation, and dilated cardiomyopathy can produce markedly increased heart weight.
- Hearts weighing about two to three times the average in several of these conditions.
- Aortic regurgitation or hypertrophic cardiomyopathy can sometimes yield three- to fourfold increases.
- These are descriptive source examples, not clinical diagnostic thresholds.

Myocardial infarction creates a regional workload shift



- Remodeling in the surviving myocardium occurs around a regional injury.
- The distribution of overload differs from globally stressed ventricles.

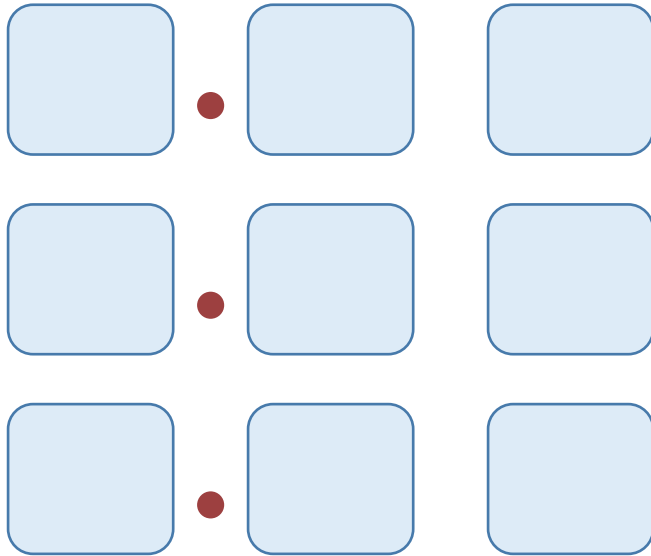
Valvular disease imposes more global loading

Post-infarction remodeling	Valvular remodeling
Regional loss of myocardial mass	Pressure/volume load on much of the chamber
Surviving cells carry extra work	Myocardium responds to shared loading
Viable myocardium hypertrophies	Global hypertrophy/dilation can occur

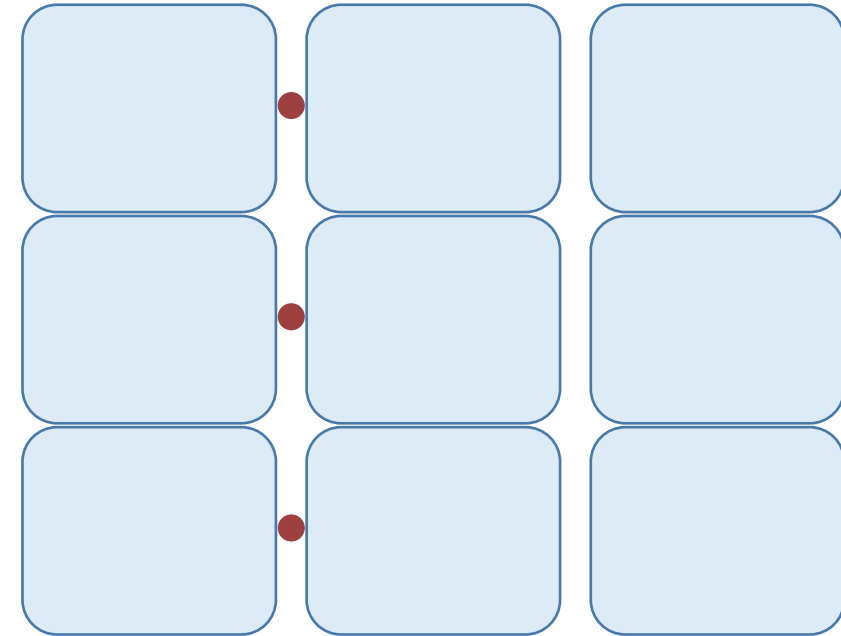
The pathologic trigger determines which regions first experience altered work.

Myocardial growth outpaces microvascular support

Schematic: Myocyte growth without proportional capillary expansion



Smaller myocytes



Hypertrophied myocytes

- Myocyte enlargement is not matched by proportional capillary-density growth.
- Relative oxygen and nutrient delivery becomes less secure.
- The mismatch is particularly consequential in pressure-overloaded myocardium.

Hypertrophy creates an oxygen supply–demand mismatch

Supply pressure

Relative capillary scarcity

Less robust nutrient delivery

Demand pressure

Greater muscle mass

Increased oxygen consumption

The enlarged heart becomes more vulnerable to ischemia-related decompensation.

Why myocardial oxygen demand increases

Mass

More hypertrophied tissue

Heart rate

Faster repetitive contractions

Inotropy

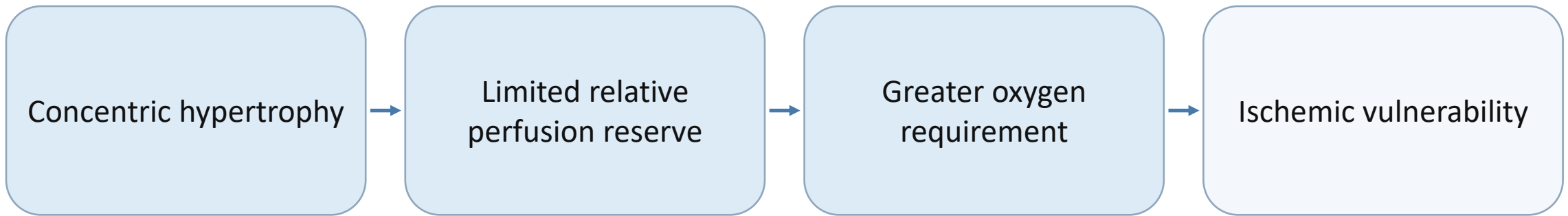
Greater force generation

Consequence

Higher myocardial oxygen use

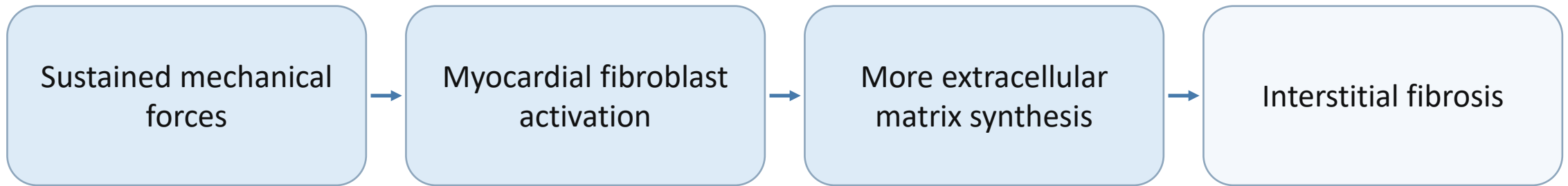
Supply does not necessarily expand proportionally as these demands increase.

Pressure-overloaded myocardium is ischemia-prone



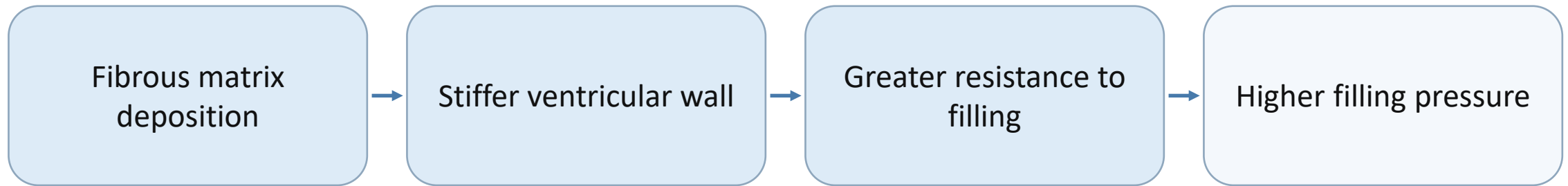
- Ischemia can compromise function even without new gross enlargement.
- A chronically adapted ventricle may cross from compensation into failure.

Mechanical stress activates fibroblasts as well



- Fibrosis is a parallel response to the same loading stimulus that drives myocyte growth.
- Myocytes and stromal cells jointly determine the remodeled myocardium.

Interstitial fibrosis resists diastolic filling



- Interstitial fibrosis can worsen function without an obvious fall in EF.
- This is a key connection between morphology and diastolic failure.

Myocyte hypertrophy and fibrosis act together

Myocyte component

Larger contractile cells

Greater oxygen demand

Stromal component

More interstitial matrix

Less compliant myocardium

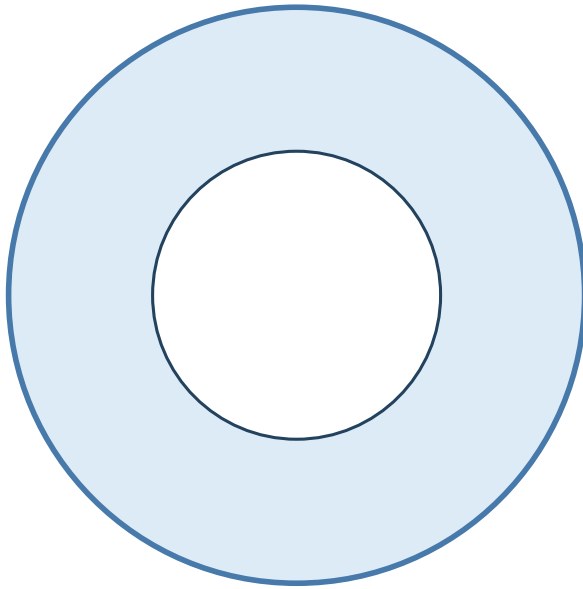
The failing heart is not explained by myocyte size in isolation.

Anatomic abnormality does not equal dysfunction severity

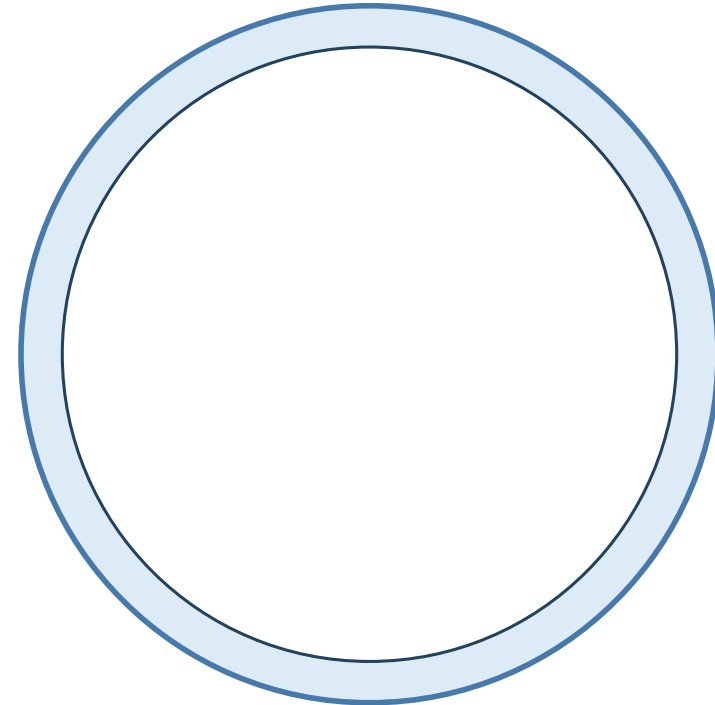
- Some heavy and dilated hearts show substantial functional failure.
- Other hearts can have comparatively modest visible abnormalities yet serious filling or contractile defects.
- Macroscopic inspection does not reveal all structural, biochemical, or molecular determinants of performance.
- Assessment requires physiological as well as morphologic interpretation.

The failing heart may be heavy, dilated, or thin-walled

Original schematic ventricular cross-sections — not clinical images



Earlier compensated

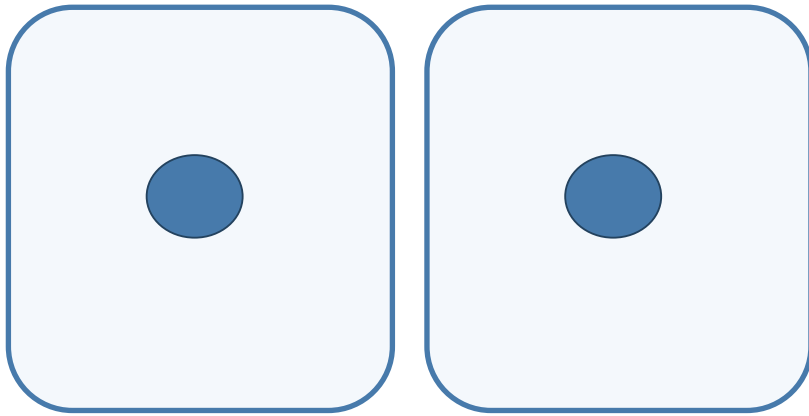


Dilated failing ventricle

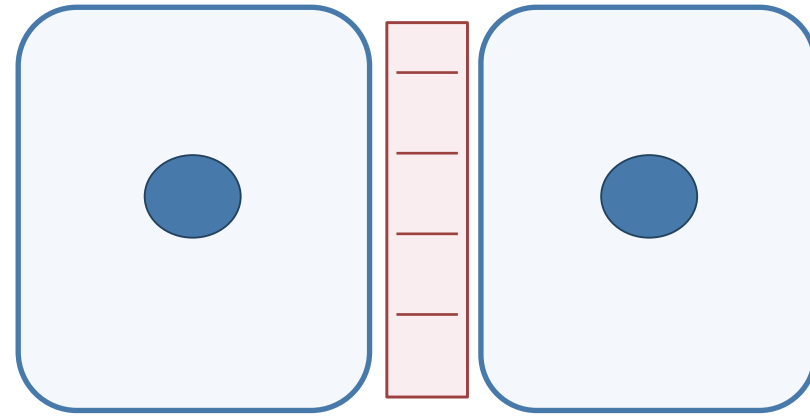
- Congestive failure generally involves heavy, often dilated hearts.
- Wall thickness may be relatively low despite greater cardiac mass.
- Histologic hypertrophy varies with the etiology and stage.

Microscopic remodeling: What to seek

Schematic — not histologic microscopy



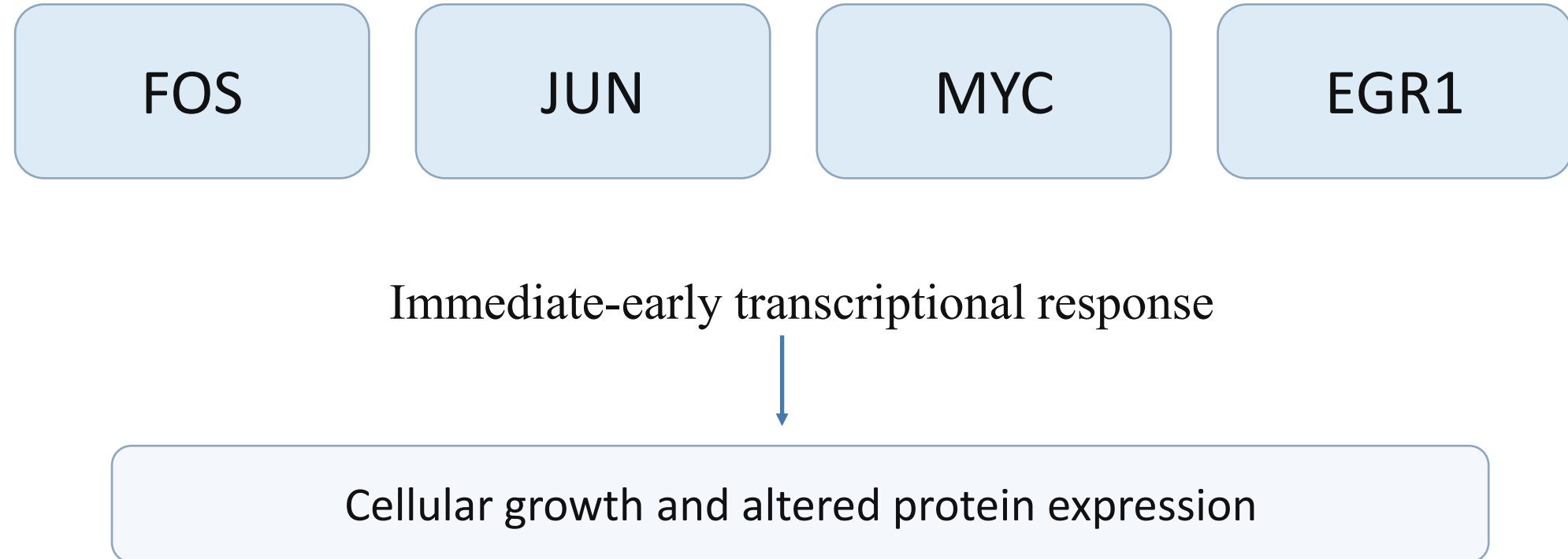
Myocytes: Little interstitial matrix



Expanded extracellular matrix

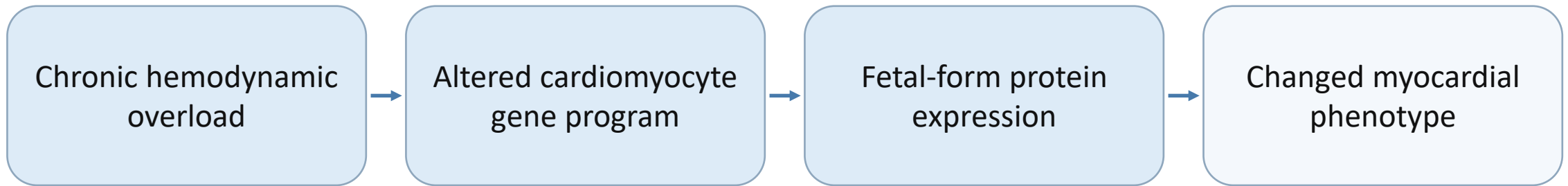
- Larger myocytes, often with enlarged nuclei.
- Interstitial fibrous tissue between myocytes.
- Neither feature alone quantifies the degree of functional failure.

Early-response genes participate in myocyte growth



- Hypertrophied cardiomyocytes express immediate-early genes.
- These transcriptional responses support growth and altered protein expression.

Prolonged overload reactivates fetal programs



- Examples include fetal forms of myosin, natriuretic peptides, and collagen.
- Molecular remodeling can be present even when gross appearance is non-specific.

Remodeling involves multiple myocardial cell states

Cardiomyocytes

Contractile-cell enlargement and gene changes

Fibroblasts

Extracellular matrix synthesis

Microvascular compartment

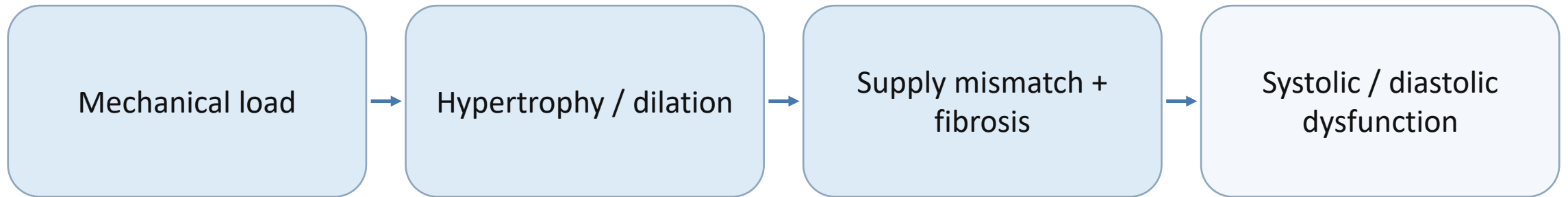
Capillary supply fails to scale

Integrated myocardium

Emergent systolic/diastolic function

Single-cell analyses are resolving cell-type and cell-state changes.

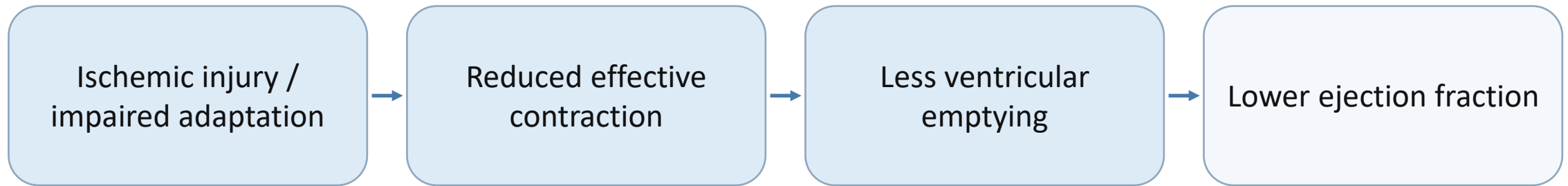
Progression pathway: Stress to dysfunction



Initially adaptive responses may become maladaptive with sustained loading

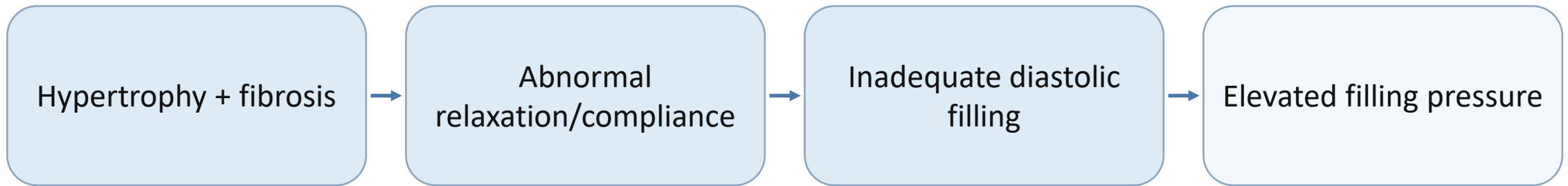
Persistent pathologic work may overwhelm compensation; This conceptual sequence is not a fixed timetable.

Systolic failure: A contractile pathway



- Ventricular dilation may accompany the process.
- LVEF reflects emptying but does not explain the entire remodeling mechanism.

Diastolic failure: A filling pathway



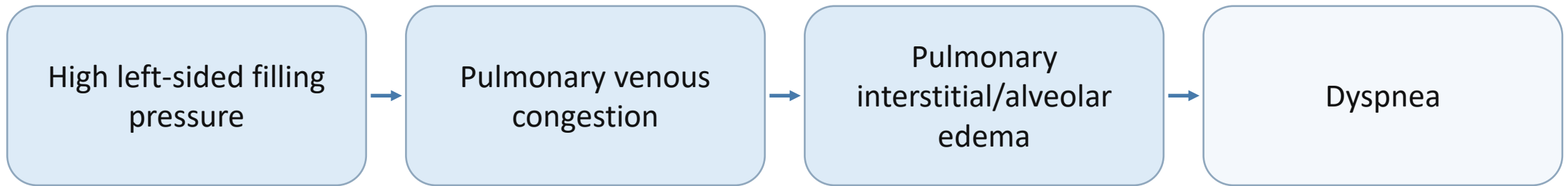
- Failure can occur despite preserved ejection fraction.
- Mechanical resistance to filling links tissue change to clinical congestion.

Different mechanisms, shared clinical consequences

Systolic pathway	Diastolic pathway
Impaired contraction	Impaired relaxation/filling
Reduced ejection fraction often evident	Ejection fraction may remain preserved
Output may fall	Output reserve may be inadequate
High filling pressure can develop	High filling pressure can develop

Forward and backward consequences are possible in either pattern.

Pulmonary congestion translates filling pressure to symptoms



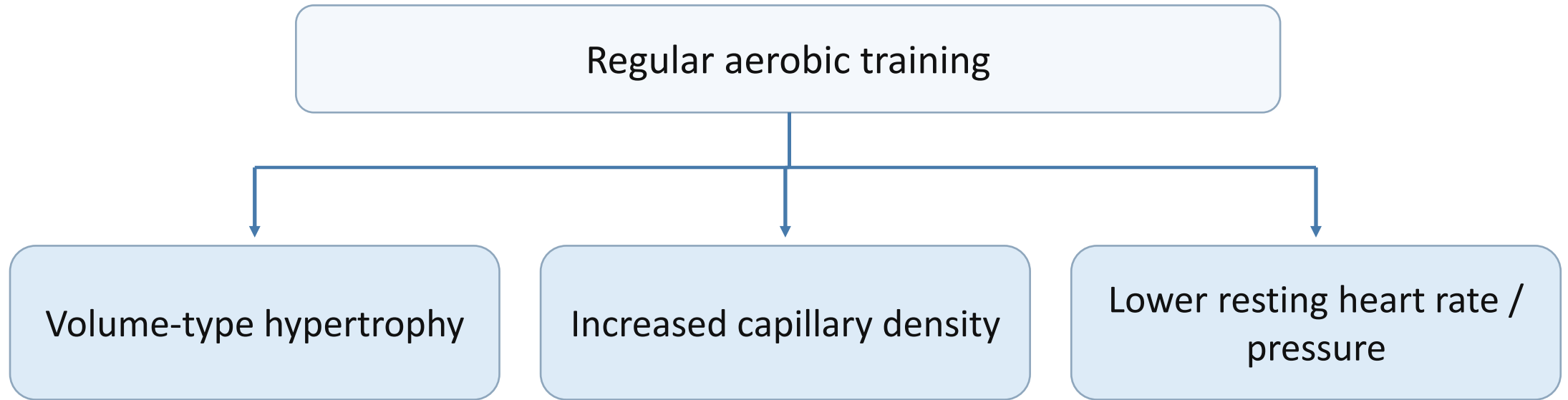
- This is a downstream clinical consequence, not the primary remodeling mechanism.
- Right-sided failure is covered separately in the adjoining unit.

Physiologic hypertrophy is a different adaptation

Exercise-associated	Persistent disease-associated
Training stimulus	Pressure/volume overload or injury
Potentially beneficial adaptation	Progression to functional vulnerability
Aerobic training may raise capillary density	Capillary density does not rise proportionally
Resting rate and blood pressure may fall	Metabolic burden often increases

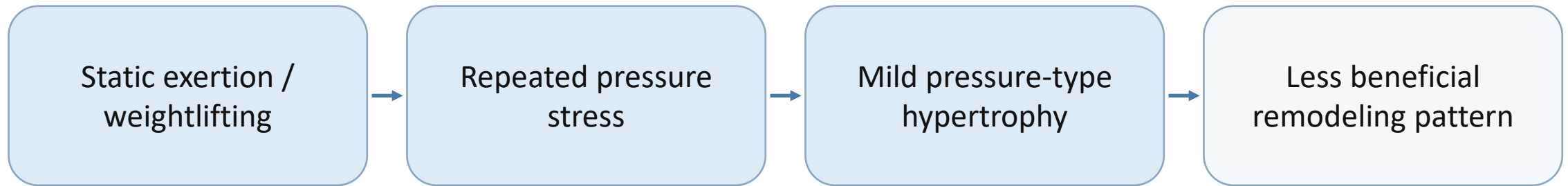
Shared enlargement does not imply the same biological consequences.

Aerobic exercise favors adaptive volume-type remodeling



- Examples include endurance activities such as long-distance running.
- Lower resting heart rate and blood pressure are noted in the source.

Static exercise produces a different loading pattern



- The text gives recurrent Valsalva maneuvers as an example of the pressure stimulus.
- Do not equate this with the severity or prognosis of pathologic hypertension.

Clinicopathologic case: Long-standing hypertension

Teaching vignette (hypothetical)

An adult with chronic systemic hypertension develops a thick left ventricular wall and gradually increasing exertional limitation.

What cellular mechanism produces the typical wall geometry?

Parallel sarcomere addition increases myocyte cross-sectional area; Fibrosis may later impair filling.

- Mechanism: Pressure overload
- Expected remodeling: Concentric hypertrophy
- Potential later deficit: Diastolic filling resistance

Clinicopathologic case: Chronic valve regurgitation

Teaching vignette (hypothetical)

A patient with long-standing valvular regurgitation has marked cavity enlargement; The ventricular wall looks only modestly thick.

Does modest wall thickness exclude hypertrophy?

No. Series sarcomere addition and dilation can increase cardiac mass without conspicuously increasing wall thickness.

- Mechanism: Volume overload
- Expected remodeling: Cavity dilation
- More useful morphologic metric: Overall cardiac mass

Clinicopathologic case: Surviving myocardium after infarction

Teaching vignette (hypothetical)

Following myocardial infarction, a ventricle develops progressive enlargement with altered function.

Why would surviving cardiomyocytes enlarge?

Loss of functioning muscle shifts workload to viable myocardium, inducing compensatory hypertrophy.

- Initiator: Regional myocardial loss
- Adaptive response: Increased work in viable muscle
- Longer-term risk: Decompensation

Clinicopathologic case: Preserved EF, high filling pressure

Teaching vignette (hypothetical)

A hypertrophied, fibrotic ventricle has preserved ejection fraction yet fills poorly and develops pulmonary congestion.

Which failure dimension explains this presentation?

Diastolic dysfunction: A stiff ventricle may require elevated filling pressures despite preserved EF.

- Myocardial substrate: Hypertrophy + interstitial fibrosis
- Physiologic deficit: Low compliance
- Clinical effect: Backward congestion

Three pitfalls when interpreting the failing heart

Pitfall 1

Thick wall $\neq$ preserved function

Pitfall 2

Normal wall thickness $\neq$ normal mass

Pitfall 3

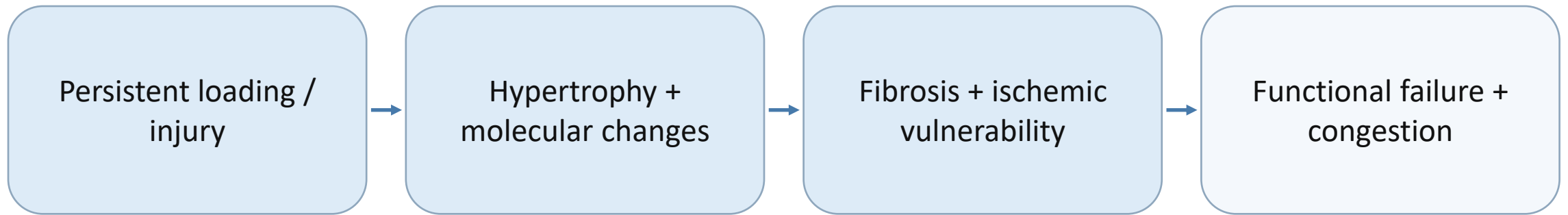
Preserved EF $\neq$ no failure

Correct approach

Integrate load, geometry, histology, and physiology

Macroscopic, cellular, and functional observations answer different questions.

Integrated mechanism: From work to congestion



- Progression is not inevitable at a fixed time or cardiac weight.
- Severity depends on the initiating insult and remaining myocardial reserve.

Five distinctions to retain

- Pressure overload: parallel sarcomeres; usually concentric wall thickening.
- Volume overload: series sarcomeres; predominantly chamber dilation.
- Hypertrophy increases demand without proportionately increasing capillary density.
- Mechanical stress drives interstitial fibrosis and resistance to filling.
- Molecular adaptation and gross anatomy do not reliably quantify functional reserve.