HYPERTENSION

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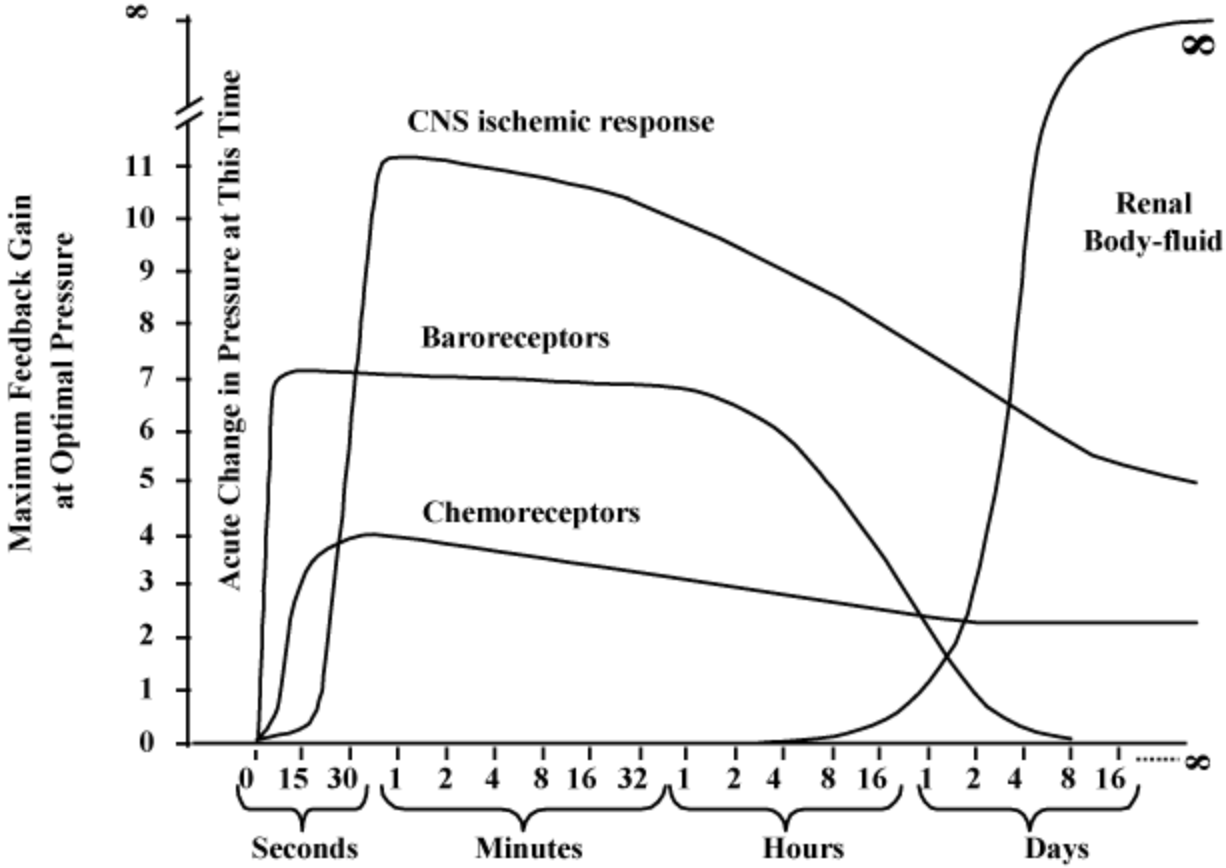
Blood pressure control mechanisms



Source: Redrawn from Guyton AC, Hall JE. *Textbook of Medical Physiology,* 11th ed. Philadelphia: Elsevier, 2006, p. 230.

Fig. 69-3 Accessed 04/01/2010

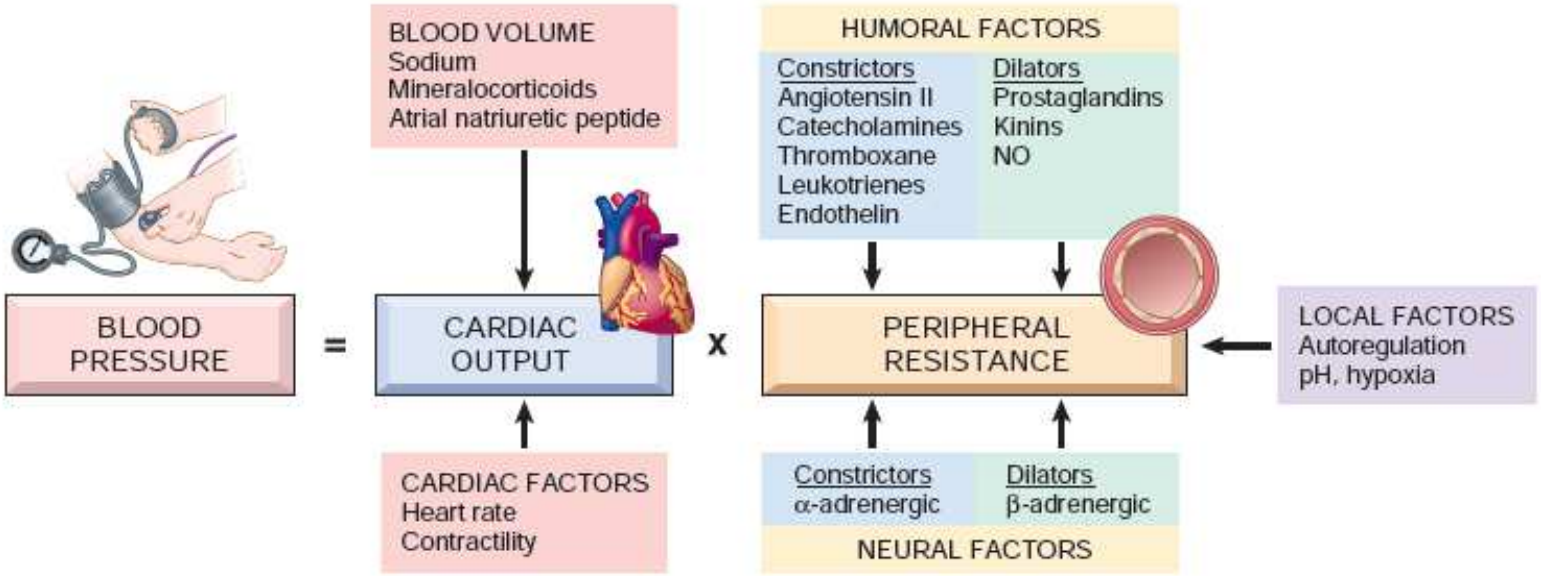


Figure 11-4 Blood pressure regulation. Diverse influences on cardiac output (e.g., blood volume and myocardial contractility) and peripheral resistance (neural, humoral, and local effectors) impact the output blood pressure.

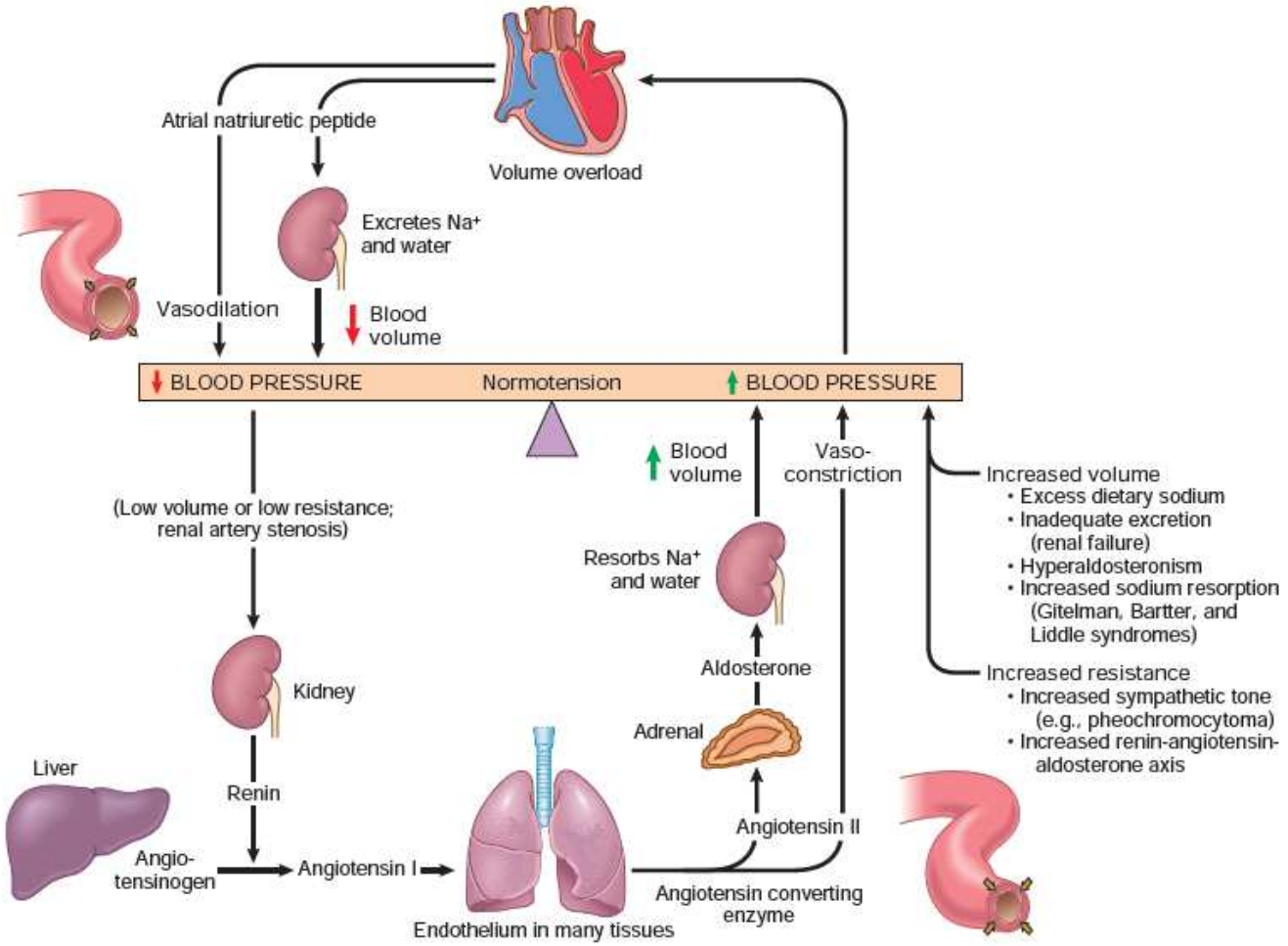


Figure 11-5 Interplay of renin-angiotensin-aldosterone and atrial natriuretic peptide in maintaining blood pressure homeostasis.

Hypertension

- Normal blood pressure is defined as a systolic blood pressure <120 mmHg and a diastolic blood pressure <80 mmHg.
- The diagnosis of hypertension is made by a confirmed systolic blood pressure 130 mmHg or a diastolic blood pressure 80 mmHg.
- There is no longer a category of pre-hypertension
- Auscultatory blood pressures are 4-15 mmHg below direct systolic blood pressure measurement, and 3-6 mmHg above direct diastolic blood pressure measurement.

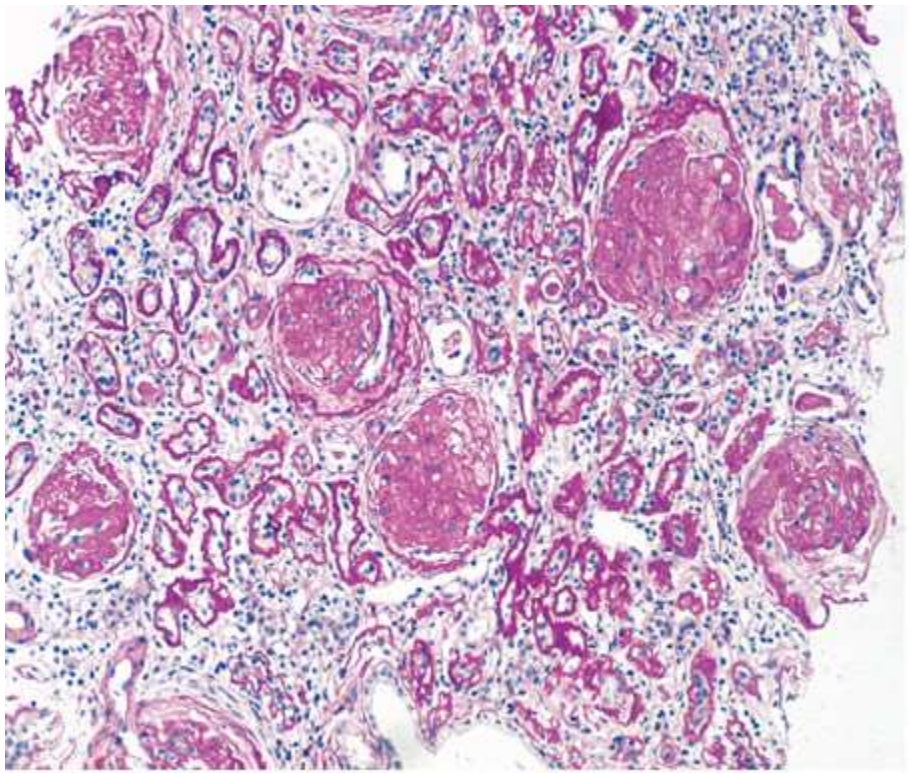
Hypertension

- Increased systolic blood pressure is caused by increased preload, increased contractility, and decreased compliance of aorta
- Increased diastolic blood pressure is caused by increased peripheral vascular resistance (arteriolar vasoconstriction) and increased heart rate
- May also be increased if viscosity increased (polycythemia, Waldenstrom)
- Excess sodium increases plasma volume (preload)
- Excess sodium increases calcium mediated contraction of arteriolar smooth muscle

Pathogenesis of hypertension

- Essential hypertension refers to those cases with no obvious etiology (85%)
- 70% of the causes of renovascular hypertension are due to arteriosclerosis of the renal artery (with renal artery stenosis).
- Fibromuscular hyperplasia of the artery is also described.
- Renin secretion increases.
- Increased arteriolar resistance (afterload) leads to cardiac hypertrophy.
- Increased circulating volume (preload) leads to dilated ventricle.

Arteriolar nephrosclerosis

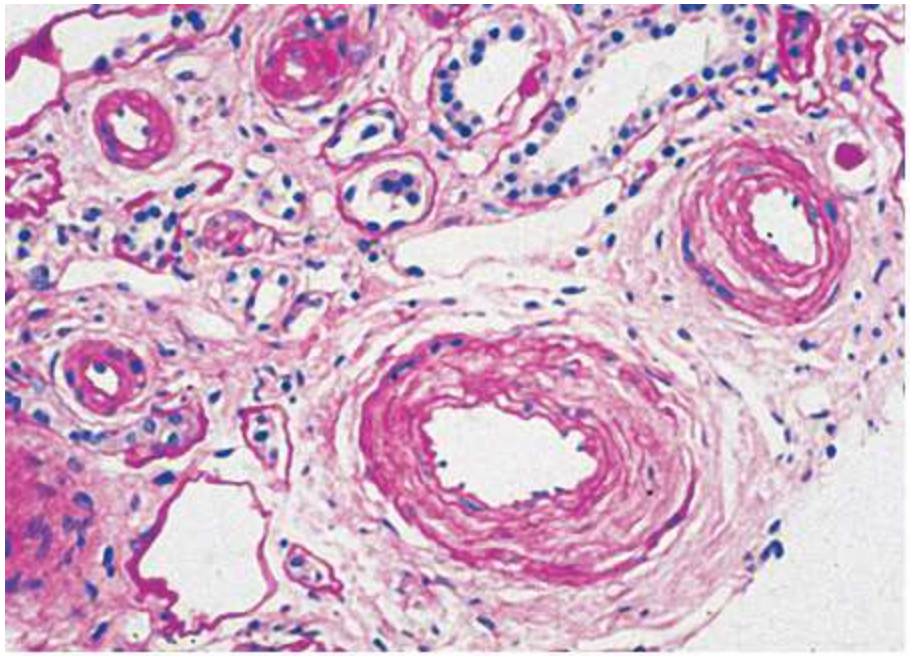


Hypertension-associated injury often manifests extensive global sclerosis of glomeruli, with accompanying and proportional tubulointerstitial fibrosis and pericapsular fibrosis, and there may be segmental sclerosis.

(ABF/Vanderbilt Collection.)

Fig. e9-19 Accessed 03/17/2010

Malignant hypertension



The vessels show disproportionately severe changes of intimal fibrosis, medial hypertrophy, and arteriolar hyaline deposits .

(ABF/Vanderbilt Collection.)

Fig. e9-20 Accessed 03/17/2010

Pathogenesis of hypertension

- Oral contraceptives stimulate angiotensinogen production.
- Mineralicorticoid production increases in 11-β hydroxylase deficiency
- Deficiency in hydroxylation in aldosterone biosynthesis
- Mineralicorticoid production increases in 17-α hydroxylase deficiency
- Impaired conversion of pregnenolone
- Desoxycorticosterone accumulates.

Pathogenesis of hypertension

- Increased mineralicorticoid receptor activity noted in 11β-hydroxysteroid dehydrogenase-2 deficiency.
- The enzyme inactivates cortisol in the kidney.
- Glycyrrhizinic and glycyrrhetinic acids in licorice inhibit the enzyme.
- Mimics hyperaldosteronism.
- 50% of those with salt-resistant hypertension will have elevated levels of aldosterone in a 24hr urine collection

Pathogenesis of hypertension

- Liddle's syndrome
- Autosomal dominant
- Caused by an alteration in the β or γ subunit of the epithelium sodium channel (E_{Nac}) that leads to its failure to be degraded by the ubiquitin system.
- Excess resorption of Na^+ and loss of K^+ from the renal tubule is noted.
- Hypertension results.
- Renin levels are low.
- Metabolic alkalosis is noted.
- Pseudohyperaldosteronism-1 involves the α or β subunit of $E_{Nac}1$.

Pathogenesis of hypertension

- Gitelman syndrome
- Autosomal recessive condition
- Involves the thiazide sensitive Na^+-Cl^- co-transporter in the distal tubule.
- Na^+, K^+, Mg^+, Cl^- lost.
- Hypochloremic metabolic alkalosis.
- Generally normotensive.
- Muscle cramps may be the initial presentation.

Pathogenesis of hypertension

- Bartter syndrome is closely related
- Involves thick ascending limb of the loop of Henle
- Often presents with hypercalcuria.
- Neonatal and classic forms.
- Alteration of the K^+ channel Kv7.4 in vessel walls is associated with maintenance of hypertension
- Leads to K^+ loss

Angiotensin II

- Angiotensin II increases proximal tubular reabsorption by binding to receptors on the luminal and basolateral membranes
- Stimulates:
- Na^+/H^+ antiporter,
- Na^+/HCO_3 cotransport
- Na^+/K^+ ATPase activity
- Na^+ reabsorption increases in the:
- Loop of Henle
- Macula densa
- Distal nephron segments

Angiotensin II

- Angiotensin II also increases reabsorption by increasing interstitial fluid colloid osmotic pressure and decreasing interstitial fluid hydrostatic pressure.
- Increases systemic vascular resistance (vasoconstriction):
- Directly stimulates vascular smooth muscle contraction
- Aguments norepinephrine release.
- It causes the release of aldosterone from the adrenal cortex.

Angiotensin II

- Na^+ excretion is decreased by increasing Na^+ reabsorption by proximal tubules of the kidney.
- Opposed by atrial natriuretic peptide.
- It causes the release of vasopressin from the posterior pituitary gland, leading to water retention by the kidney.
- Opposed by atrial natriuretic peptide.
- Angiotensin I is the precursor to Angiotensin II and has no direct actions.

Aldosterone

- Aldosterone binds to mineralocorticoid receptors
- Activates transcription to stimulate synthesis or activation of the Na^+-K^+-ATPase pump on the basolateral epithelial membrane
- Activates the amiloride-sensitive Na^+ channels on the luminal side of the epithelial membrane.
- <u>These effects on the genome are mediated by activation of gene transcription and require 60 to 90 minutes to occur after administration of aldosterone</u>.

Aldosterone

- Aldosterone also exerts rapid non-genomic effects on the cardiovascular and renal systems.-
- Aldosterone increases the Na^+ current in the cortical collecting tubule
- In a few minutes after application:
- Activates the amiloride-sensitive channel
- Stimulates the Na^+-H^+ exchanger
- Aldosterone stimulates Na^+ reabsorption and K^+ secretion.
- 24h urine aldosterone elevated in primary aldosteronism

Nitric oxide and renal function

- Reduced nitric oxide (NO) synthesis decreases pressure natriuresis and increases blood pressure.
- Decreased endothelial-derived nitric oxide synthesis impairs renal Na^+ excretory function by:
- Increasing basal renal vascular resistance
- Enhancing the renal vascular responsiveness to vasoconstrictors such as Angiotensin II or norepinephrine
- Activating the renin–angiotensin system.

Nitric oxide and renal function

- Reductions in NO synthesis also impair sodium excretory function
- Directly increasing tubular reabsorption
- Altering intrarenal renal interstitial hydrostatic pressure or medullary blood flow.

- Vasopressin vasoconstricts
- Pulmonary arteries not affected

Other controls of renal function

- TNF-α, IL-1, and endothelin-1 also function as vasoconstrictors.
- Activation of the endothelin-a receptor constricts, while the endothelin-b receptor dilates renal vessels.
- Prostaglandins are produced locally in the kidney.
- Their production is stimulated by the same forces that stimulate sympathetic activity and angiotensin II production.
- Prostaglandins are vasodilatory and clearly protective of renal blood flow.

Natriuretic peptides

- Plasma levels of atrial and brain natriuretic peptide are elevated in conditions associated with enhanced sodium excretion.
- Acute blood volume expansion consistently elevates circulating levels of atrial natriuretic peptide .
- Chronic increases in dietary sodium intake also raise circulating levels of atrial natriuretic peptide.

Natriuretic Peptides

- Bind to Na^+/K^+-ATPase.
- Inhibit Na^+ transporter in the nephron
- Increase GFR and filtration fraction
- K^+ sparing
- Decrease renin release
- Alter intracellular Na^+ gradients in vascular smooth muscle cells
- Vasodilatation of veins and arterioles
- Indirectly inhibit the Na^+/Ca^{2+} exchanger causing intracellular calcium to rise in vascular smooth muscle cells

Natriuretic Peptides

- Myosin light chain phosphorylation leads to contraction
- Relaxes as cAMP generated
- ANP and BNP facilitate cGMP formation, leading to myocyte relaxation
- When binding sites are saturated (contractility maximized), Ca^{2+} enters mitochondria, reducing ATP production
- Profibrotic in heart and kidney
- Associated with Ca^{2+} accumulation in coronary arteries as well as heart valves
- Implicated in the pathogenesis of hypertension

Table 4 – Comparison between the patients' characteristics in relation to BNP values ≥ 1,400 and <1,400 pg/dL

	BNP		
Characteristics	≥1,400 pg/dL (n = 78)	<1,400 pg/dL (n = 110)	p
Age (years)	58.7 ± 15.0	58.9 ± 14.0	0.901
Male gender - n (%)	44 (56.4)	65 (59.1)	0.714
Cause of HF - n (%):			
Chagasic	29 (37.2)	20 (18.2)	0.003
Ischemic	15 (19.2)	34 (30.9)	0.072
Non-ischemic (non-chagasic)	34 (43.6)	56 (50.9)	0.322
Vasoactive drugs - n (%)	57 (73.1)	57 (51.8)	0.005
LVEF (%)	23.5 ± 6.6	28.3 ± 10.8	0.002
Baseline urea (mg/dL)	92.0 ± 45.4	74.5 ± 40.6	0.002
Baseline creatinine (mg/dL)	1.7 ± 0.7	1.6 ± 0.7	0.102
BNP (pg/dL)	2,734.0 ± 995.4	781.5 ± 341.8	<0.001
In-hospital death	17 (21.8)	12 (10.9)	0.042
1-year death	40 (51.3)	36 (32.7)	0.011

HF: Heart failure; LVEF: left ventricular ejection fraction; BNP: type-B natriuretic peptide.

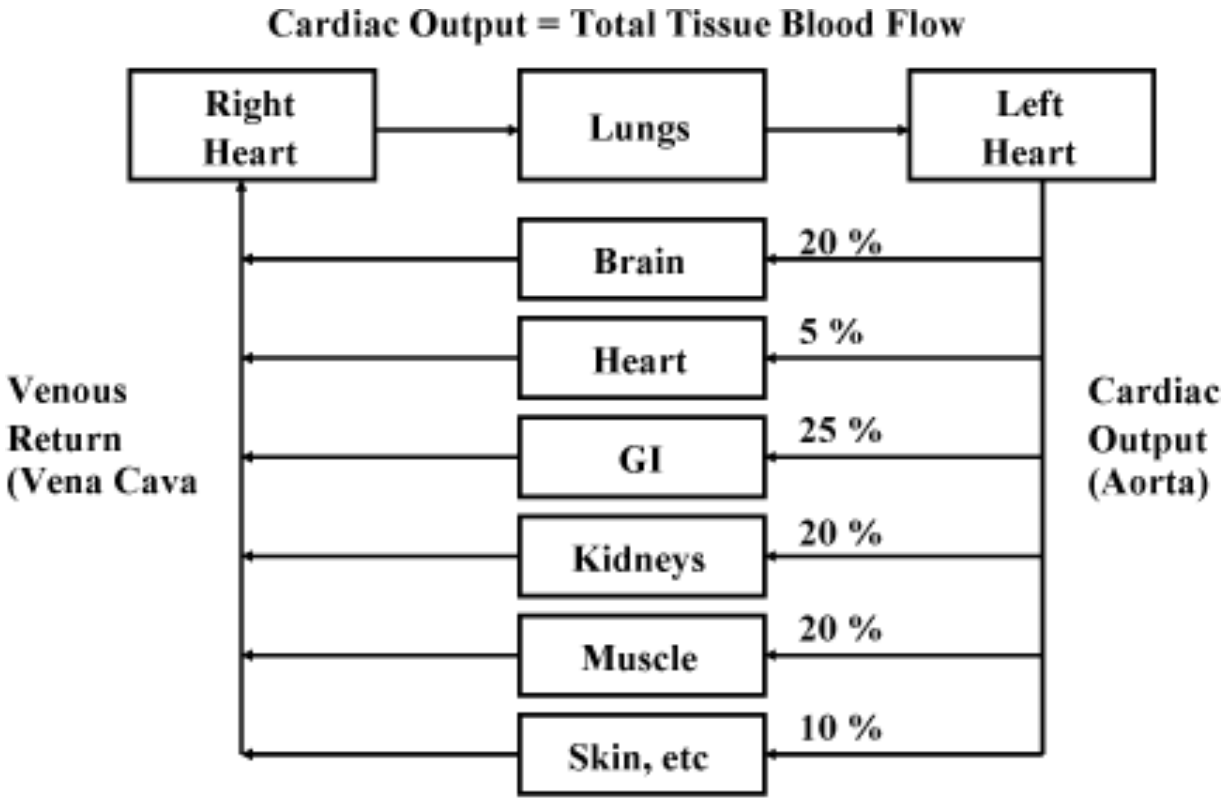
BNP levels also reflect 30 and 180 day mortality post surgery

http://www.scielo.br/img/revistas/abc/v100n3/en_a11tab04.jpg
Accessed 01/10/2020

Hypertension

- Stage 1, the milder (systolic 130 to 159 mmHg and/or diastolic 80 to 99 mmHg) and most common form of hypertension, accounts for approximately 80 percent of hypertension.
- Stage 2 hypertension includes those with systolic blood pressure 160 mmHg and/or diastolic blood pressure 100 mmHg.
- Isolated systolic hypertension is defined as systolic blood pressure of 140 mmHg and diastolic blood pressure <90 mmHg and staged appropriately.

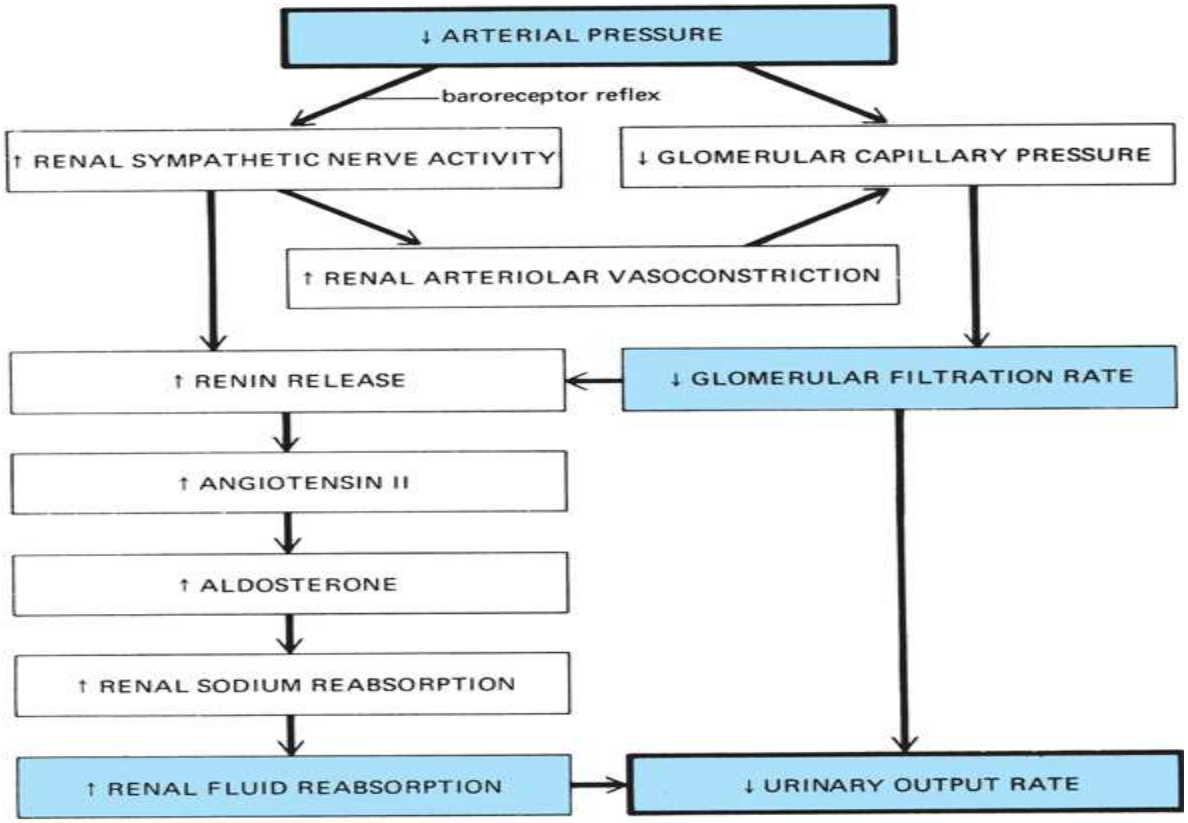
Organ distribution of cardiac output



Source: Fuster V, O'Rourke RA, Walsh RA, Poole-Wilson P: *Hurst's The Heart*, 12th Edition: http://www.accessmedicine.com

Fig. 69-1 Accessed 04/01/2010

Homeostatic mechanism

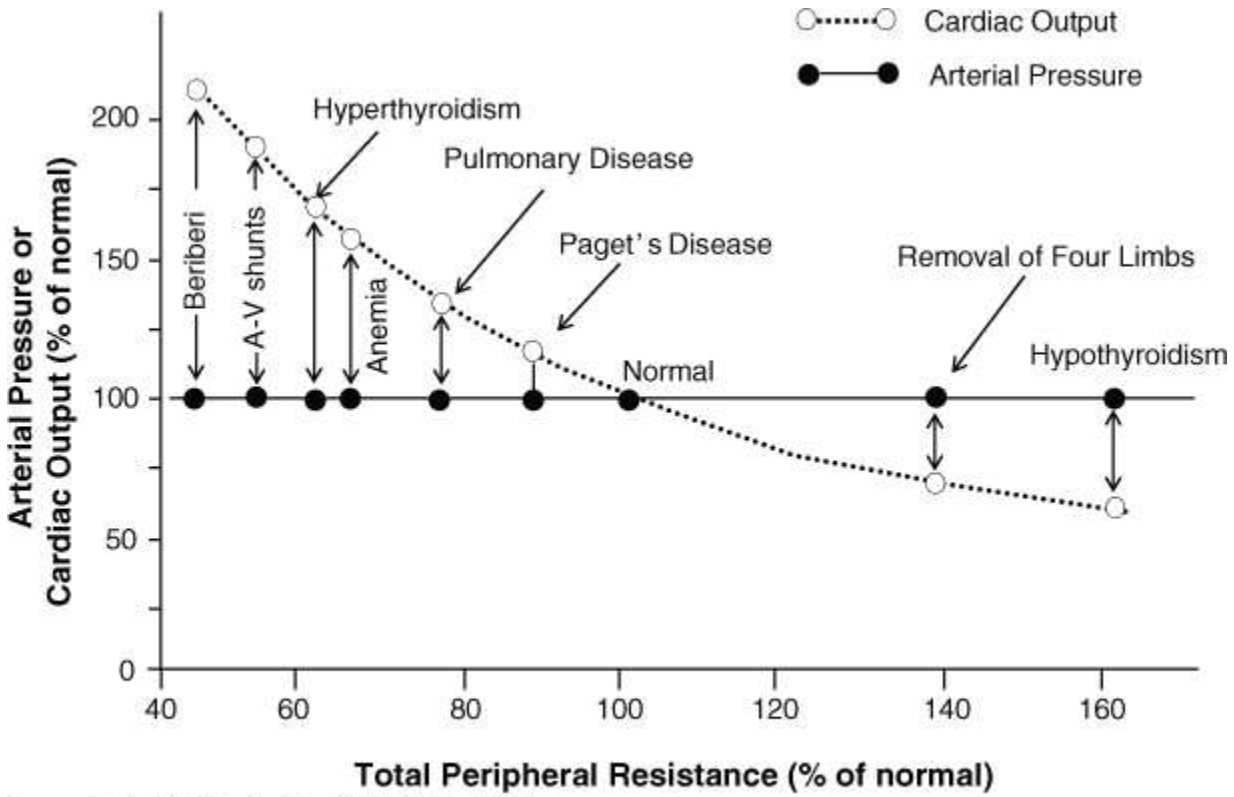


Source: Mohrman DE, Heller LJ: *Cardiovascular Physiology*, 6th Edition: http://www.accessmedicine.com

Fig. 9-9 Accessed 02/01/2010

Marked changes in fluid intake rate have rather minor influences on the arterial pressure of a normal individual.

Arterial pressure and peripheral vascular resistance



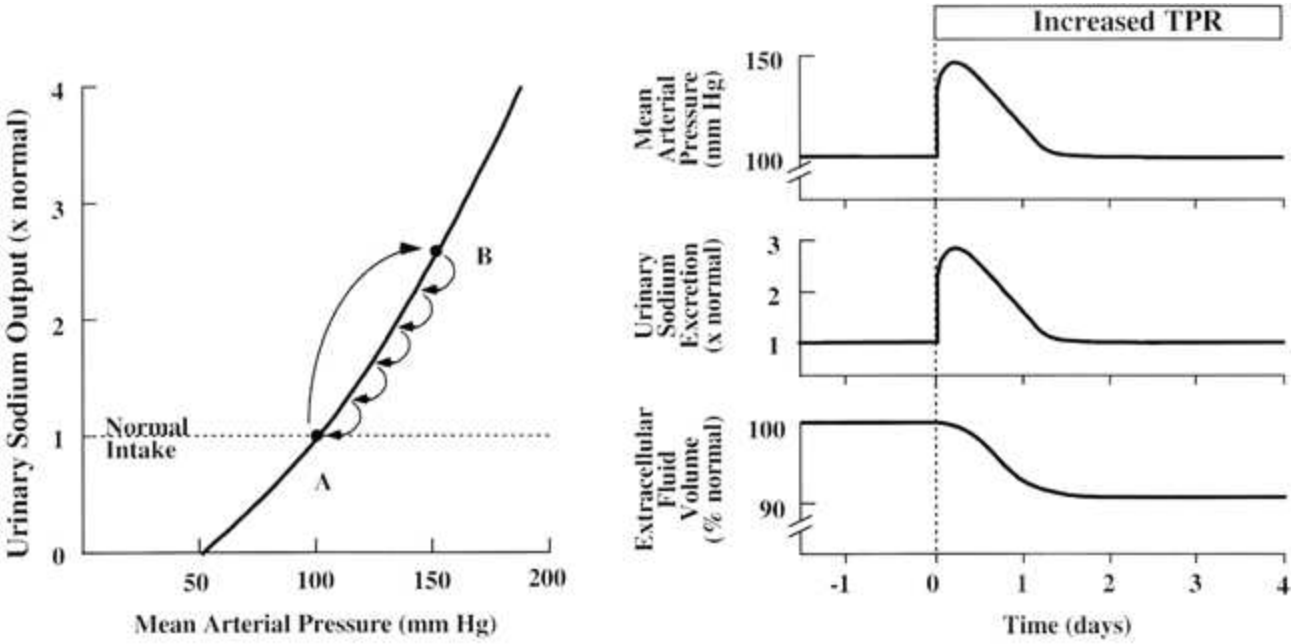
Source: Redrawn from Guyton AC, Hall JE. *Textbook of Medical Physiology,* 11th ed. Philadelphia: Elsevier, 2006.

Fig. 69-2 Accessed 04/01/2010

Arterial pressure and peripheral vascular resistance

- If the kidneys are functioning normally, with a change in total peripheral vascular resistance and concomitant reciprocal effect on cardiac output, there is no long-term effect on arterial pressure.
- The renal–body fluid feedback control mechanism does not stop functioning until the arterial pressure returns all the way back to its original control level.
- There is a shift of pressure natriuresis that appears to initiate and sustain the hypertension.

Long-term effects of increased peripheral vascular resistance



If there is no change in natriuresis, elevated blood pressure cannot be sustained because Na^+ excretion exceeds intake, reducing fluid volume until blood pressure returns to normal and sodium balance is re-established. Sodium sensitive only if functional nephron loss.

Source. Redrawn from Hall JE. The kidney, hypertension, and obesity. *Hypertension* 2003;41:625–633.
Fig. 69-5 Accessed 04/01/2010

Arterial pressure and urinary excretion of Na^+

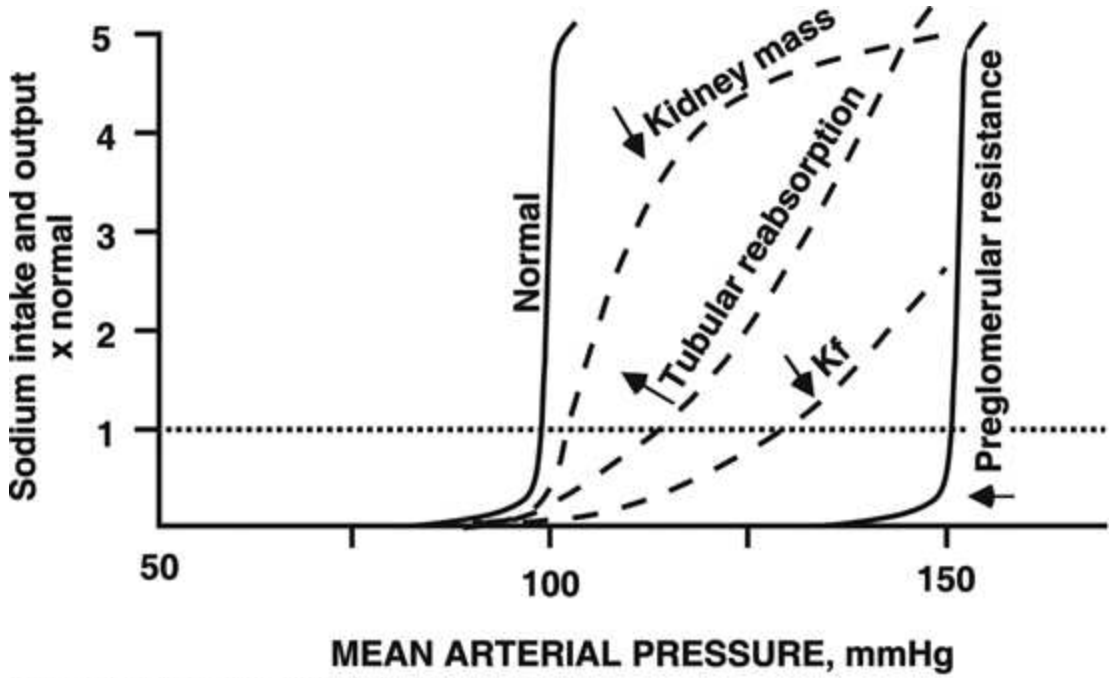


Fig. 69-6 Accessed 04/01/2010

Note that increased preglomerular resistance causes salt-insensitive hypertension, whereas the other renal abnormalities cause salt-sensitive hypertension.

Arterial pressure and Na^+ intake and excretion

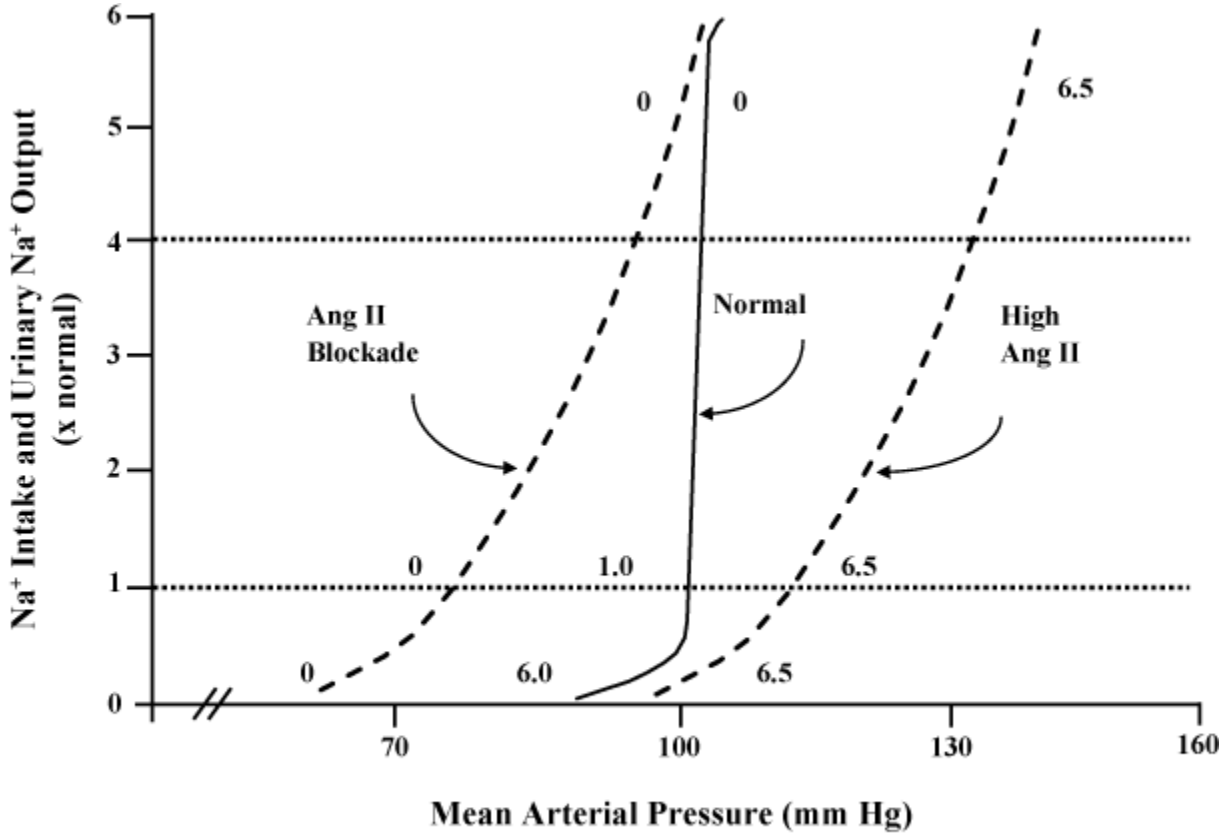
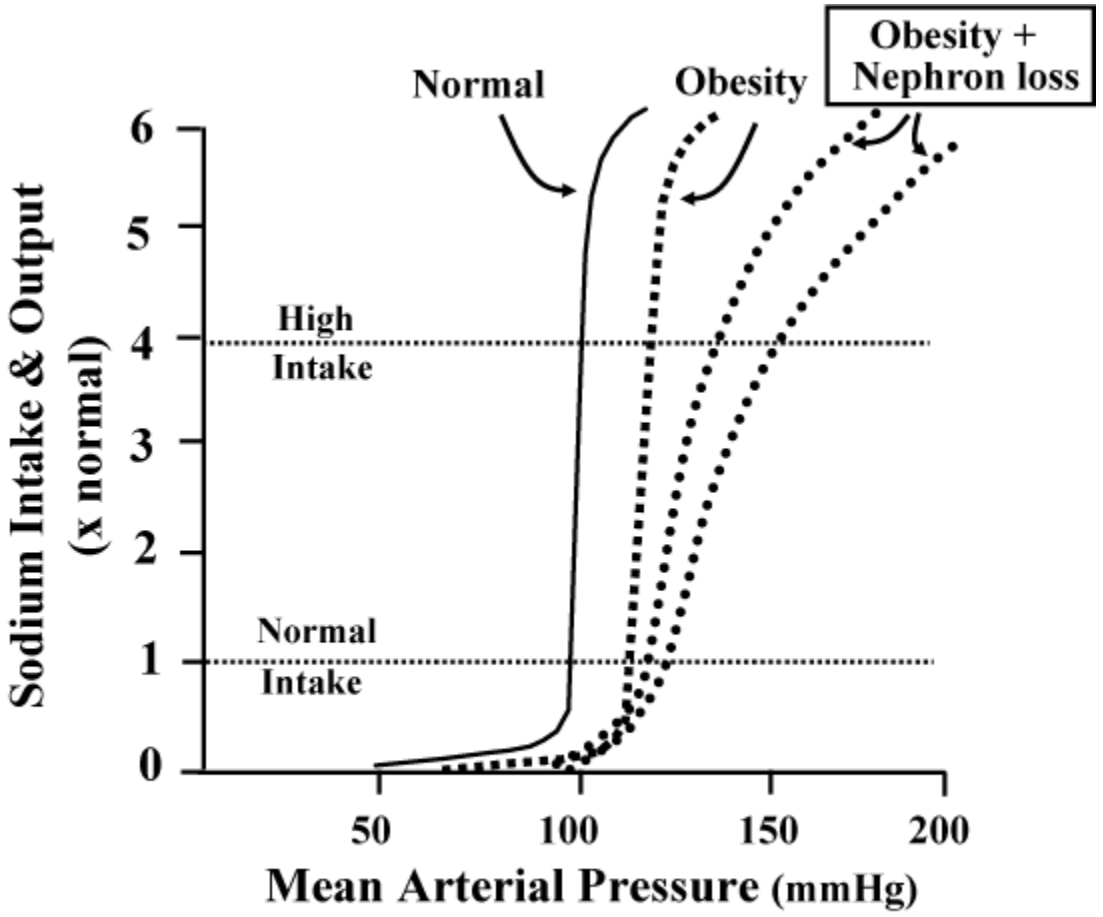


Fig. 69-9 Accessed 04/01/2010

Source: Redrawn from Hall JE, Guyton AC, Smith MJ Jr, et al. Blood pressure and renal function during chronic changes in sodium intake: role of angiotensin. *Am J Physiol* 1980;239:F271–F280.

Obesity, renal pressure, natriuresis



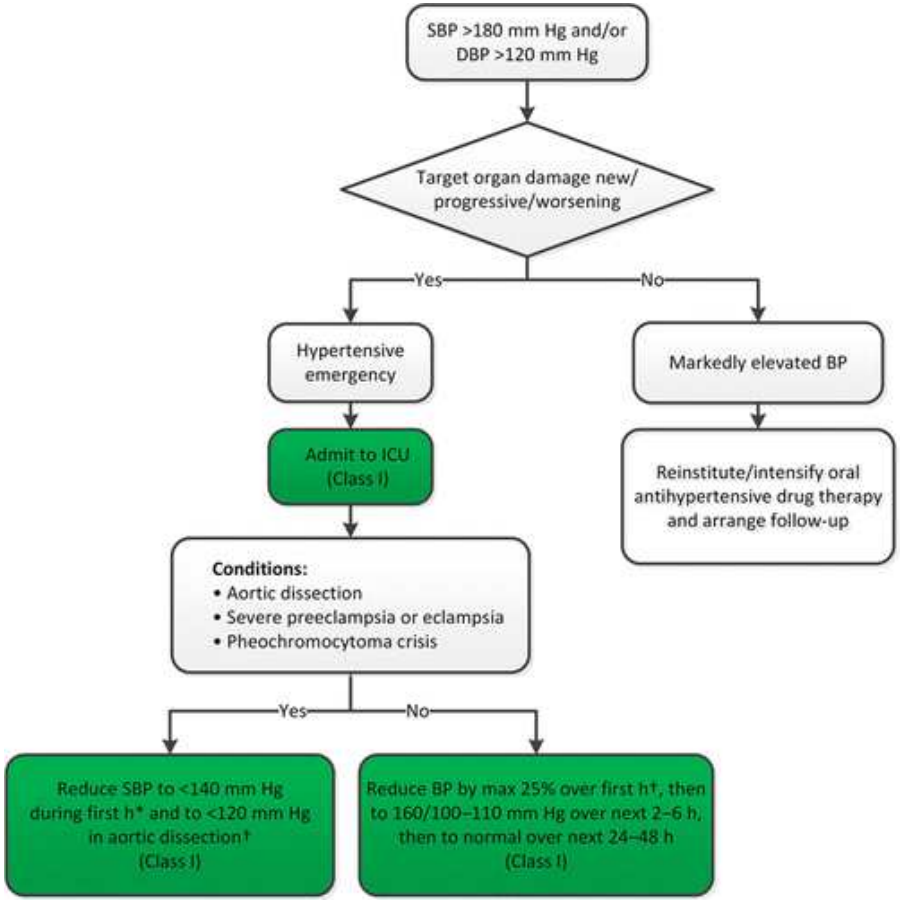
Source: Fuster V, O'Rourke RA, Walsh RA, Poole-Wilson P: *Hurst's The Heart*, 12th Edition: http://www.accessmedicine.com

With chronic obesity lasting for many years, there may be a gradual loss of nephron function, further impairment of pressure natriuresis, increasing salt sensitivity, and higher arterial pressures.

Fig. 69-19
Accessed 04/01/2010

Hypertensive emergency

- Defined as uncontrolled hypertension that will lead to acute organ damage if not controlled within one hour or presentation.
- Use agents with short half-life.
- Diuretics may compound the problem as increased movement of fluid through the kidney is sensed by the macula densa.
- Sympathetic activity is increased (as with low $Na^{\pm}$ state) and vasoconstriction results.
- Lower mean arterial pressure by 25% in the first two hours, achieving a blood pressure of 160/100 mmHg within 6 hours.



Paul K. Whelton. Hypertension. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, Volume: 71, Issue: 6, Pages: e13-e115, DOI: (10.1161/HYP.0000000000000065)

Hypertensive emergency

- A patient with malignant hypertension always has retinal papilledema
- The pathologic hallmark of malignant hypertension is fibrinoid necrosis of the arterioles, which occurs systemically, but specifically in the kidneys.
- Patients with malignant hypertension have lower total cholesterol, LDL, and BMI values than do other hypertensives.
- However, the median estimated glomerular filtration rate is higher in the normotensive and hypertensive patients than in those with malignant hypertension.

Hypertensive emergency

- The most common clinical presentations of hypertensive emergencies are:
- Cerebral infarction (24.5%),
- Pulmonary edema (22.5%)
- Hypertensive encephalopathy (16.3%)
- Congestive heart failure(12%).

Hypertensive emergency

- Hypertensive emergencies are characterized by severe hypertension (>180/120 mm Hg) in association with target organ dysfunction
- Median survival was 14 days for those with neurovascular emergencies and 50 days for those with cardiovascular emergencies
- The in-hospital and one-year mortality for those with hypertensive emergency are 13% and 39%, respectively.

Hypertensive emergency

- Annual all-cause mortality per 100 patient-years was 2.6 for the patients with malignant hypertension, compared to 0.2 and 0.5 for normotensives and hypertensives, respectively
- These patients develop fatal complications if untreated, and more than 90% will not survive beyond 1-2 years
- With hypertensive emergencies, the initial treatment goal is to rapidly (over 1-6 hours) lower the diastolic blood pressure to 100-110 mm Hg

Hypertensive emergency

- The organs most commonly affected by severe hypertension are:
- Brain (headache, confusion/encephalopathy, stroke, hemorrhage)
- Heart (chest pain, myocardial infarction, pulmonary edema)
- Large blood vessels (aortic dissection)
- Kidneys (acute hypertensive nephrosclerosis, renal failure)
- Eye (retinopathy)
- Placenta (eclampsia)
- Microangiopathic hemolytic anemia.

Hypertensive emergency

- Other treatable hypertensive emergencies include:
- Pheochromocytoma crisis
- Food or drug interactions with monoamine-oxidase inhibitors
- Sympathomimetic drug use (cocaine)
- Rebound hypertension after abrupt cessation of some antihypertensive drugs such as clonidine.

Treating hypertensive emergency

- Hypertensive emergency with end-organ effects in pediatric patients requires immediate, modest BP reduction with metoprolol.
- Hypertensive women who become pregnant or plan to become pregnant should be transitioned to methyldopa, nifedipine, and/or labetalol during pregnancy.
- ACE inhibitors, angiotensin receptor blockers, and direct renin inhibitors are to be avoided
- Oral nifedipine is as effective as intravenous hydralazine in treating acute hypertensive emergency in pregnant patients.

Treating hypertensive emergency

- For adults with severe preeclampsia or eclampsia, or pheochromocytoma crisis,
- Lower SBP to below 140 mm Hg during the first hour.
- If aortic dissection, to below 120 mm Hg during the first hour.
- For all other adults, reduce the SBP to a maximum of 25% within the first hour
- Then, if the patient is clinically stable, lower the BP to 160/100 -110 mm Hg over the next 2-6 hours, and then cautiously to normal over the following 24-48 hours

Table 12. Hypertensive Emergencies Requiring Immediate BP Lowering

Clinical Presentation	Timeline and Target BP	First Line Treatment	Alternative
Malignant hypertension with or without TMA or acute renal failure	Several hours, MAP −20% to −25%	Labetalol Nicardipine	Nitroprusside Urapidil
Hypertensive encephalopathy	Immediate, MAP −20% to −25%	Labetalol Nicardipine	Nitroprusside
Acute ischaemic stroke and SBP >220 mm Hg or DBP >120 mm Hg	1 h, MAP −15%	Labetalol Nicardipine	Nitroprusside
Acute ischaemic stroke with indication for thrombolytic therapy and SBP >185 mm Hg or DBP >110 mm Hg	1 h, MAP −15%	Labetalol Nicardipine	Nitroprusside
Acute hemorrhagic stroke and SBP >180 mm Hg	Immediate, 130<SBP<180 mm Hg	Labetalol Nicardipine	Urapidil
Acute coronary event	Immediate, SBP <140 mm Hg	Nitroglycerine Labetalol	Urapidil
Acute cardiogenic pulmonary edema	Immediate, SBP <140 mm Hg	Nitroprusside or nitroglycerine (with loop diuretic)	Urapidil (with loop diuretic)
Acute aortic disease	Immediate, SBP <120 mm Hg and heart rate <60 bpm	Esmolol and nitroprusside or nitroglycerine or nicardipine	Labetalol or metoprolol
Eclampsia and severe preeclampsia/ HELLP	Immediate, SBP <160 mm Hg and DBP <105 mm Hg	Labetalol or nicardipine and magnesium sulphate	

Adapted from van den Born et al.[127]

Treating hypertensive emergency

- In hypertensive encephalopathy, the treatment guidelines are to reduce the mean arterial pressure (MAP) by 25% over 8 hours.
- Labetalol, nicardipine, or esmolol are the preferred medications
- Nitroprusside and hydralazine should be avoided.
- For acute ischemic stroke, the preferred medications are labetalol and nicardipine.
- After initiating drug therapy but before administering tPA, the blood pressure should be maintained at less than 180/105 mm Hg for 24 hours.

Treating hypertensive emergency

- For acute intracerebral hemorrhage or subarachnoid hemorrhage, the preferred medications are labetalol, nicardipine, and esmolol.
- Avoid nitroprusside and hydralazine.
- Systolic blood pressure is maintained <160 mmHg for 24 hours if there is evidence of increased intracranial pressure
- Else, <130 mmHg

Treating hypertensive emergency

- In aortic dissection, the preferred medications are labetalol, nicardipine, nitroprusside (with beta-blocker), esmolol, and morphine sulfate.
- Avoid beta-blockers if there is aortic valvular regurgitation or suspected cardiac tamponade.
- Avoid nitroprusside if renal or liver damage
- For acute coronary syndrome, beta blockers and nitroglycerin are the preferred drugs.
- Note that thrombolytics are contraindicated if the BP is above 185/100 mm Hg.
- Note that nitrates administered in the presence of phosphodiesterase type 5 (PDE-5) inhibitors may induce profound hypotension.

Treating hypertensive emergency

- In acute heart failure, the preferred medications are IV or sublingual nitroglycerin and IV enalaprilat.
- Treat with vasodilators (in addition to diuretics) for a systolic blood pressure of 140 mm Hg.
- In adults with hypertension at an increased risk of heart failure, the optimal BP should be below 130/80 mm Hg.

Treating hypertensive emergency

- In hypertensive adults with reduced ejection fraction (HFrEF), nondihydropyridine CCBs are not recommended for treatment.
- In hypertensive adults with preserved ejection fraction (HFpEF) and symptoms of volume overload, prescribe diuretics to control BP.
- For those with persistent hypertension after management of volume overload, prescribe ACEIs or ARBs and beta blockers titrated to achieve an systolic blood pressure <130 mm Hg.

Treating hypertensive emergency

- Diazepam, phentolamine, and nitroglycerin/nitroprusside are the preferred drugs in treating pheochromocytoma or cocaine toxicity.
- However, avoid beta-adrenergic antagonists before administering phentolamine.
- Hypertension and tachycardia from cocaine toxicity rarely require specific treatment.
- Alpha-adrenergic antagonists (phentolamine) are the preferred agents for cocaine-associated acute coronary syndromes.

Treating hypertensive emergency

- In eclampsia or preeclampsia, the preferred medications are hydralazine, labetalol, and nicardipine.
- Avoid nitroprusside, ACE inhibitors, ARBs, and renin inhibitors.
- In women with eclampsia or preeclampsia, the SBP should lowered to below 140 mm Hg during the first hour.

Treating hypertensive emergency

- If the platelet count is less than 100,000 cells/fL, the BP should be maintained below 150/100 mm Hg.
- Patients with eclampsia or preeclampsia should also be treated with IV magnesium sulfate to avoid seizures.

Treating hypertensive emergency

- Perioperative beta blockers are the first choice in patients undergoing vascular procedures or in patients with an intermediate or high risk of cardiac complications.
- In those with preoperative hypertension undergoing major surgery, consider perioperative discontinuation of ACEIs or ARBs.

- Hypertensive urgencies are characterized by severe hypertension without target organ dysfunction.
- The one-year mortality for those experiencing an episode of hypertensive urgency is approximately 9%.6
- With hypertensive urgencies, the goal is to lower the blood pressure more slowly, over 24-48 hours.
- Even without treatment, 99.5% of those with blood pressures chronically in the range of hypertensive urgency are unlikely to experience myocardial infarction, stroke, or TIA acutely.

Treating hypertensive urgency

- Ensure that patients do not have symptoms and/or signs of end-organ damage.
- This can be done with a brief review of systems and a physical examination.
- In select cases, an electrocardiogram and a chest x-ray may be warranted.
- Search for common causes of treatable hypertension in hospitalized patients:
- These include pain, nausea, withdrawal syndromes, and holding of usual antihypertensive medications.

Treating hypertensive urgency

- In those patients without symptoms and/or signs of end-organ damage,
- Allow 30 minutes of rest, followed by reassessment.
- Do not administer antihypertensive medications to acutely lower blood pressure.

Table 5. Options to Treat Arterial Hypertension in Patients With AIS Who Are Candidates for Emergency Reperfusion Therapy*

COR IIb	LOE C-EO
Patient otherwise eligible for emergency reperfusion therapy except that BP is >185/110 mm Hg:	
Labetalol 10–20 mg IV over 1–2 min, may repeat 1 time; or	
Nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5–15 min, maximum 15 mg/h; when desired BP reached, adjust to maintain proper BP limits; or	
Clevidipine 1–2 mg/h IV, titrate by doubling the dose every 2–5 min until desired BP reached; maximum 21 mg/h	
Other agents (eg, hydralazine, enalaprilat) may also be considered	
If BP is not maintained ≤185/110 mm Hg, do not administer alteplase	
Management of BP during and after alteplase or other emergency reperfusion therapy to maintain BP ≤180/105 mm Hg:	
Monitor BP every 15 min for 2 h from the start of alteplase therapy, then every 30 min for 6 h, and then every hour for 16 h	
If systolic BP >180–230 mm Hg or diastolic BP >105–120 mm Hg:	
Labetalol 10 mg IV followed by continuous IV infusion 2–8 mg/min; or	
Nicardipine 5 mg/h IV, titrate up to desired effect by 2.5 mg/h every 5–15 min, maximum 15 mg/h; or	
Clevidipine 1–2 mg/h IV, titrate by doubling the dose every 2–5 min until desired BP reached; maximum 21 mg/h	
If BP not controlled or diastolic BP >140 mm Hg, consider IV sodium nitroprusside	

AIS indicates acute ischemic stroke; BP, blood pressure; COR, class of recommendation; IV, intravenous; and LOE, Level of Evidence.
*Different treatment options may be appropriate in patients who have comorbid conditions that may benefit from rapid reductions in BP such as acute coronary event, acute heart failure, aortic dissection, or preeclampsia/eclampsia.
Data derived from Jauch et al.[1]

https://www.ahajournals.org/doi/10.1161/STR.0000000000000211

Intravenous labetalol

- Non-selective β-blocker with α-blocker properties as well.
- Maintains cardiac output, renal, cerebral, coronary blood flow.
- Decreases peripheral vascular resistance by diminishing sympathetic vascular tone.
- Not for use in acute heart failure.
- Drug of choice if hypertensive encephalopathy or cerebral hemorrhage.
- If myocardial ischemia, use with nitroglycerin.

Intravenous labetalol

- Use in acute post-operative hypertension
- Use in eclampsia
- Use in aortic dissection
- Do not use if reactive airway disease

Intravenous nitroglycerin

- Dilates venous vessels at lower dose than required for arterial vessels.
- Reduces preload and cardiac output.
- Dilates coronary arteries.
- Does not increase myocardial Oxygen demand.
- Reflex tachycardia.
- If myocardial ischemia or infarction, use with labetalol.
- If acute pulmonary edema with systolic dysfunction. use with nitroprusside or nicardipine or fenoldopam and loop diuretic.
- Do not use in volume depleted patients.

Intravenous nitroprusside

- Dilates arterial and venous vessels with equal facility.
- Increases myocardial Oxygen demand.
- Decreases cerebral blood flow.
- If aortic dissection, use with β-blocker.
- If acute pulmonary edema with systolic dysfunction, use with nitroglycerin and a loop diuretic.
- Thiocyanate metabolite may poison electron transport mechanism in cell.
- Renal or hepatic disease as contraindication for use.

Intravenous nicarpidine

- Vasoselective L calcium channel blocker.
- Smooth muscle relaxation.
- Use in hypertensive encephalopathy
- Limits arterial spasm
- If used in acute pulmonary edema and systolic dysfunction, use with nitroglycerin and a loop diuretic.
- Not for use in heart failure.
- Use in acute post-operative hypertension
- Use if renal insufficiency
- Preferred for obstetric use (e.g. Eclampsia)
- Do not use if severe aortic stenosis.

Intravenous fenoldopam

- Vasodilator.
- Acts on peripheral dopamine-1 receptors.
- Renal protective.
- Use in hypertensive encephalopathy or cerebral infarction
- If acute pulmonary edema with systolic dysfunction, use with nitroglycerin and loop diuretic.
- Use if renal insufficiency
- Do not use in patients with glaucoma
- Do not use if increased intracranial pressure
- Do not use if sulfite allergy

Intravenous phentolamine

- Acts on peripheral α-receptors
- Drug of choice in hypertension resulting from cocaine use as well as in pheochromocytoma

Table 6. Simplified Classification of Hypertension Risk according to additional Risk Factors, Hypertension-Mediated Organ Damage (HMOD), and Previous Disease*

Other Risk Factors, HMOD, or Disease	High-Normal SBP 130–139 DBP 85–89	Grade 1 SBP 140–159 DBP 90–99	Grade 2 SBP ≥160 DBP ≥100
No other risk factors	Low	Low	Moderate / High
1 or 2 risk factors	Low	Moderate	High
≥3 risk factors	Low / Moderate	High	High
HMOD, CKD grade 3, diabetes mellitus, CVD	High	High	High

*Example based on a 60 year old male patient. Categories of risk will vary according to age and sex.

Table 2. Comparison of Major Hypertension Guidelines

Organization (Reference)	Definition of Hypertension, *mm Hg*	Target SBP, *mm Hg*			Target DBP, *mm Hg*	Preferred Initial Drug Therapy	Other Drug Considerations	Drug Therapy for Resistant Hypertension
		General or Low CV Risk	High CV Risk*	Elderly†				
VA/DoD (7)	≥130/90	<130	-	<130 Strongest evidence to support <150 with additional benefit to lowering when SBP 130-150	<90	Thiazide diuretic, ACEI, ARB, or CCB	Suggest thiazide in patients aged ≥65 y	Spironolactone
ACC/AHA (4)	≥130/80	<130	<130	<130	<80	Thiazide diuretic, ACEI, ARB, or CCB	If BP ≥140/90 and average BP more than 20/10 mm Hg above target BP, recommend 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination	Maximize diuretic therapy Spironolactone
ACP/AAFP (56)	-	-	<140	<150	-	-	-	-
ESC/ESH (57)	≥140/90	<130 (120-129)	-	<140 (130-139)	<80	Thiazide diuretic, ACEI, ARB, CCB, or β-blocker	Preference for initial 2-drug therapy with a single combination pill	Spironolactone
NICE (58)	≥140/90	<140	<140	<150	<90	If age <55 y: ACEI or ARB If age ≥55 y: CCB or thiazide-like diuretic	-	Spironolactone

ACC/AHA = American College of Cardiology/American Heart Association; ACEI = angiotensin-converting-enzyme inhibitor; ACP/AAFP = American College of Physicians/American Academy of Family Physicians; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium-channel blocker; CV = cardiovascular; DBP = diastolic blood pressure; ESC/ESH = European Society of Cardiology/European Society of Hypertension; NICE = National Institute for Health and Care Excellence; SBP = systolic blood pressure; VA/DoD = U.S. Department of Veterans Affairs/U.S. Department of Defense.

* Defined by the ACC/AHA as a 10-year risk for CV events >10% or known CV disease, diabetes mellitus, or chronic kidney disease; by the ACP/AAFP as known CV disease, diabetes mellitus, prior stroke, metabolic syndrome, or chronic kidney disease; and by NICE as a 10-year risk for CV events >10% or target organ damage, established CV disease, diabetes mellitus, or chronic kidney disease.

† Defined as age >60 y in the VA/DoD and ACP/AAFP guidelines, >65 y in the ESH/ESC guidelines, and >80 y in the ACC/AHA and NICE guidelines.

Treatment guidelines

- The relationship between systemic arterial pressure and cardiovascular morbidity or mortality appears to be linear above 115/75 mm Hg,
- The 2017 ACC/AHA guideline defined hypertension as an SBP of 130 mm Hg or greater or a DBP of 80 mm Hg or greater (or both)
- Lower SBP below 130 mm Hg in all patients
- Combining the DASH diet with sodium restriction (2300mg/d) consistently produces larger decreases in blood pressure than either intervention alone across diverse subgroups
- Exercise and weight loss

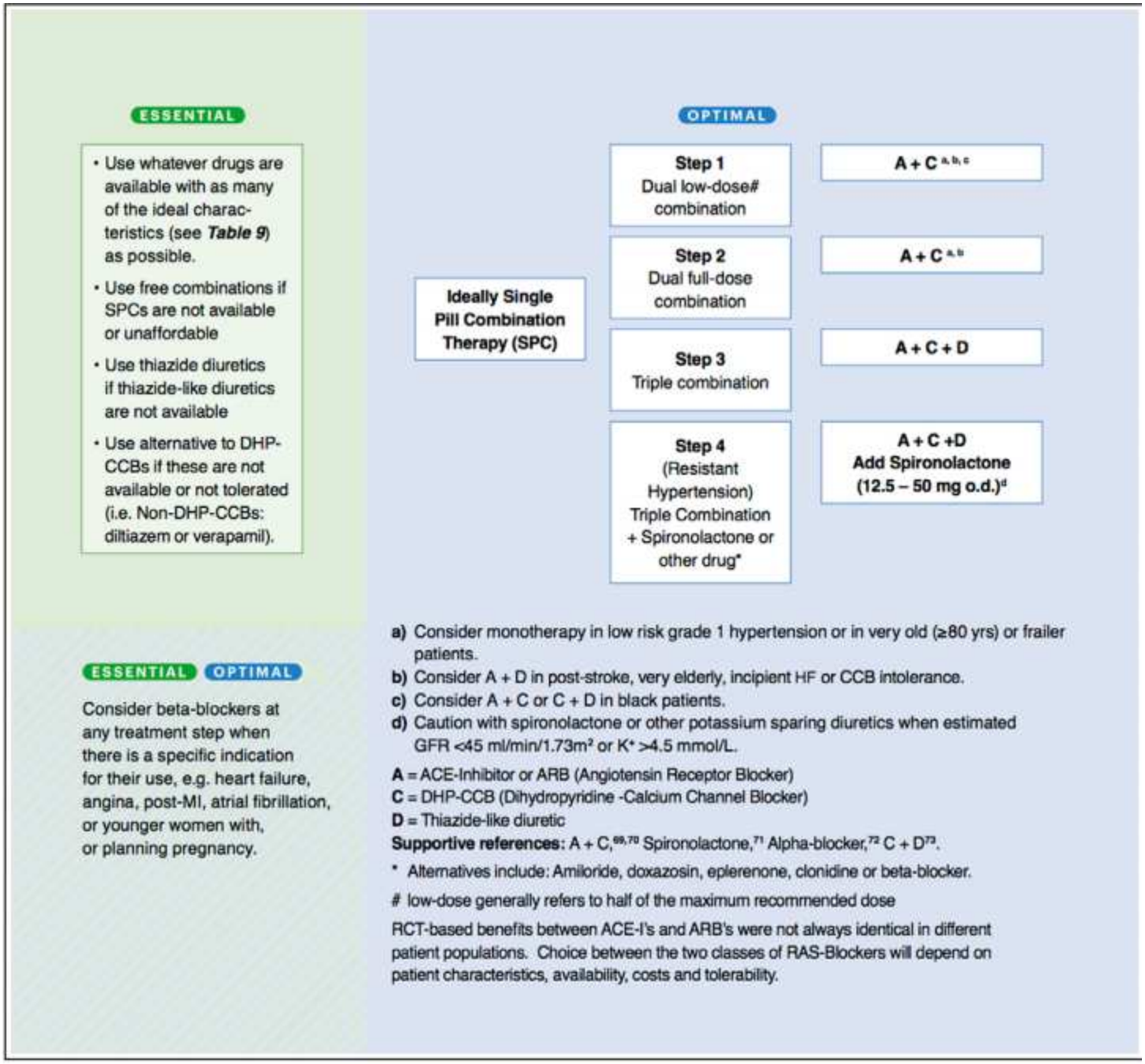


Figure 4. ISH core drug-treatment strategy. Data from references 69–73. Ideal characteristics of drug treatment (see Table 9).

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	Comment
For most patients, combination antihypertensive therapy should include an ACEI or ARB, a thiazide diuretic, or a calcium channel blocker.[4-6]	A	Consistent evidence showing reduced morbidity and mortality with each of those four drug classes in RCTs included in guidelines
Patients with chronic kidney disease who have proteinuria should be prescribed an ACEI or ARB as part of combination therapy.[40,41]	A	Consistent evidence from RCTs showing reduced morbidity and mortality
The combination of an ACEI and an ARB should be avoided.[43]	B	RCT showed that benefit is outweighed by increased morbidity

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; RCT = randomized controlled trial.

A = consistent, good-quality patient-oriented evidence; **B** = inconsistent or limited-quality patient-oriented evidence; **C** = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to https://www.aafp.org/afpsort.

Smith, DK, Lennon, RP, Carlsgaard, PB, “Managing hypertension using combination chemotherapy,” Am Fam Physician. 2020 Mar 15;101(6):341-349.

Anti-hypertensive therapy

- 2020 ISH Guidelines
- ACE inhibitors or angiotensin receptor blockers (ARB) with dihydropyridine Calcium channel blockers are the first choice in adult patients (>18 yo) with chronic renal disease or diabetes mellitus regardless of race
- Diuretics should be considered in those with West African parentage
- Thiazides are more effective in the elderly, the obese, smokers, and those of African parentage
- Chlorthalidone or indapamide is preferred over hydrochlorothiazide

Anti-hypertensive therapy

- Third drug to be added is a diuretic
- ACEI and ARB or direct renin inhibitor are not to be used together
- Add spironolactone or finerenone (non-steroidal mineralicorticoid blocker) if resistant to diuretic, ACEI/ARB, CCB triple therapy
- Aldosterone is elevated in 50% of patients with difficult to treat hypertension.
- Spironolactone is used with caution if estimated GFR <45 ml/min/1.73m^2 BSA or K^+>4.5

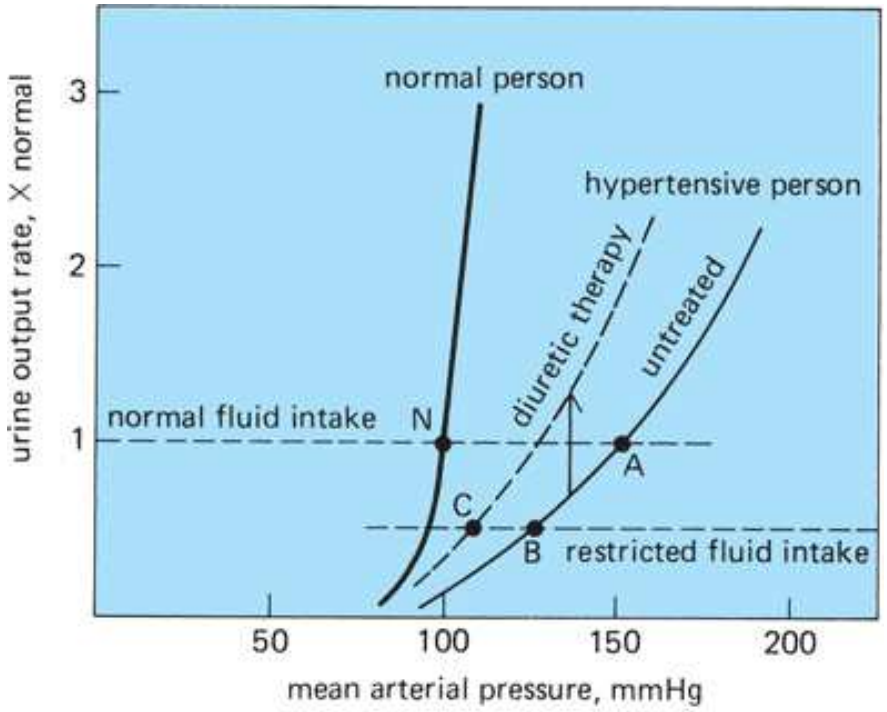
Anti-hypertensive therapy

- Sodium glucose transport inhibitors are useful anti-glycemic therapy in diabetic patients (type 2) and slow deterioration of kidney function
- Drug resistance is defined as persistent hypertension despite the simultaneous use of three different drugs (calcium channel blocker/ARB or ACE inhibitor/diuretic) with one being a diuretic at >50% of maximal dose
- Chlorthalidone is preferred over hydrochlorthiazide
- Mineralicorticoid inhibitor as fourth drug
- Treatment of obstructive sleep apnea with CPAP not associated with improved outcomes

Anti-hypertensive therapy

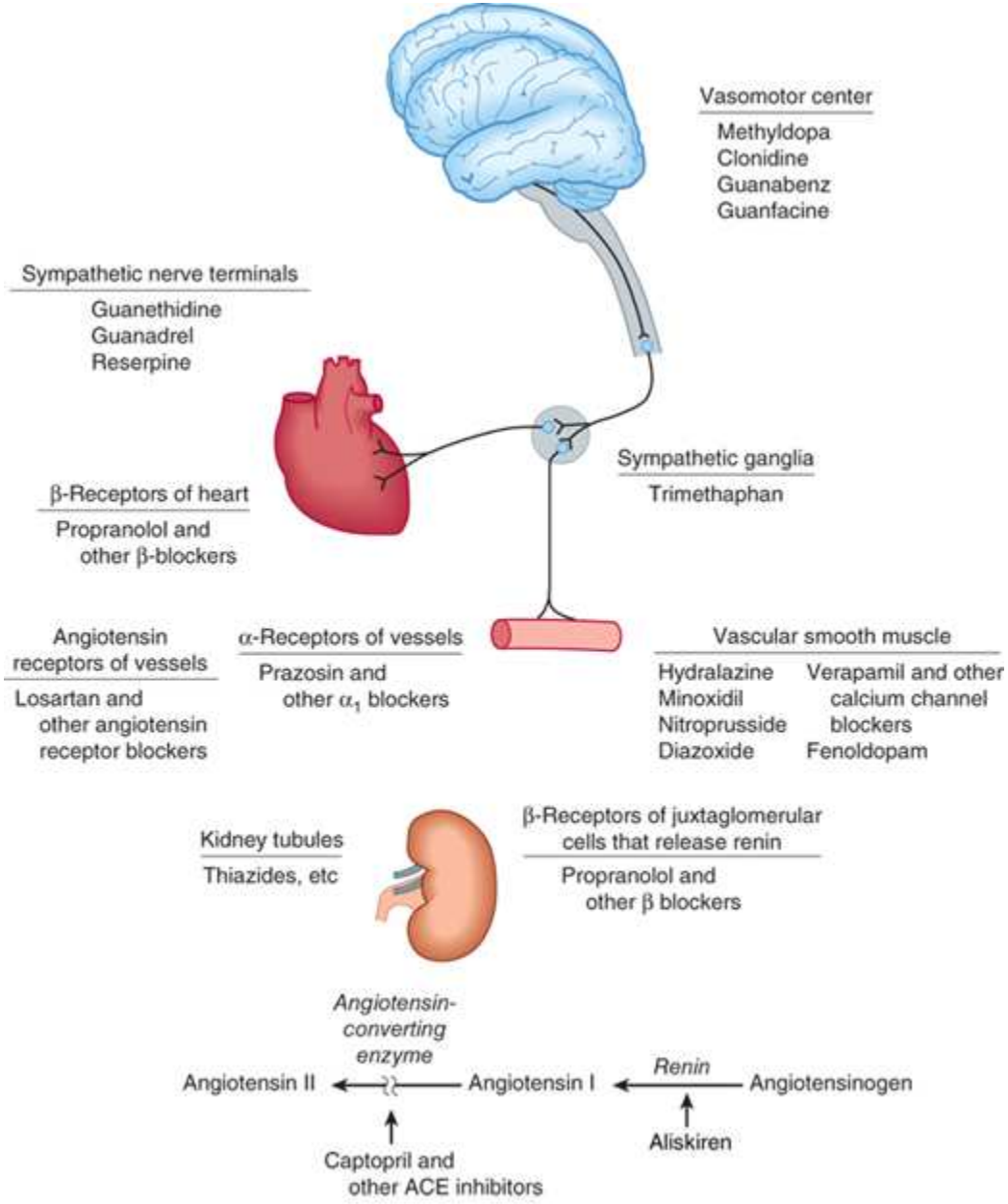
- ACE inhibitors reduce incidence of all cardiac events as compared to ARBs
- Aldosterone receptor blockers are effective in all groups.
- Non-dihydropyrimidine calcium channel blockers are employed if vasopsasm.
- They lower contractility and increase the PR interval, however.
- Do not use with β-blockers
- May use β-blockers if specific condition mandates

Renal function curves in hypertension and hypertension therapy

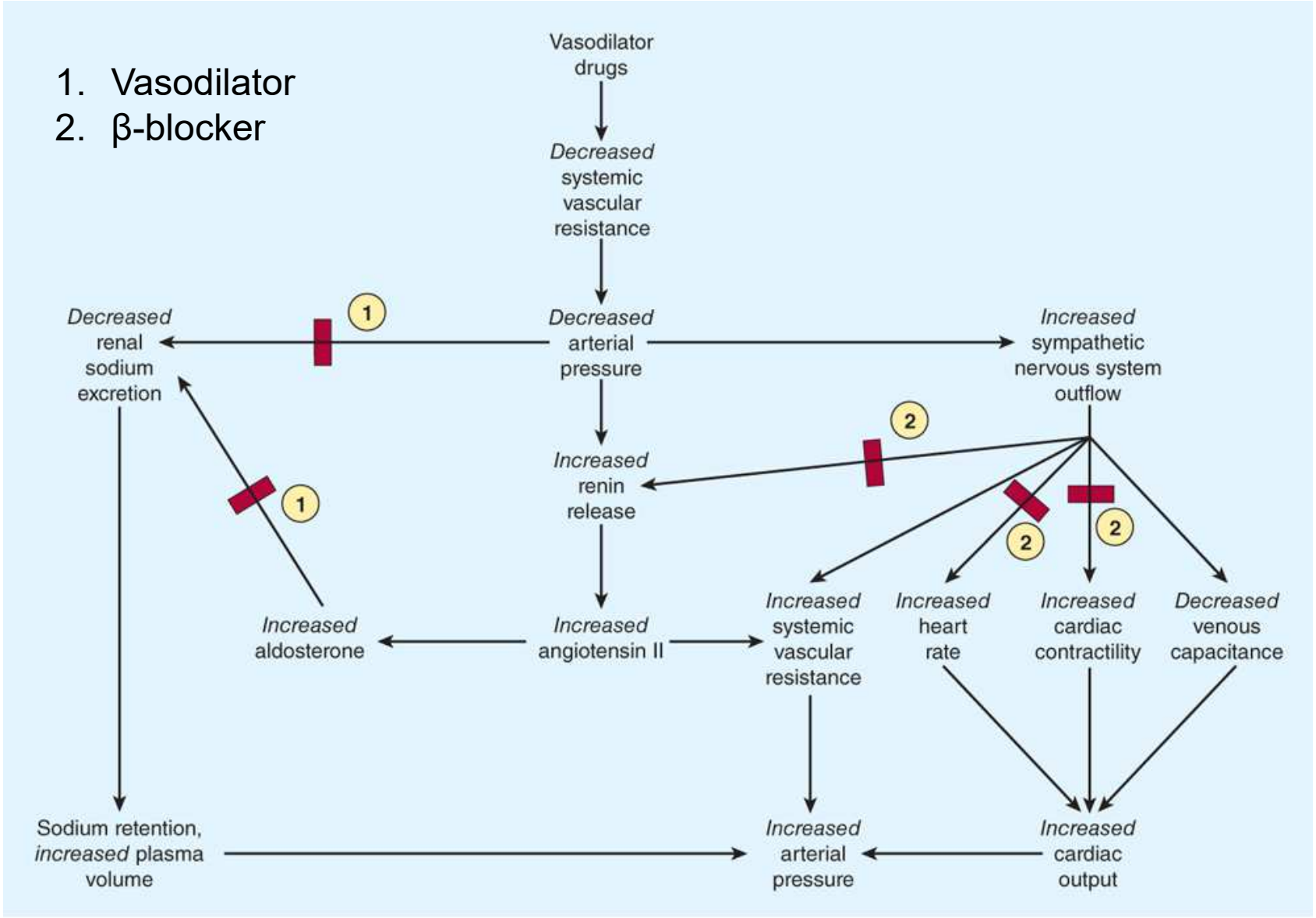


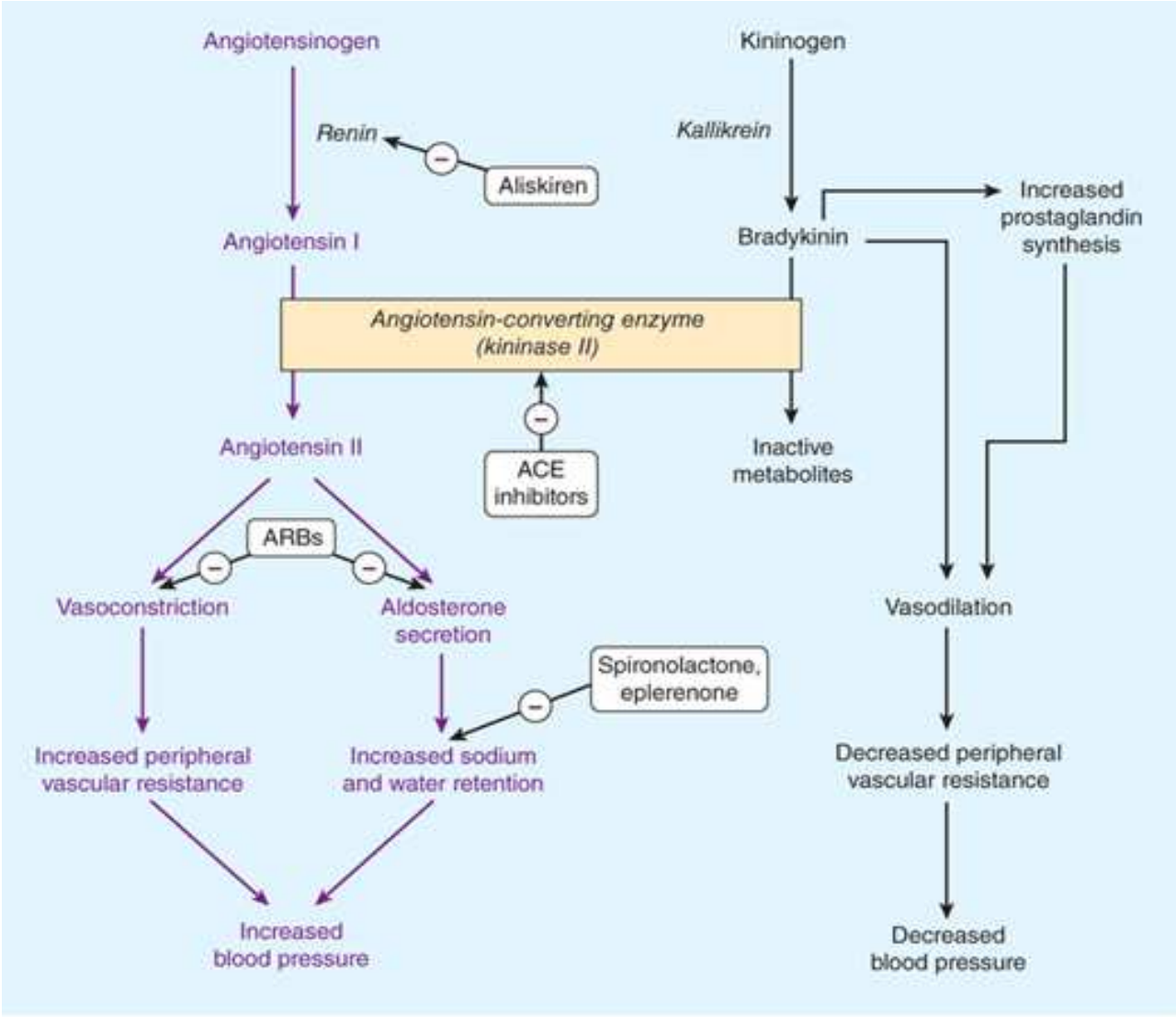
Source: Mohrman DE, Heller LJ: *Cardiovascular Physiology*, 6th Edition: http://www.accessmedicine.com

Fig. 11-5 Accessed 02/01/2010



1. Vasodilator
2. β-blocker





Diuretics

Class	Mechanism of action	Adverse effects
Thiazide	Inhibits Na^+ /Cl^- symporter in distal tubule, leading to diminished reabsorption of Na^+; Ca^{2+} reabsorption increases	Uric acid excretion impaired; worsen lipid profile, hyperglycemia; hypokalemia;
Loop Furosemide, Butamide	Inhibits Na^+-K^+-Cl^- channel in ascending limb of loop of Henle (block reabsorption); increase Ca^{2+} loss as lumen positive potential falls	Uric acid excretion impaired; hypokalemia; ototoxic
Potassium Sparing Triamterene Spironolactone Finerenone	Inhibit Na^+ transport in distal tubule and collecting duct Aldosterone antagonist Mineralicorticoid blocker	Hyperkalemia
Carbonic Anhydrase Inhibitor	Inhibit conversion of bicarbonate to CO_2 in proximal convoluted tubule	Metabolic acidosis; paresthesias
Osmotic	Enhance water excretion	

Anti-hypertensive agents

Agent	Mechanism	Adverse effects
Methyldopa Clonidine	Centrally acting α_2 agonists	Positive Coomb's test Rebound hypertension
Prazosin, doxazosin, terazosin, phentolamine	α-blockers	Relax bladder sphincter (treat urinary hesitancy)
Propanolol Atenolol, metoprolol, esmolol Carvedilol	Non selective β-blockers β_1-blockers Mixed α and β blockers	Bradycardia may be noted with all β-blockers Bronchoconstriction is not seen with selective blockers Decreased systemic vascular resistance is noted with all; cardiac output also falls
Nifedipine, amlodipine	Vasoselective L-type Calcium channel blockers	Constipation, bradycardia
Diltiazem	Nonselective L-type Calcium channel blocker	Diminished cardiac contractility

Anti-hypertensive agents

Agent	Mechanism	Adverse effects
Nitroprusside	Nitrous oxide release	Cyanide generation
Nitroglycerin	Nitrous oxide release	
Hydralazine	Opens K+ channels	Drug induced SLE
Minoxidil		Hirsutism, Sodium retention
Captopril, lisinopril, enalapril	Angiotensin converting enzyme and bradykinin inhibitors	Cough, hyperkalemia, proteinuria, angioedema, fetal renal defects
Losartan, valsartan	Angiotensin II receptor blockers	Cough, hyperkalemia, proteinuria, angioedema, fetal renal defects
Fenoldopam	Peripheral D1-receptor blocker	