

Mechanisms of Hypertrophy

Cellular sensing • signaling • protein synthesis • cardiac adaptation

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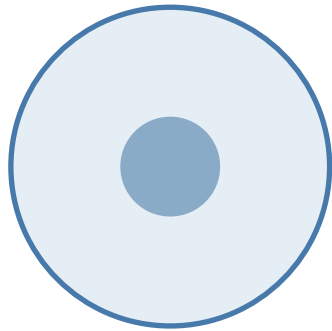
What students should be able to explain

- Define hypertrophy as enlargement of preexisting cells through new intracellular material.
- Trace mechanical and humoral stimuli to protein synthesis and contractile gene expression.
- Contrast physiologic growth with pathologic, potentially maladaptive cardiac hypertrophy.
- Explain fetal-gene reprogramming, atrial natriuretic factor, and the route to heart failure.

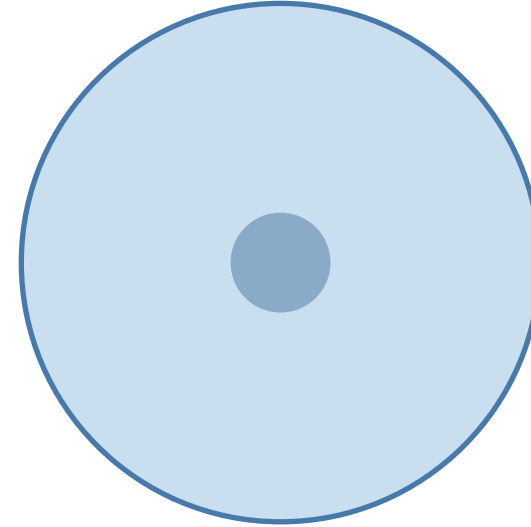
Cellular adaptation is a regulated response

- Adaptations are changes in cell size, number, phenotype, metabolic activity, or function.
- They develop when the cellular environment or functional demand changes.
- Hypertrophy is the size-increasing adaptation; It may be physiologic or pathologic.
- Persistent stress can turn an initially useful adaptation into tissue injury.

Hypertrophy means a larger cell, not more cells



Protein synthesis

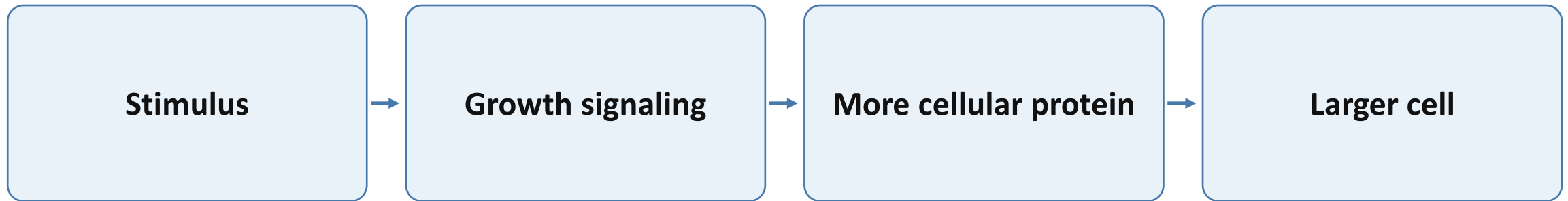


Baseline cell
smaller cytoplasmic volume

Hypertrophied cell
more intracellular structures

Schematic — not histology

The core material balance of hypertrophy

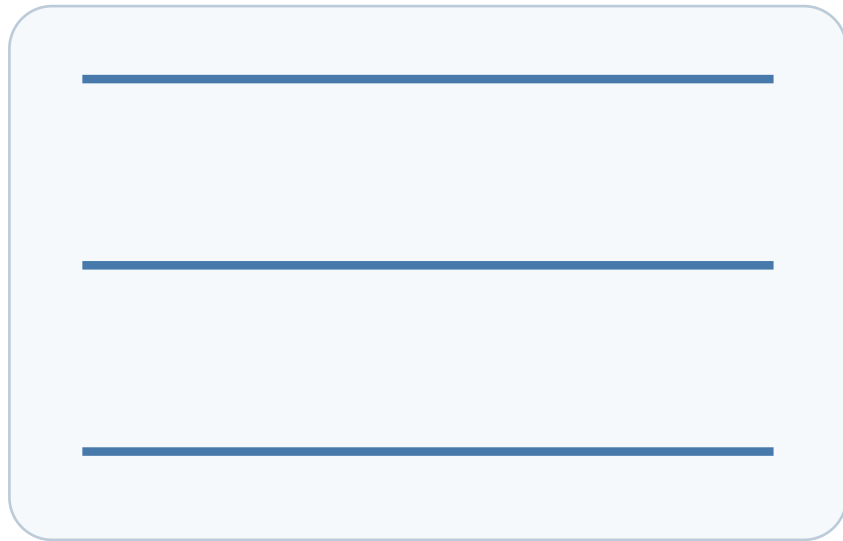


An increase in synthesis and assembly of structural components explains the gain in cell volume.

What physically enlarges a hypertrophied cell?

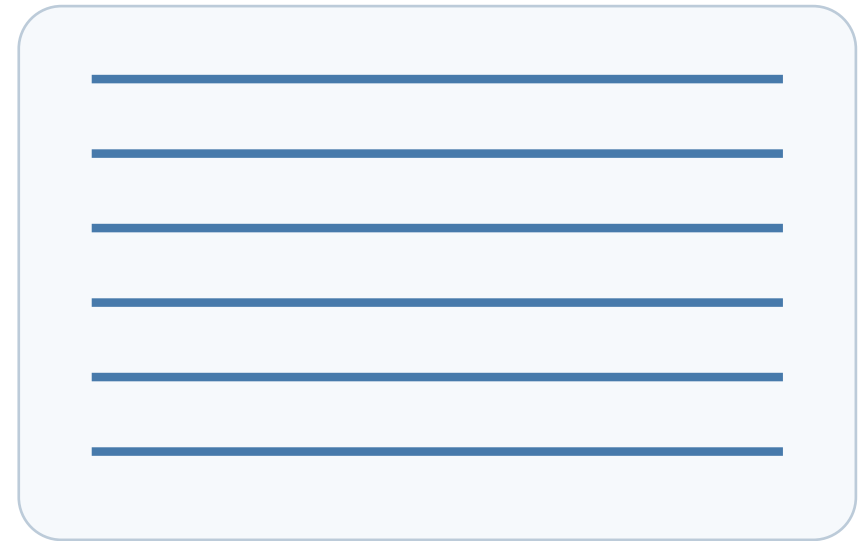
- New intracellular structural components accumulate within the existing cell.
- Muscle cells synthesize additional contractile proteins and myofilaments.
- The larger cell contributes more tissue mass without requiring a new cell.
- A size increase is not equivalent to accumulation of water during reversible swelling.

Additional myofilaments increase muscle-cell content



Baseline

↑ Synthesis and
assembly



After hypertrophic stimulation

Schematic — not histology

Hypertrophy and hyperplasia are different responses

Hypertrophy

- Cell size increases.
- Preexisting cells become larger.
- Can occur in cells with little division capacity.

Hyperplasia

- Cell number increases.
- Requires cells able to proliferate.
- Can coexist with hypertrophy in an organ.

Both can enlarge an organ, but the cellular mechanisms are distinct.

Why cardiac muscle relies on hypertrophy

- Cardiac myocytes have very limited capacity to increase their number by division.
- When work demand rises, increasing the size of preexisting myocytes is the dominant growth response.
- New contractile protein initially increases force-generating capability.
- The heart is a major model for studying molecular hypertrophy.

Three contexts that produce cell enlargement

Increased workload

Resistance loading can enlarge skeletal muscle fibers.

Pressure overload

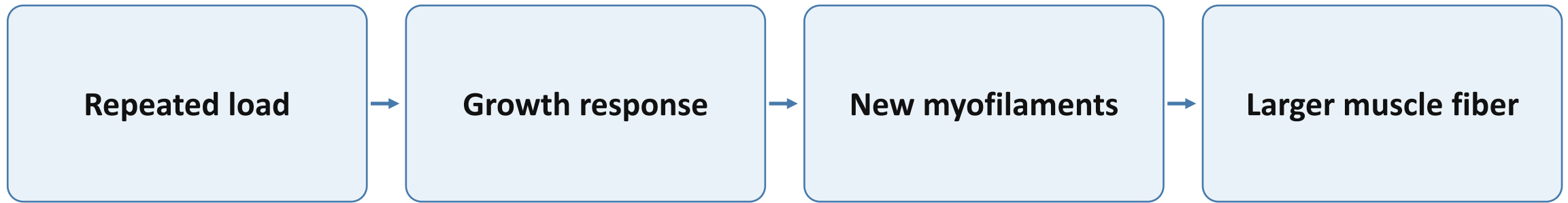
Hypertension or valvular disease drives cardiac enlargement.

Hormonal stimulation

Pregnancy-related estrogen signaling enlarges uterine smooth muscle.

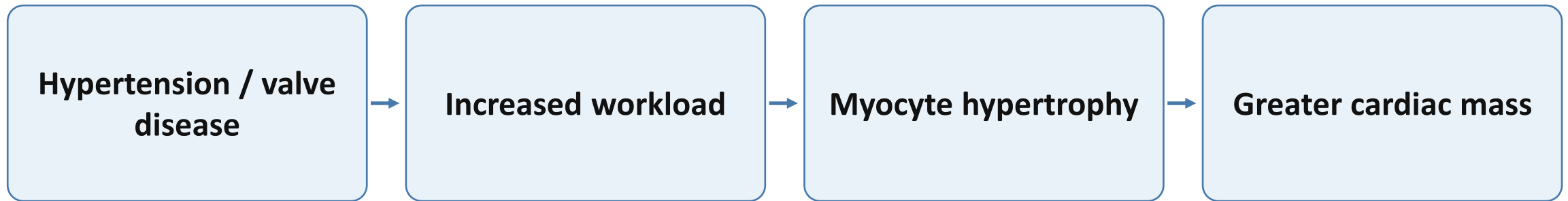
Distinct triggers converge on an increase in cellular protein and size.

Skeletal muscle: Functional demand to growth



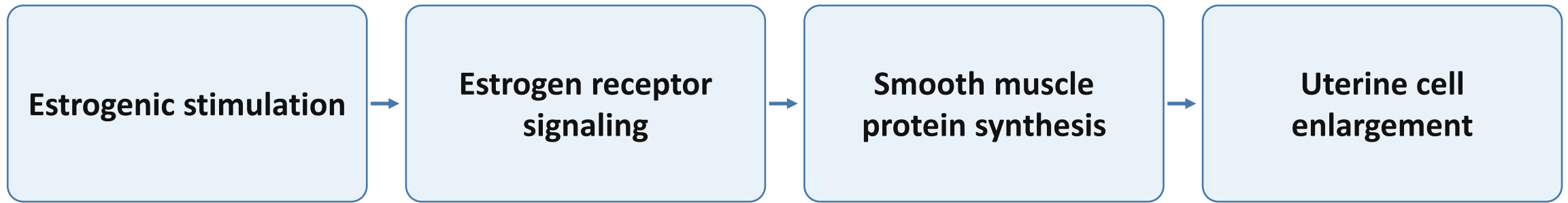
The effect arises mainly from enlargement of individual skeletal muscle fibers.

Pressure overload: Why the heart enlarges



Early compensation does not guarantee that the enlarged heart will remain functionally adequate.

Pregnancy: A receptor-mediated example



The gravid uterus as an example of mainly smooth muscle hypertrophy.

Physiologic and pathologic hypertrophy

Physiologic settings

- Functional demand or hormonal stimulation.
- Exercise-induced skeletal muscle growth.
- Pregnancy-associated uterine smooth muscle growth.

Pathologic cardiac setting

- Sustained pressure overload.
- Hypertension or diseased valves.
- Can progress from adaptation to cardiac dysfunction.

The key difference includes the nature and persistence of the stimulus—not cell size alone.

Mechanism overview: Stimulus to phenotype



Multiple pathways converge on protein production; The diagram is a synthesis, not a single linear kinase cascade.

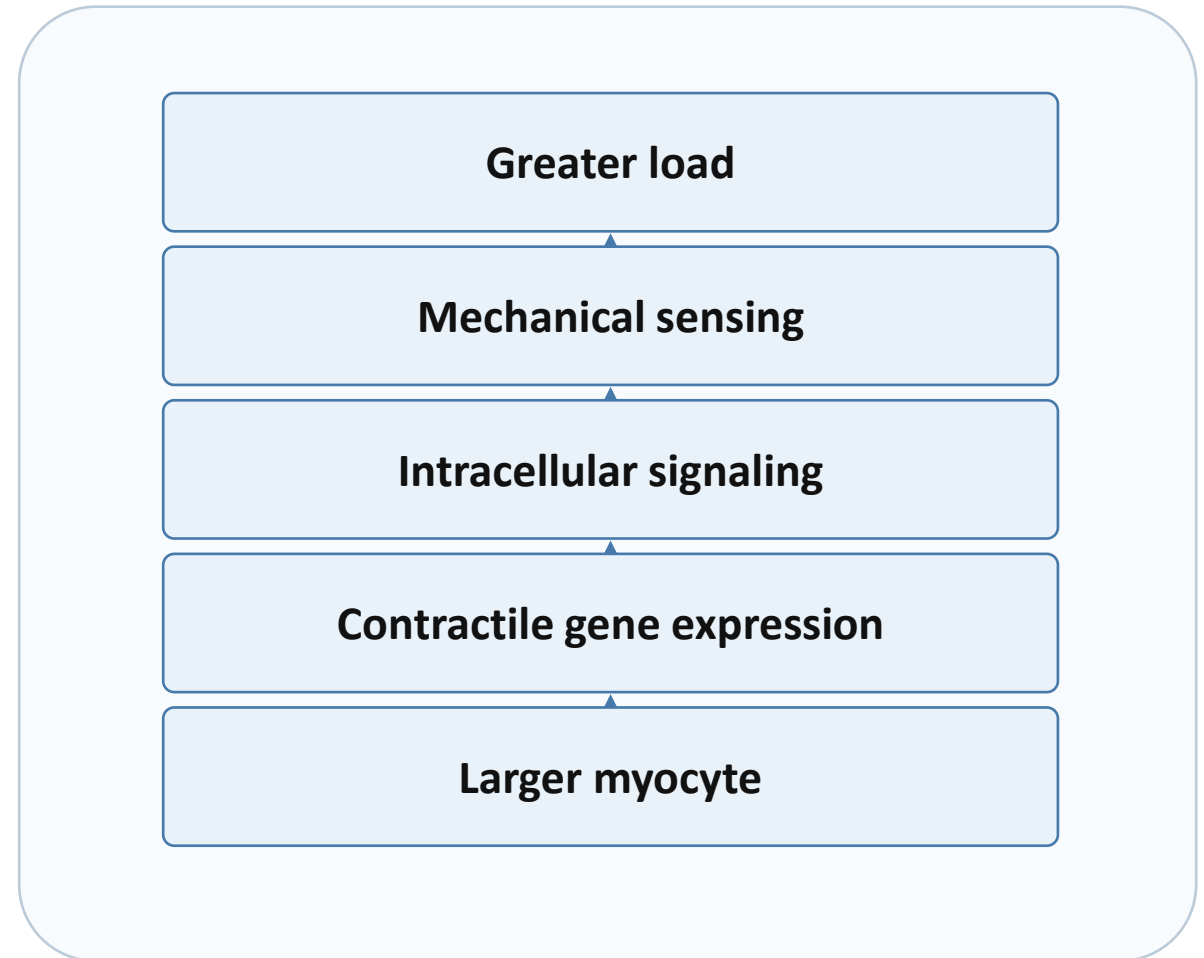
Mechanical sensors detect increased load

- Mechanical sensors within cells respond to greater physical demand.
- They convert the increased mechanical load into intracellular signaling responses.
- The resulting network modifies gene expression and protein production.
- The source does not define one universal mechanosensor or a single obligatory route.

Mechanical loading becomes a growth signal

A mechanically induced sequence

- The input is increased force or workload rather than a newly added cell.
- The sensor response activates multiple downstream pathways.
- Transcriptional changes drive new contractile proteins.



Schematic

Growth factors also drive the response

- Hypertrophy is stimulated by growth factors as well as direct effects of mechanical force.
- Pathways may induce additional growth-factor production.
- Growth-factor signaling can reinforce the cellular enlargement program.
- Signals may converge even when their initiating stimuli differ.

Two emphasized signaling families

PI3K/AKT

Postulated by Robbins as especially important in physiologic or exercise-associated hypertrophy.

GPCR-initiated

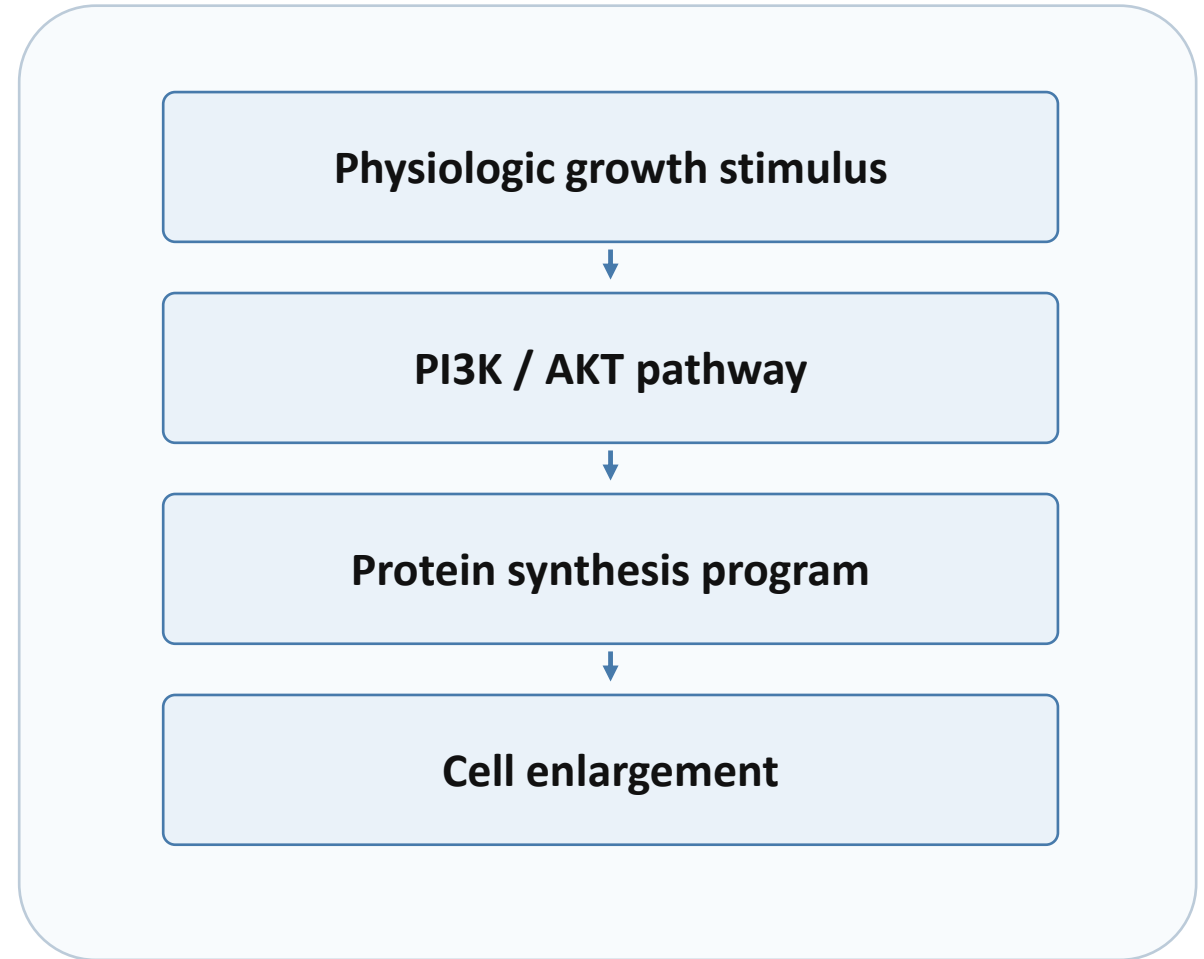
Activated by multiple growth factors and vasoactive agents; Emphasized in pathologic hypertrophy.

These are relative emphases, not mutually exclusive switches.

PI3K/AKT as a physiologic growth route

Textbook emphasis

- PI3K denotes phosphoinositide 3-kinase.
- AKT is a downstream signaling component named with PI3K.
- This signaling axis particularly to exercise-associated hypertrophy.



Schematic

Do not interpret pathway preference as exclusivity

Supported statement

- PI3K/AKT is postulated to be more important in physiologic hypertrophy.
- GPCR pathways are thought more important in pathologic hypertrophy.

Unsupported oversimplification

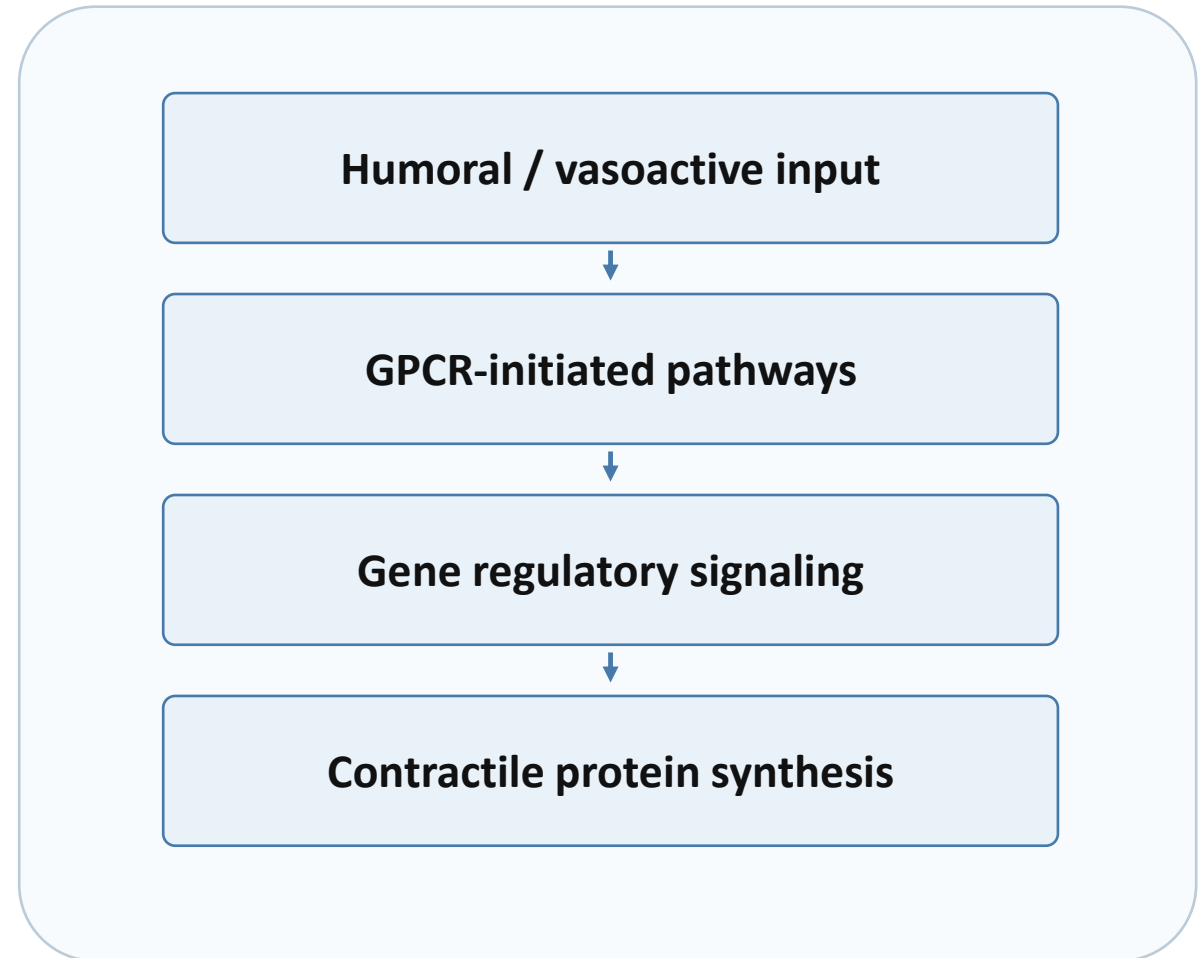
- PI3K/AKT occurs only in exercise.
- GPCR signals occur only in disease.
- One receptor or one pathway alone explains all hypertrophy.

A complex downstream network rather than an exclusive binary choice.

GPCR-initiated signaling in hypertrophy

Textbook emphasis

- G-protein–coupled receptors participate in growth-related signaling.
- Growth factors and vasoactive agents can initiate these responses.
- The source associates this route more strongly with pathologic hypertrophy.



Schematic

Named signals that appear in the network

Growth factors

TGF- β , insulin-like growth factor 1 (IGF-1), fibroblast growth factor.

Vasoactive agents

α -adrenergic agonists, endothelin-1, and angiotensin II.

Mechanical input

Increased physical load detected by cellular mechanical sensors.

The groups are sources of hypertrophic signaling, not a claim that each factor acts via the same receptor.

Growth factors act within a signaling web

- Increased TGF- β , IGF-1, and fibroblast growth factor production among pathway outputs.
- These mediators represent growth-related inputs or reinforcement of the hypertrophic program.
- The excerpt does not assign a unique quantitative contribution to any of these growth factors.
- Different inputs feed into transcriptional control and new contractile protein expression.

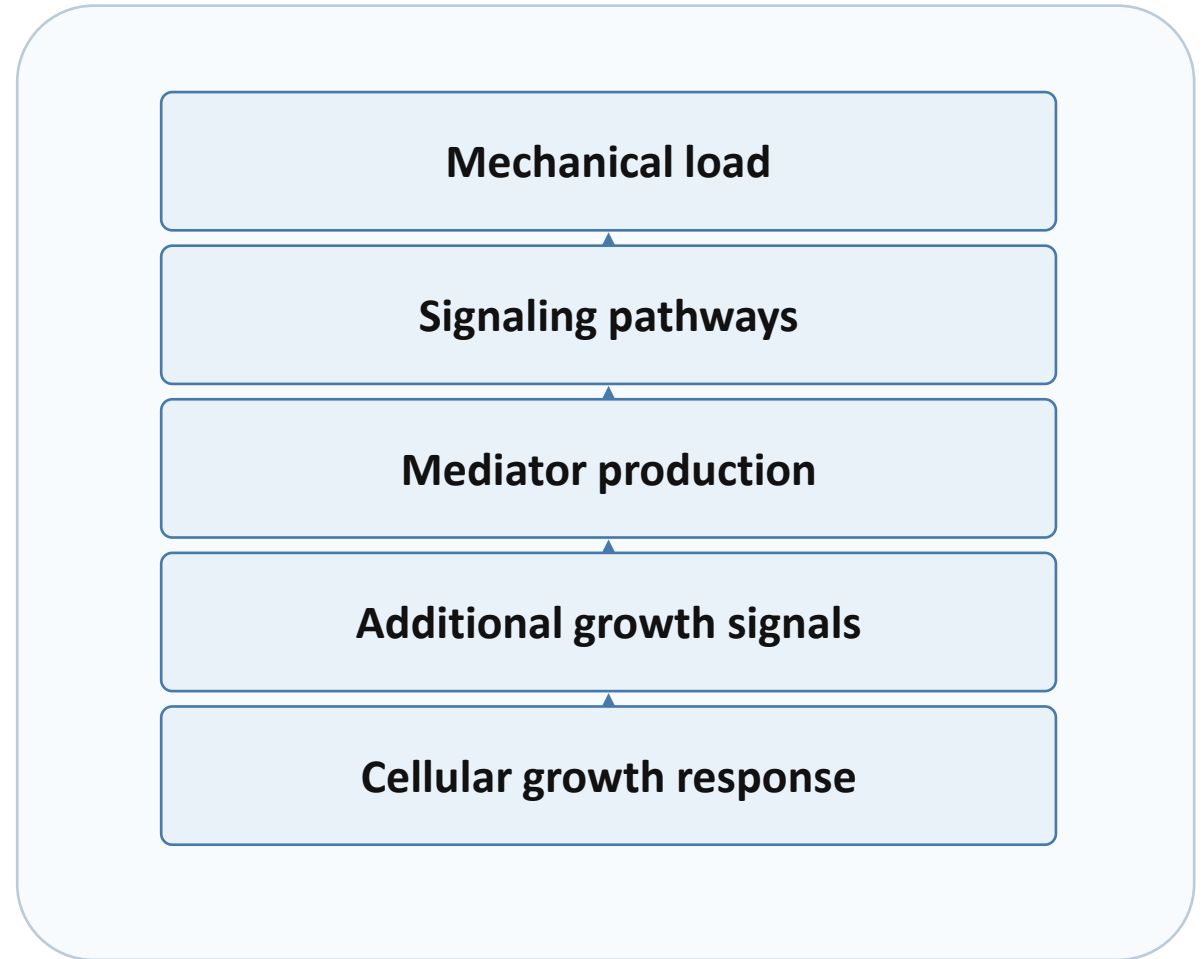
Vasoactive agents also signal to myocytes

- The named vasoactive mediators are α -adrenergic agonists, endothelin-1, and angiotensin II.
- Their importance is not limited to immediate circulatory effects in the described model.
- They participate in hypertrophy-associated signaling responses.
- These agents are in the network upstream of transcriptional regulation.

Signals can reinforce signaling

A network, not a solitary arrow

- Mechanical sensing activates intracellular signaling.
- Some activated routes increase growth-factor and vasoactive-mediator production.
- Those mediators contribute further inputs to the overall growth program.

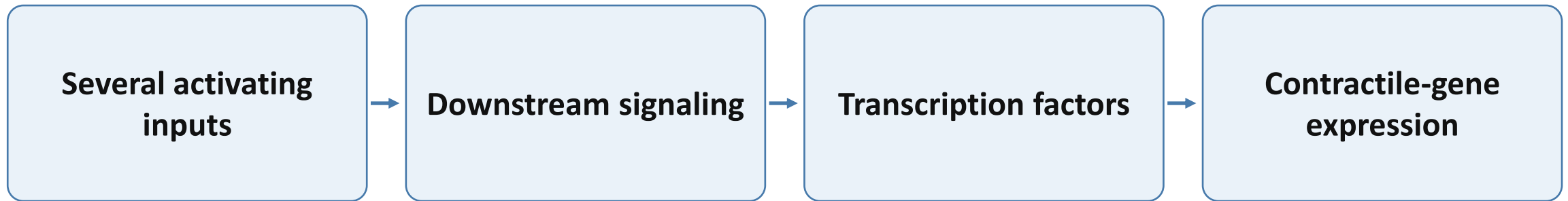


Schematic

What each upstream component contributes

Component	Role in hypertrophy	Typical textbook emphasis
Mechanical sensors	Detect increased physical load	Load-responsive input
PI3K / AKT	Intracellular growth signaling	Physiologic / exercise
GPCR-initiated routes	Transmit humoral / vasoactive signals	Pathologic cardiac growth
Growth and vasoactive agents	Sustain or provide growth-related inputs	Signal-network mediators

Convergence occurs at gene regulation



Different stimuli can produce the same larger-cell endpoint through shared gene-expression responses.

Transcription factors named

GATA4

One of the transcription factors activated by hypertrophy-associated signaling.

NFAT

Nuclear factor of activated T cells; Listed as a growth-program transcription factor.

MEF2

Myocyte enhancer factor 2; Participates in contractile-gene regulation.

The excerpt names these regulators without mapping a unique upstream pathway to each one.

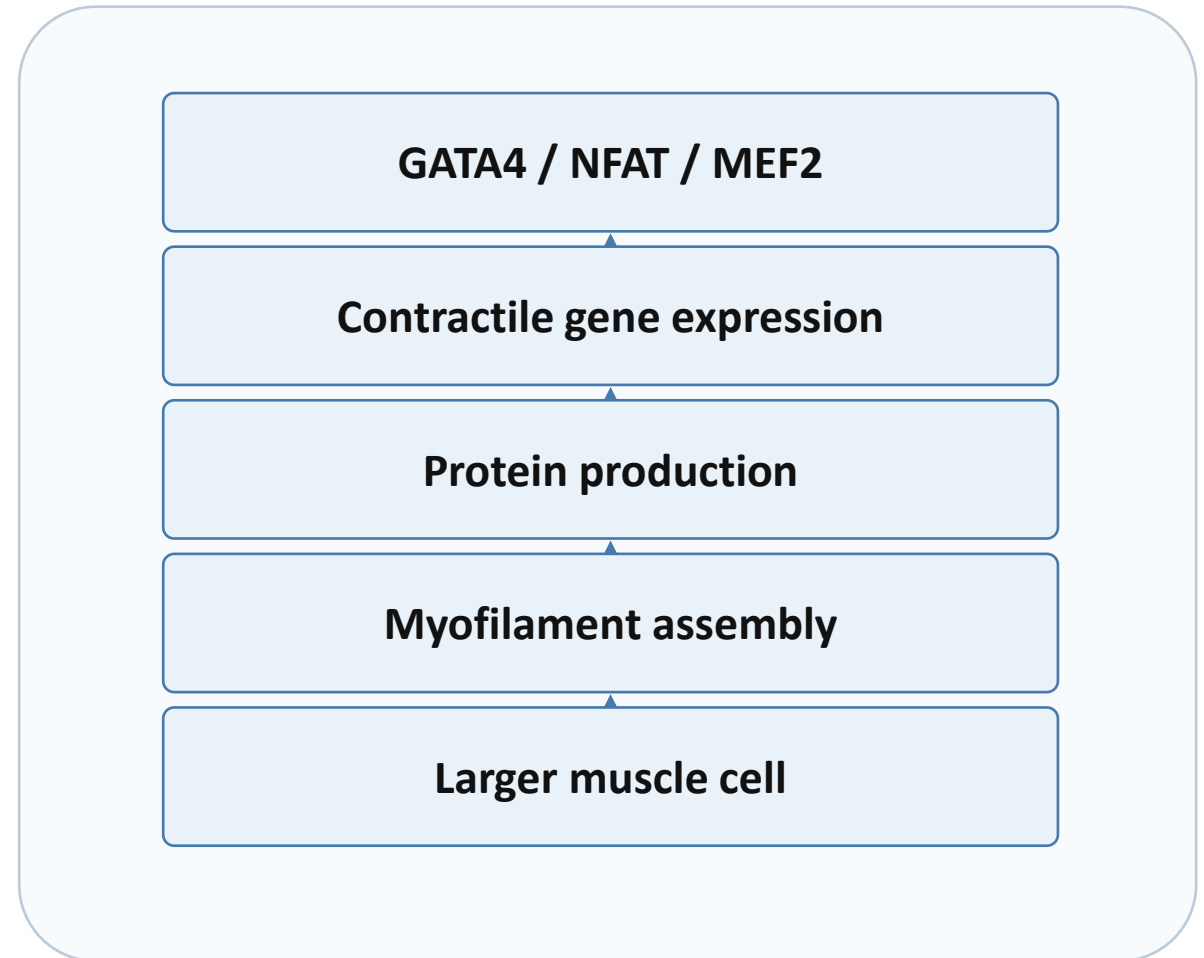
What transcription-factor activation achieves

- Signaling inputs alter activity of transcription factors rather than directly enlarging a cell.
- Activated factors increase expression of genes encoding contractile proteins.
- New proteins must then be synthesized and assembled as cellular structures.
- This explains why the growth response is more than acute mechanical stretch.

Gene expression creates a structural phenotype

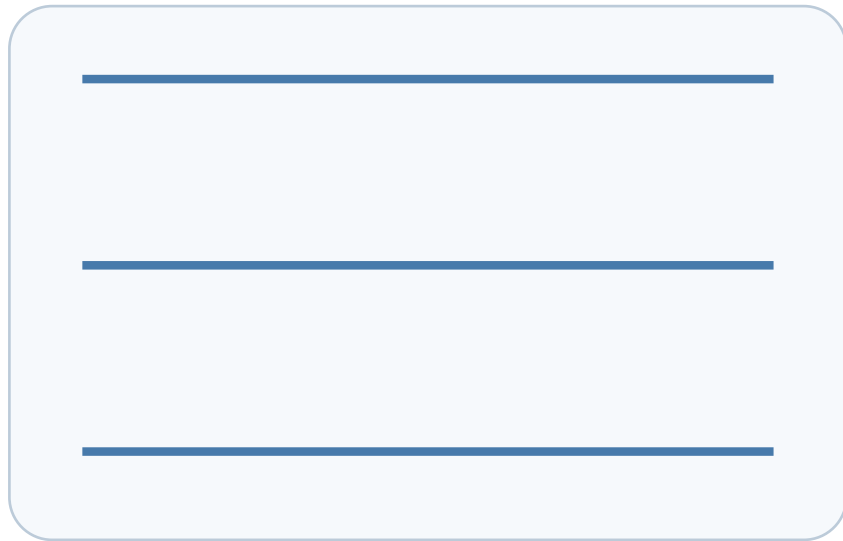
Follow the causal chain

- Mechanical and receptor-linked routes converge on transcriptional control.
- Contractile protein genes are expressed more strongly.
- The cell synthesizes additional structural material.



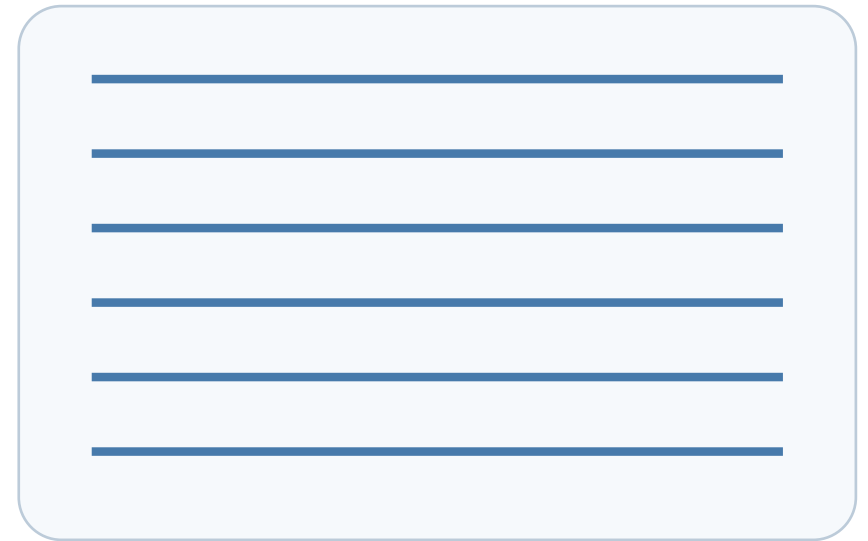
Schematic

More myofilaments explain stronger contraction



Baseline

↑ Synthesis and
assembly



After hypertrophic stimulation

Schematic — not histology

Cell enlargement can initially improve function

- More myofilaments allow each muscle cell to generate greater force.
- The enlarged cell supports higher work capacity of the whole muscle.
- This is the compensatory rationale for increased myocardial mass.
- The improvement is conditional: Continuing stress can exceed adaptive capacity.

Structure and function are linked but distinct

Structural adaptation

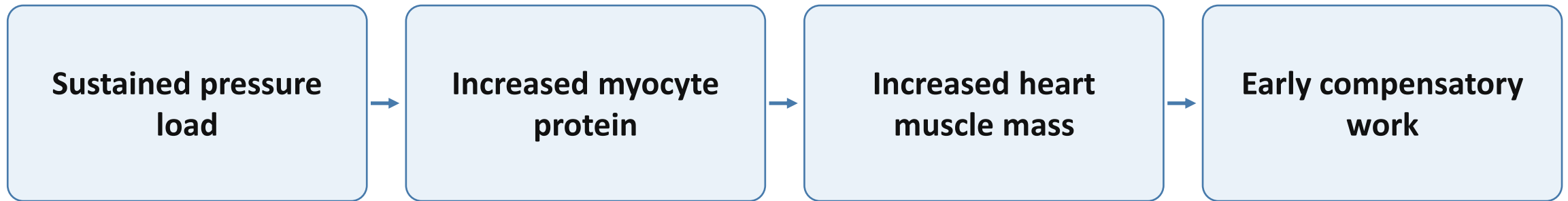
- Increased intracellular protein.
- Additional myofilaments.
- Increased myocyte size and tissue mass.

Functional response

- Greater force-generation capacity.
- Initially greater ability to meet workload.
- Not proof of long-term preserved function.

Cell growth explains early compensation but does not exclude later dysfunction.

An initially useful cardiac response



Cardiac hypertrophy can temporarily maintain performance against elevated demand.

Why cardiac hypertrophy is a central model

- Cardiac growth is readily linked to a definable stimulus: Increased hemodynamic demand.
- Myocytes mainly enlarge rather than increase in number.
- The same process reveals both adaptive cellular responses and maladaptive limits.
- The key question becomes when structural growth stops preserving function.

Recognizing hypertrophy in three organs

Setting	Dominant stimulus	Cellular response
Skeletal muscle after resistance loading	Increased functional demand	Larger individual muscle fibers
Pressure-overloaded heart	Increased myocardial workload	Larger cardiomyocytes
Gravid uterus	Estrogenic hormone signaling	Mainly larger smooth muscle cells

Mechanistic vignette: Chronic hypertension

A person with long-standing elevated arterial pressure develops increased left ventricular muscle mass. The discussion is restricted to the cellular adaptation, not clinical staging.

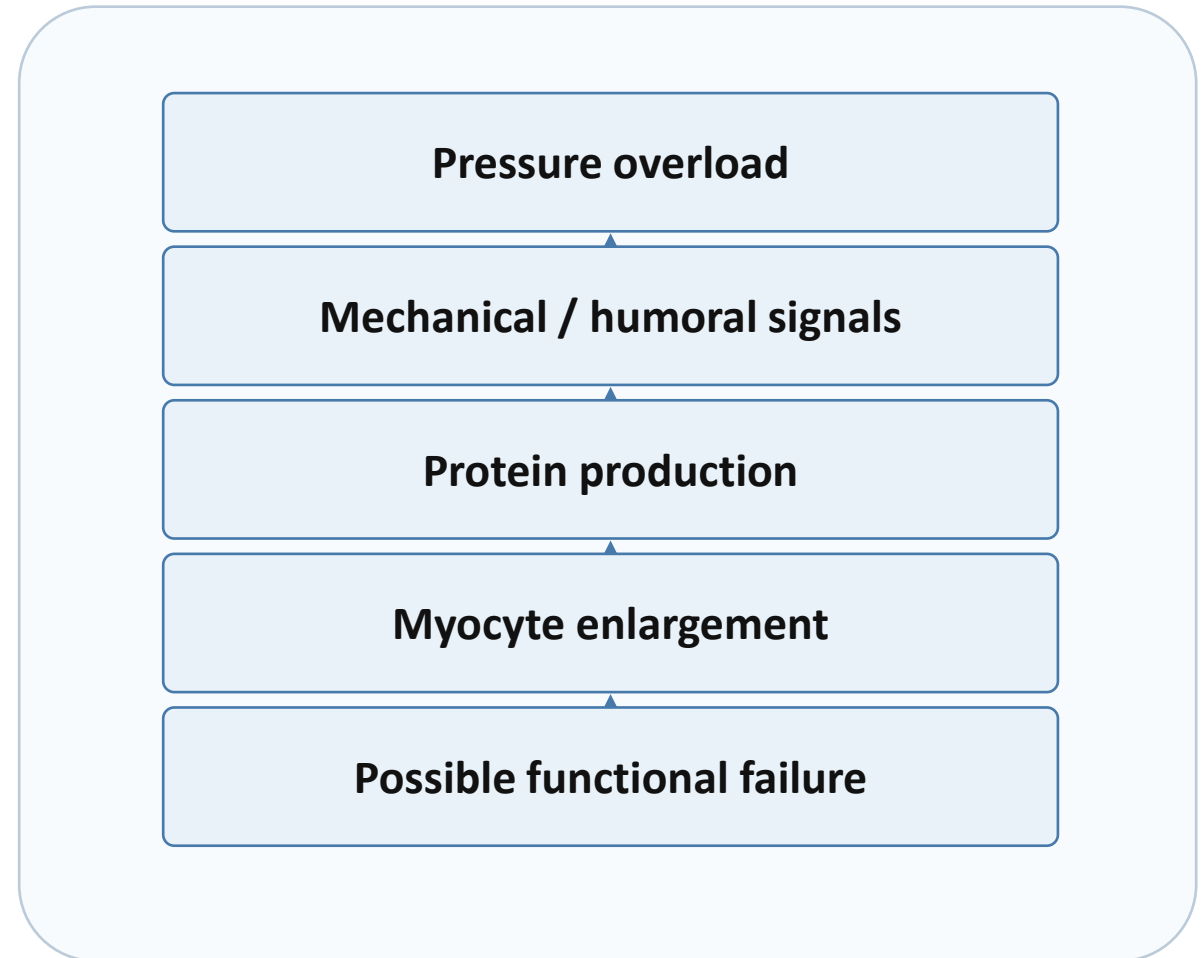
Explain the mechanism:

- Identify the stimulus detected by cardiac myocytes.
- Trace the signal to greater contractile protein production.
- Explain why the enlargement can later become maladaptive.

Hypertensive hypertrophy: Mechanism explained

Causal interpretation

- High pressure imposes greater work on cardiomyocytes.
- Mechanosensing and growth-related signaling increase contractile gene expression.
- Persistent load eventually can overwhelm the compensatory response.



Schematic

Mechanistic vignette: Resistance training

A healthy adult begins sustained resistance training and develops larger skeletal muscles without a presumed increase in the number of mature muscle fibers.

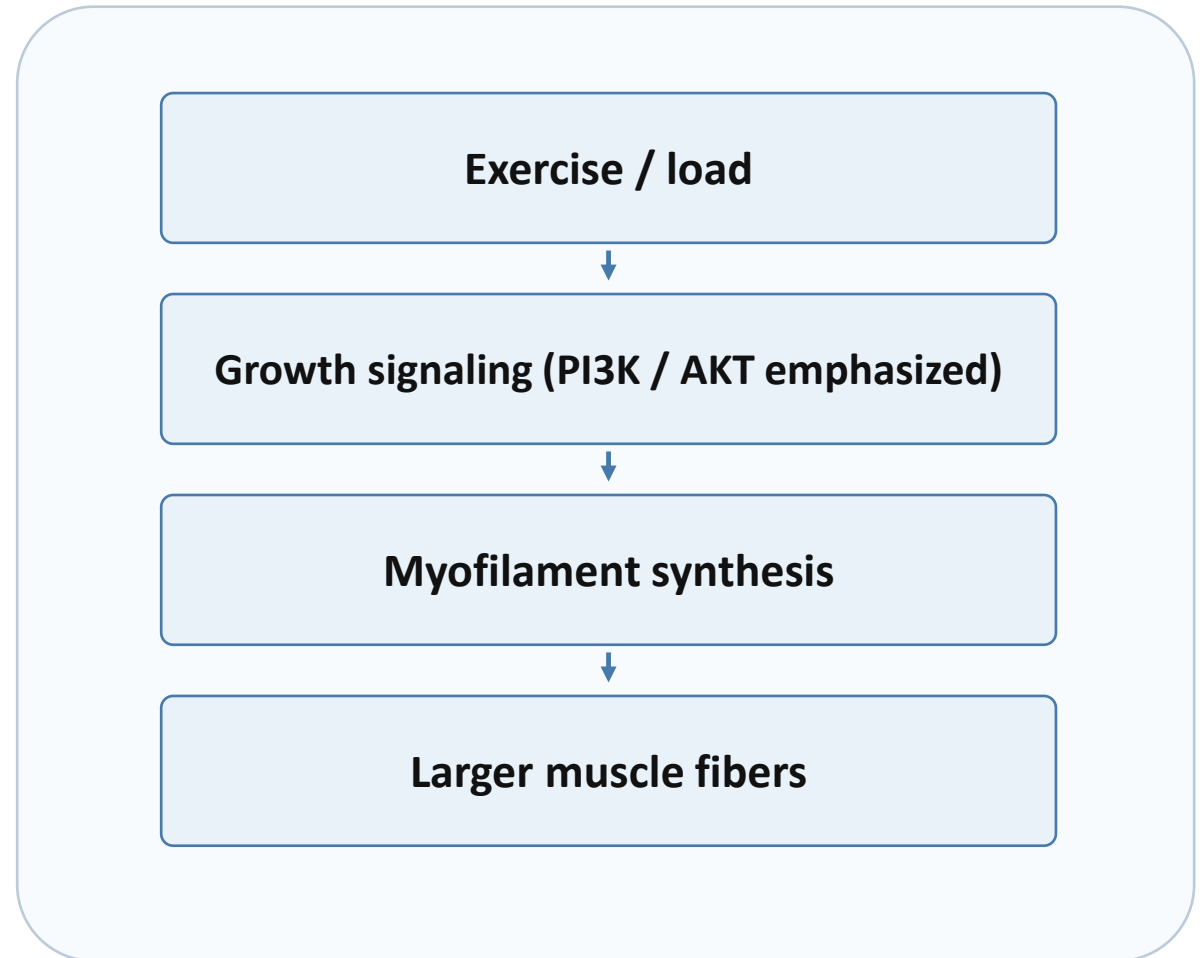
Explain the mechanism:

- What increases at the level of an individual fiber?
- Why is “more muscle cells” the wrong primary explanation?
- Which emphasized growth pathway is linked to physiologic hypertrophy?

Resistance-training hypertrophy: Interpretation

Causal interpretation

- Repeated functional demand stimulates new contractile protein synthesis.
- The hypertrophic fiber becomes larger and contains more myofilaments.
- PI3K/AKT particularly with exercise-related growth.



Schematic

Mechanistic vignette: Pregnancy

During pregnancy the uterus becomes much larger; A microscopy comparison is described, but no authentic textbook image is reproduced in this lecture.

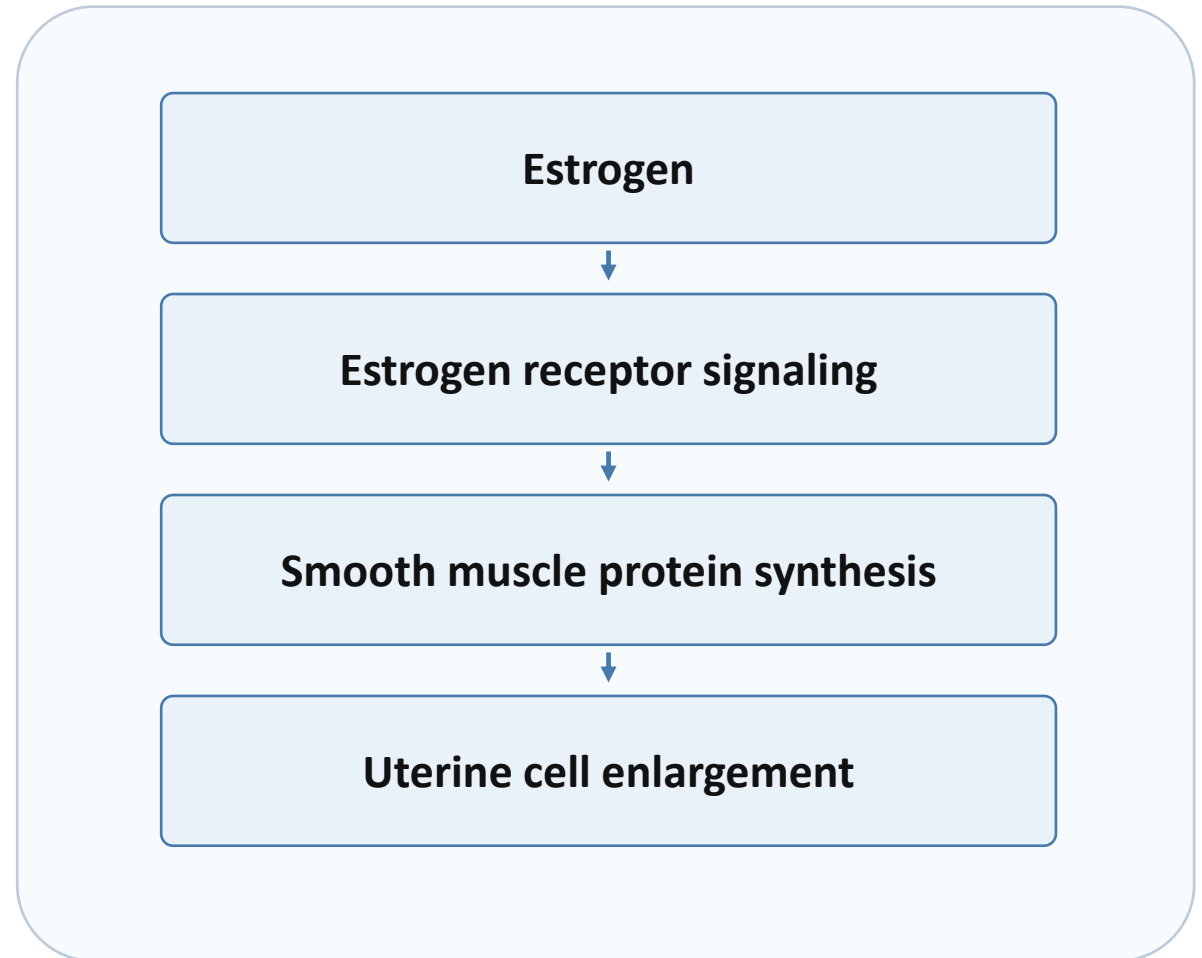
Explain the mechanism:

- Name the hormonal stimulus identified.
- Which receptor family mediates the growth response?
- What changes inside each enlarged smooth muscle cell?

Pregnancy-associated hypertrophy: Interpretation

Causal interpretation

- Estrogenic signaling acts through estrogen receptors.
- Uterine smooth muscle protein synthesis increases.
- Individual smooth muscle cells enlarge; Other growth mechanisms can coexist.

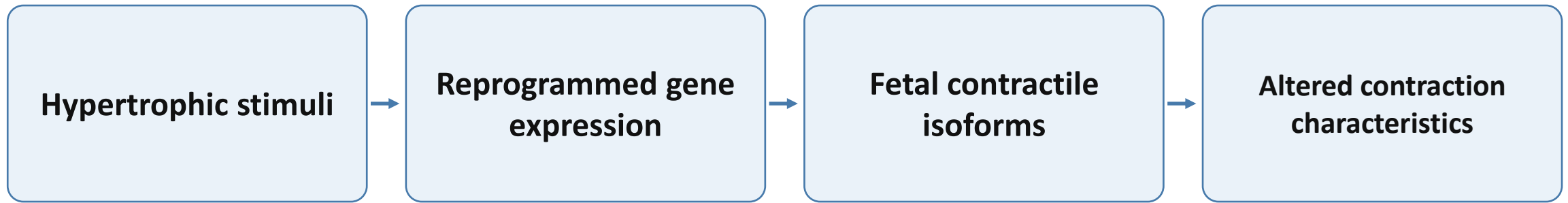


Schematic

Cardiac hypertrophy alters the gene program

- Cardiac myocytes do not simply make more of every existing adult protein.
- Re-expression of fetal contractile-protein isoforms.
- Adult-type contractile gene expression can be replaced by developmentally distinct isoforms.
- The altered protein composition changes contraction characteristics.

Adult-to-fetal contractile isoform shift



A change in myosin heavy-chain isoform expression as an example.

Myosin heavy-chain isoforms: Textbook example

α -myosin heavy chain

- Identified by Robbins as an adult-type isoform in its example.
- Represents part of the baseline contractile program.

β -myosin heavy chain

- Becomes more prominent in the described hypertrophic switch.
- Produces slower, more energetically economical contractions.

The source describes a representative programmatic shift; It gives no numerical isoform fractions.

Why the isoform shift matters functionally

- Contractile-protein identity affects contraction properties, not just muscle mass.
- The β isoform produces slower contractions.
- The same isoform is characterized as more economical energetically.
- Thus transcriptional remodeling modifies the quality of contraction as well as cell size.

A hypertrophied myocyte changes on three levels

Structure

More cellular proteins and contractile components enlarge the myocyte.

Gene program

Contractile isoform expression shifts toward a fetal-type pattern.

Stress response

Induction of adaptive-response gene products such as atrial natriuretic factor.

Hypertrophy is a coordinated structural and transcriptional response.

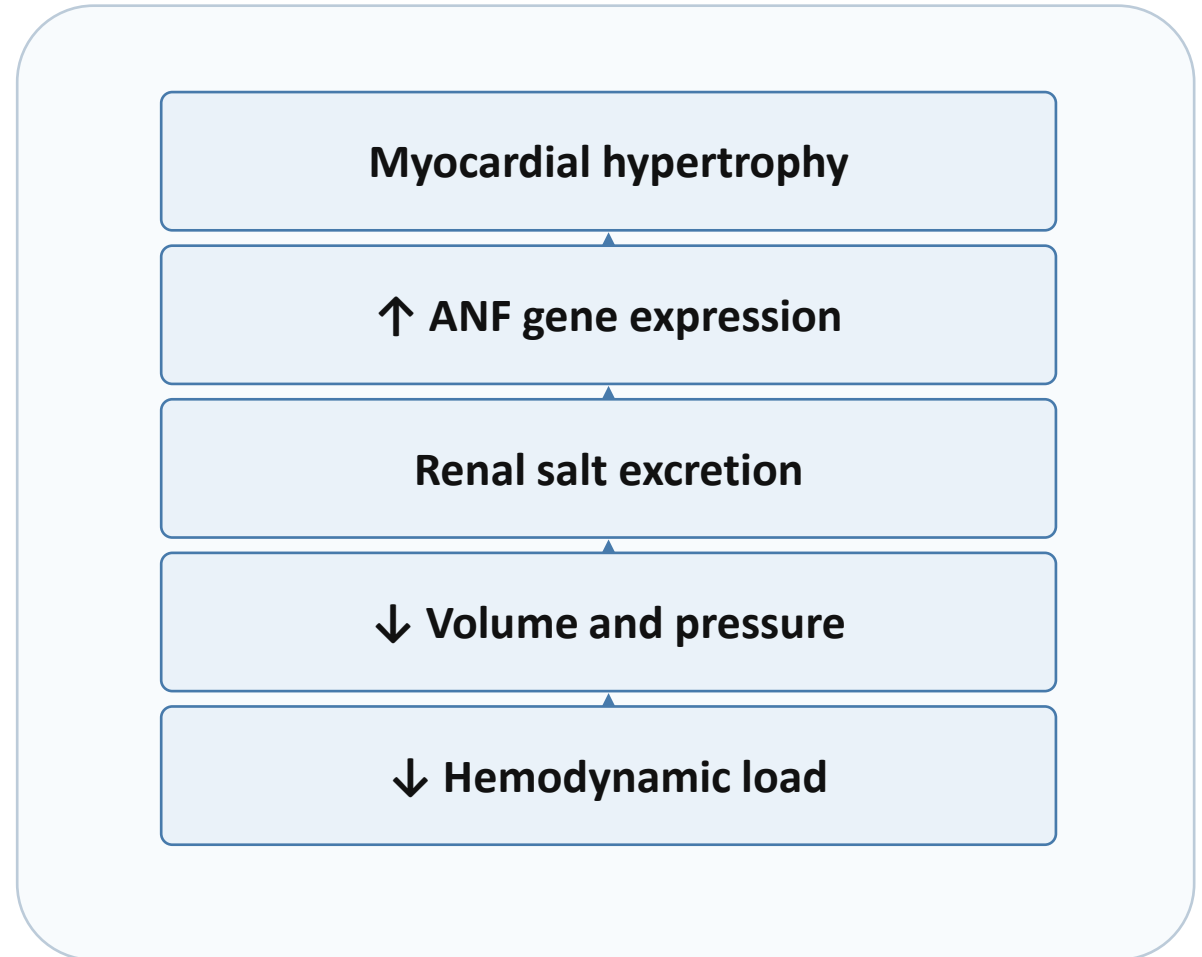
Stress-response genes are part of hypertrophy

- Not all altered gene products are directly contractile.
- The cardiac stress response changes expression of additional genes.
- Increased atrial natriuretic factor gene expression.
- This connects a local cardiac adaptation with systemic hemodynamic regulation.

Atrial natriuretic factor reduces hemodynamic load

Textbook-described compensatory effect

- Atrial natriuretic factor is a peptide hormone.
- It promotes renal salt excretion.
- Lower blood volume and blood pressure tend to reduce load on the heart.



Schematic

Contractile and counter-regulatory responses

Contractile remodeling

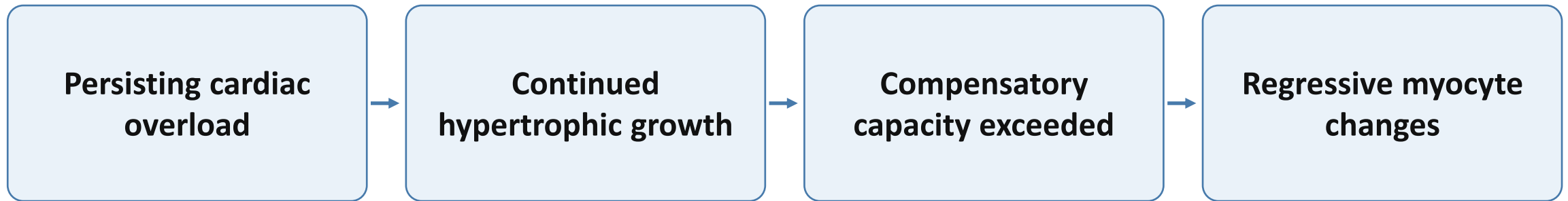
- New myofilaments.
- Increased myocyte size.
- Greater force capacity early in adaptation.

Stress counter-regulation

- Increased atrial natriuretic factor.
- Renal salt loss.
- Reduced volume and pressure, relieving load.

The hypertrophy program both supports work and attempts to reduce the burden.

The adaptive program has a limit



Myocardial growth ultimately cannot compensate for an indefinitely increasing burden.

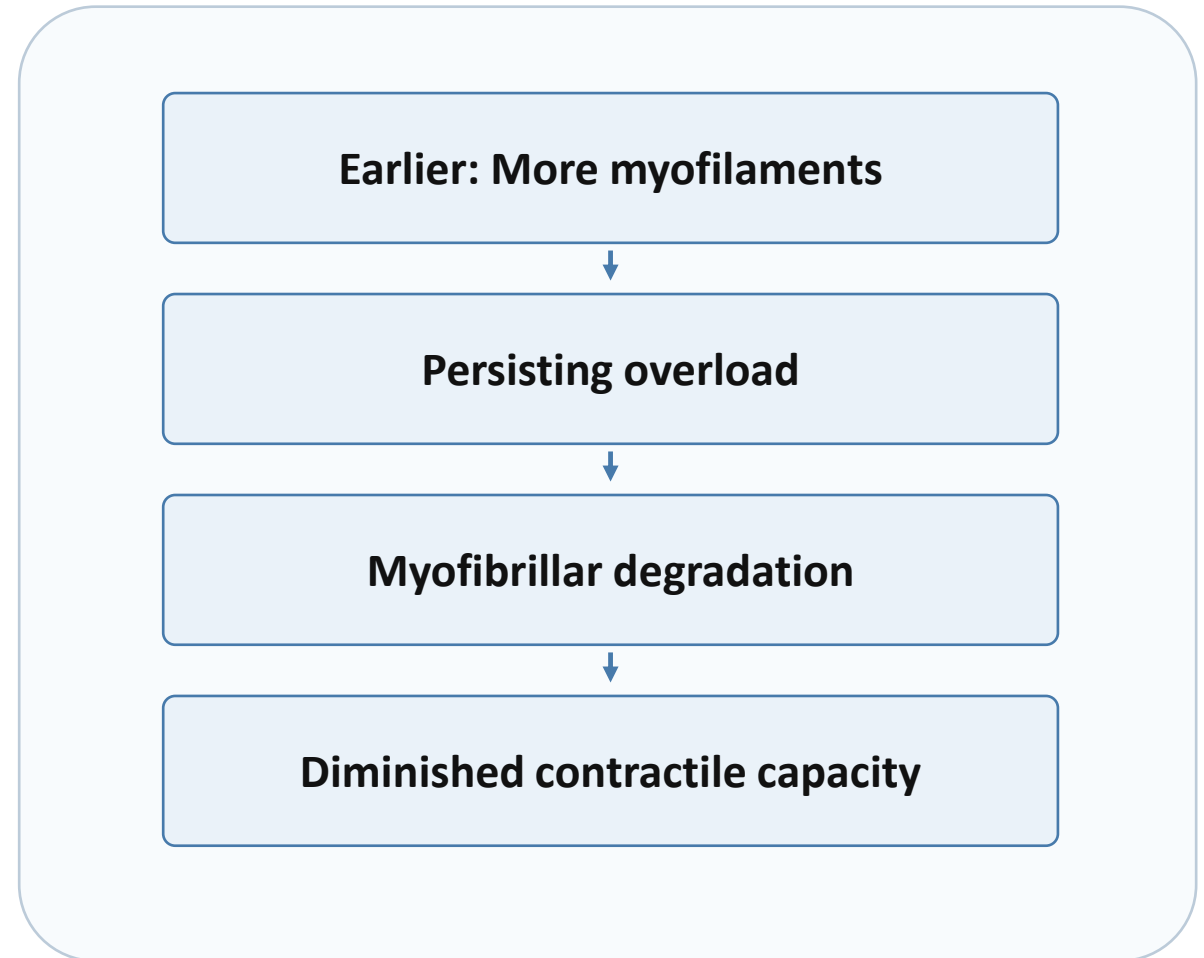
What marks the maladaptive transition?

- The enlarging cardiac muscle reaches a limit of functional compensation.
- Regressive changes emerge in myocardial fibers.
- The most important described change is degradation and loss of contractile myofibrils.
- With severe progression, individual myocytes may die.

Myofibrillar loss defeats earlier gains

Reversal of the compensatory logic

- Early hypertrophy works by adding contractile protein.
- Maladaptation includes degradation and loss of myofibrillar elements.
- Loss of those structures compromises the cell's ability to support workload.



Schematic

Myocyte death is a severe late event

- Myocyte death can occur in extreme cardiac hypertrophy.
- Cell loss adds injury to an already insufficient adaptive response.
- It is not necessary to assume that all hypertrophied myocytes die.
- The broader outcome can be progression toward cardiac failure.

The sequence from adaptation to heart failure



This is the source's central example of adaptation progressing to injury when stress persists.

Two possible trajectories of a growth response

Demand is accommodated

- Protein synthesis increases cellular capacity.
- Greater myocyte size serves the immediate need.
- Function may remain adequate for a period.

Demand remains excessive

- Myocyte growth reaches a functional limit.
- Contractile elements regress.
- Heart failure may result.

The stimulus and durability of compensation determine whether growth remains useful.

Follow the chain: Stimulus to clinical consequence

Stage	What occurs	Why it matters
Initiation	Mechanical or humoral input	Begins growth signaling
Execution	Transcription and protein synthesis	Enlarges the preexisting myocyte
Compensation	More contractile machinery	Supports greater workload
Maladaptation	Myofibrillar loss $\pm$ cell death	Contributes to failure

Common conceptual errors to avoid

- Hypertrophy does not, by definition, require the formation of new cells.
- PI3K/AKT and GPCR signaling are emphases, not mutually exclusive categories.
- A larger heart is not necessarily a better-functioning heart.
- Fetal-gene reprogramming changes protein type as well as total amount.
- Atrial natriuretic factor is a counter-regulatory signal, not a contractile protein.

Apply the mechanism: Four linked findings

A pressure-overloaded heart has increased cardiomyocyte size, altered myosin heavy-chain isoform expression, increased atrial natriuretic factor expression, and, later, myofibrillar loss.

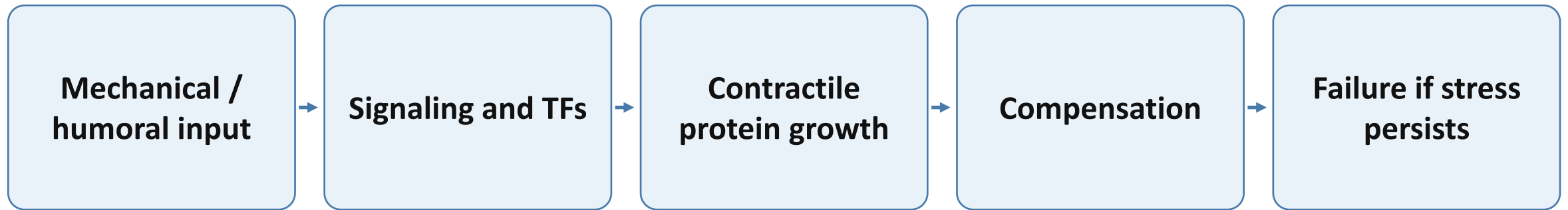
Explain the mechanism:

- Which findings are structural growth, gene reprogramming, and compensatory feedback?
- Which observation indicates failure of the adaptive response?

Worked interpretation: Assign each finding

- Larger cardiomyocyte: Increased intracellular protein and structural material.
- Isoform shift: Altered transcriptional expression of contractile protein variants.
- Atrial natriuretic factor: Response that promotes salt loss and reduces hemodynamic load.
- Myofibrillar loss: Regressive injury associated with decompensation.

Synthesis: One continuous causal model



The same stimulus-response framework explains both early benefit and the possibility of late injury.

Final mechanistic principles

- Cell enlargement arises from synthesis and assembly of additional cellular proteins.
- Mechanical inputs and humoral factors engage PI3K/AKT, GPCR-initiated, and related networks.
- GATA4, NFAT, and MEF2 contribute to increased contractile gene expression.
- The cardiac response includes isoform switching and atrial natriuretic factor induction.
- Persisting overload can cause myofibrillar loss, myocyte death, and cardiac failure.

Reference and figure note

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Chapter 2: Cell Injury, Cell Death, and Adaptations — Hypertrophy and Mechanisms of Hypertrophy.
- Mechanism illustrations in this lecture are original editable schematics, not published pathology images.
- No gross or microscopic textbook photographs are reproduced.