Zdravila, ki se uporabljajo pri pešanju srca

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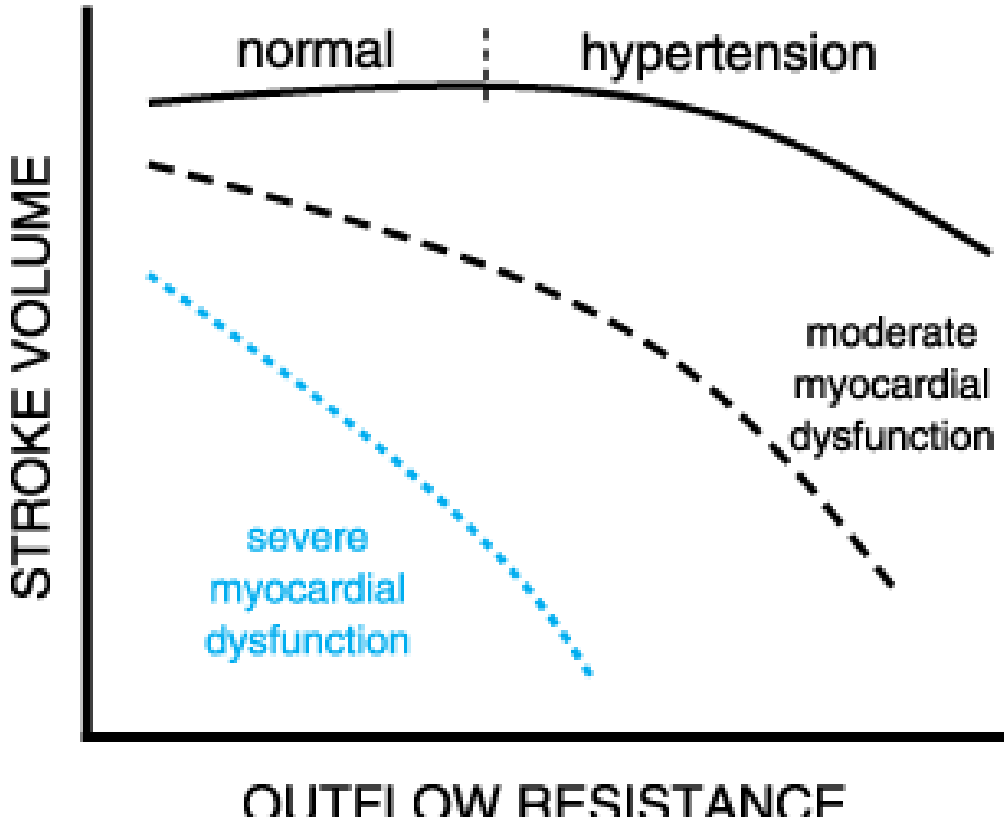
Pešanje srca (PS)

- Nesposobnost črpanja krvi v skladu s potrebami tkiv (ob normalnem polnilnem tlaku)
- Slabše prenašanje napora

Relationship between ventricular outflow resistance and stroke volume in patients with systolic ventricular dysfunction.



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Vzroki

- Koronarna bolezen
- Ishemična bolezen srca $\Rightarrow$ miokardni infarkt
- Hipertenzija
- Bolezni zaklopk
- Kongenitalne srčne hibe
- Kardiomiopatija

Vse to privede do hipertrofije oz. do zadebelitve stene ventriklov $\Rightarrow$ neugodno remodeliranje

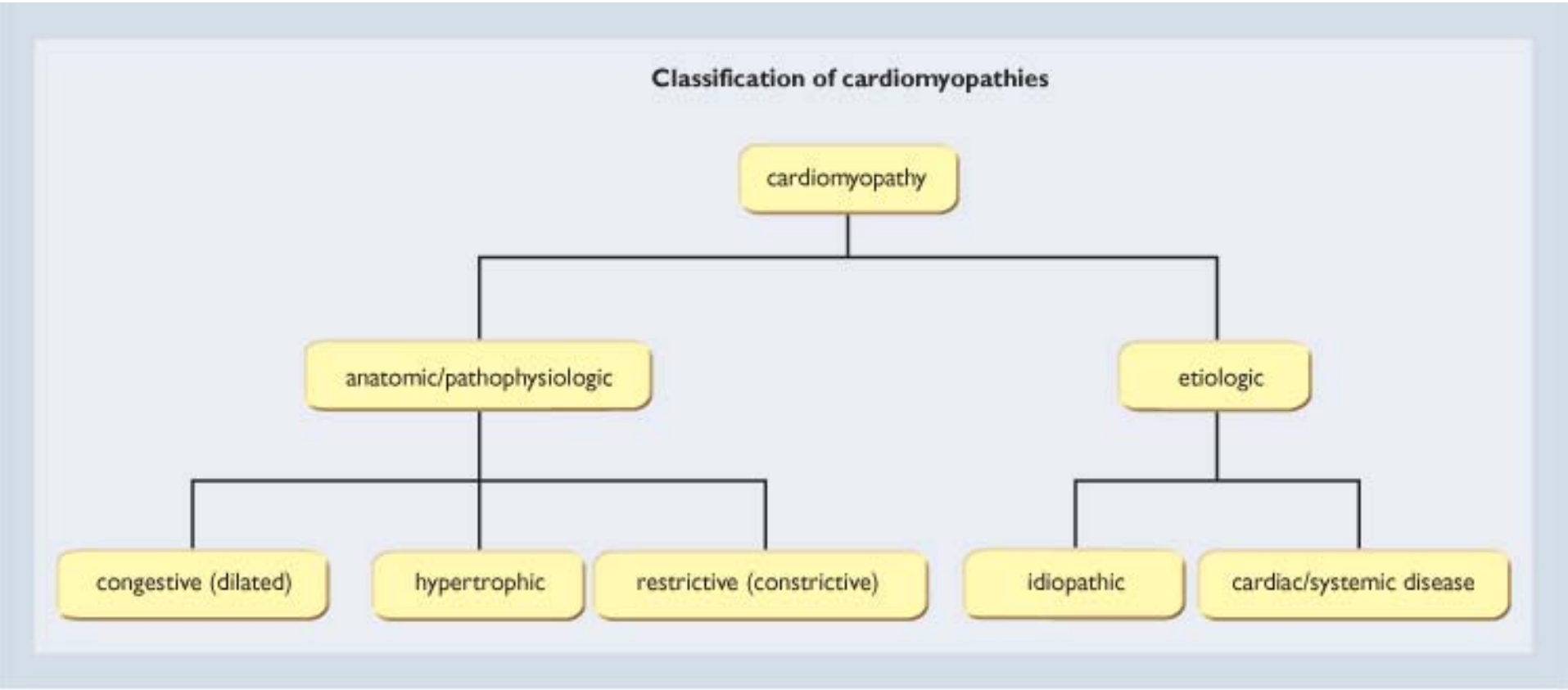


Figure 13.20 Classification of cardiomyopathies based upon anatomic, pathophysiologic and etiologic considerations.

Simptomi PS

Akutno	*Kronično*
Tahikardija	Različne aritmije
Težko dihanje (kratka sapa)	Hipertenzija
Edem (periferni in/ali pljučni)	Kardiomegalija
Slabše prenašanje napora	Edem (periferni / pljučni)

Klinične značilnosti PS

- Zmanjšana moč kontrakcije
- Zmanjšan minutni volumen
- Zmanjšana perfuzija tkiv
- Povečan periferni upor
- Edemi

Oblike in značilnosti

- Pešanje levega srca (najbolj pogosta oblika): zmanjšan minutni volumen, znižan arterijski pritisk, zastoj v pljučih
- Pešanje desnega srca: dispneja, edem in utrujenost
- Kompenzatorni mehanizmi v začetni fazi in kratkoročno olajšajo, v kasni fazi in dolgoročno pa poslabšajo simptome.

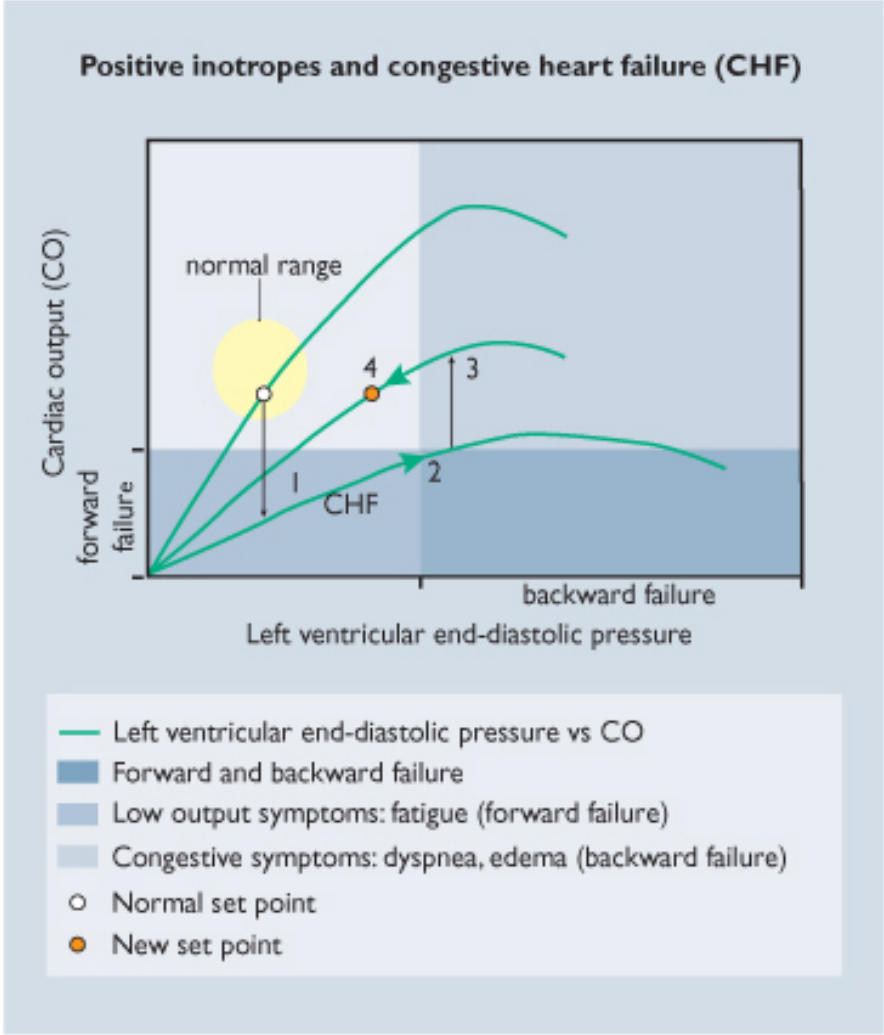


Figure 13.25 The Frank-Starling curve, positive inotropes and congestive heart failure (CHF). Normal cardiac output is determined by the pressure in the left ventricle at end-diastole. In CHF, the set point for cardiac output is reduced and cardiac output falls (1). Compensatory neurohumoral responses become activated which increase end-diastolic pressure and improve cardiac output; however, this can give rise to backward failure (2). Positive inotropic agents increase cardiac output (3). The improved cardiac output reduces the drive for a high end-diastolic pressure, and decompensation occurs to a new set point (4).

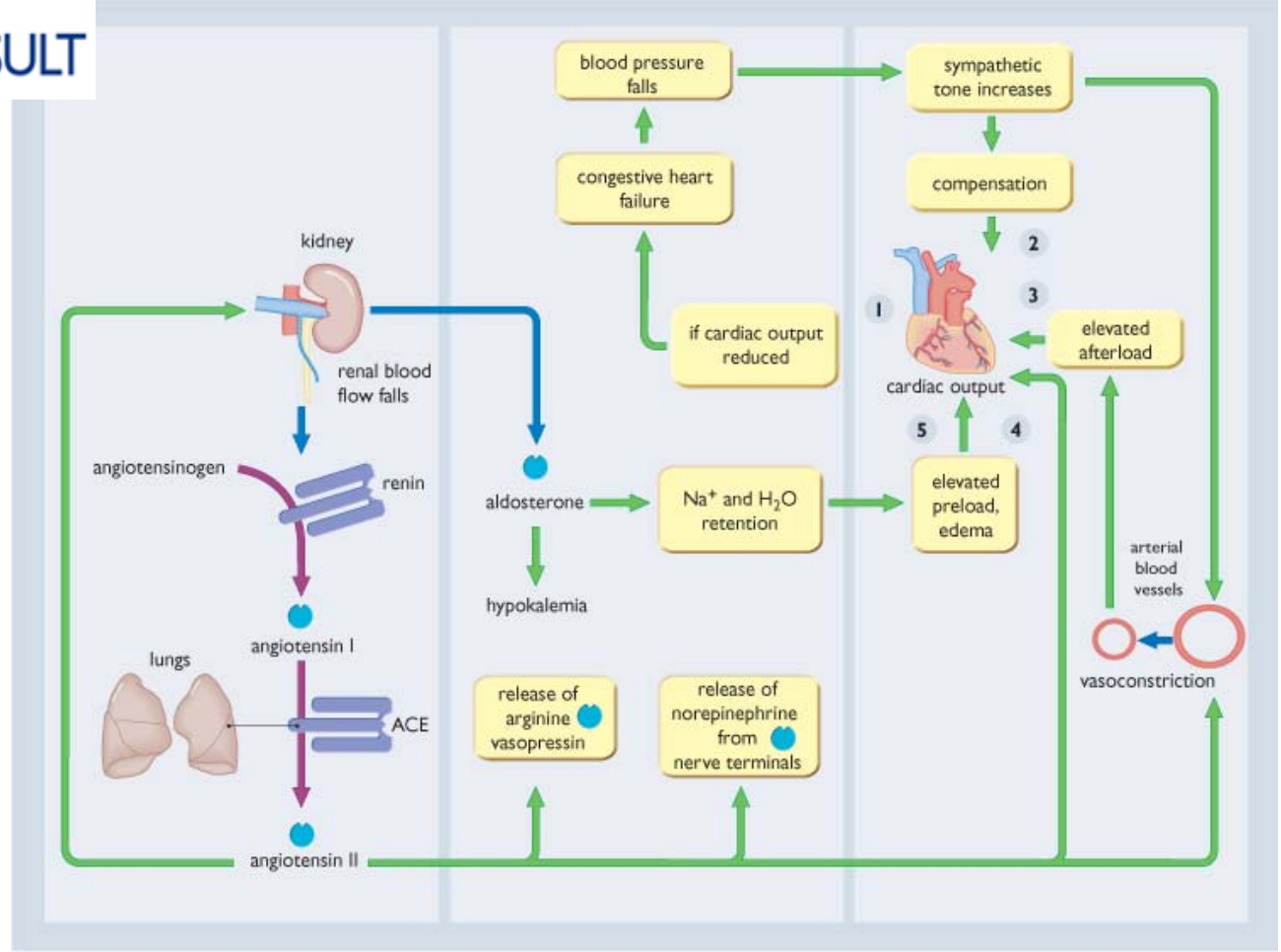
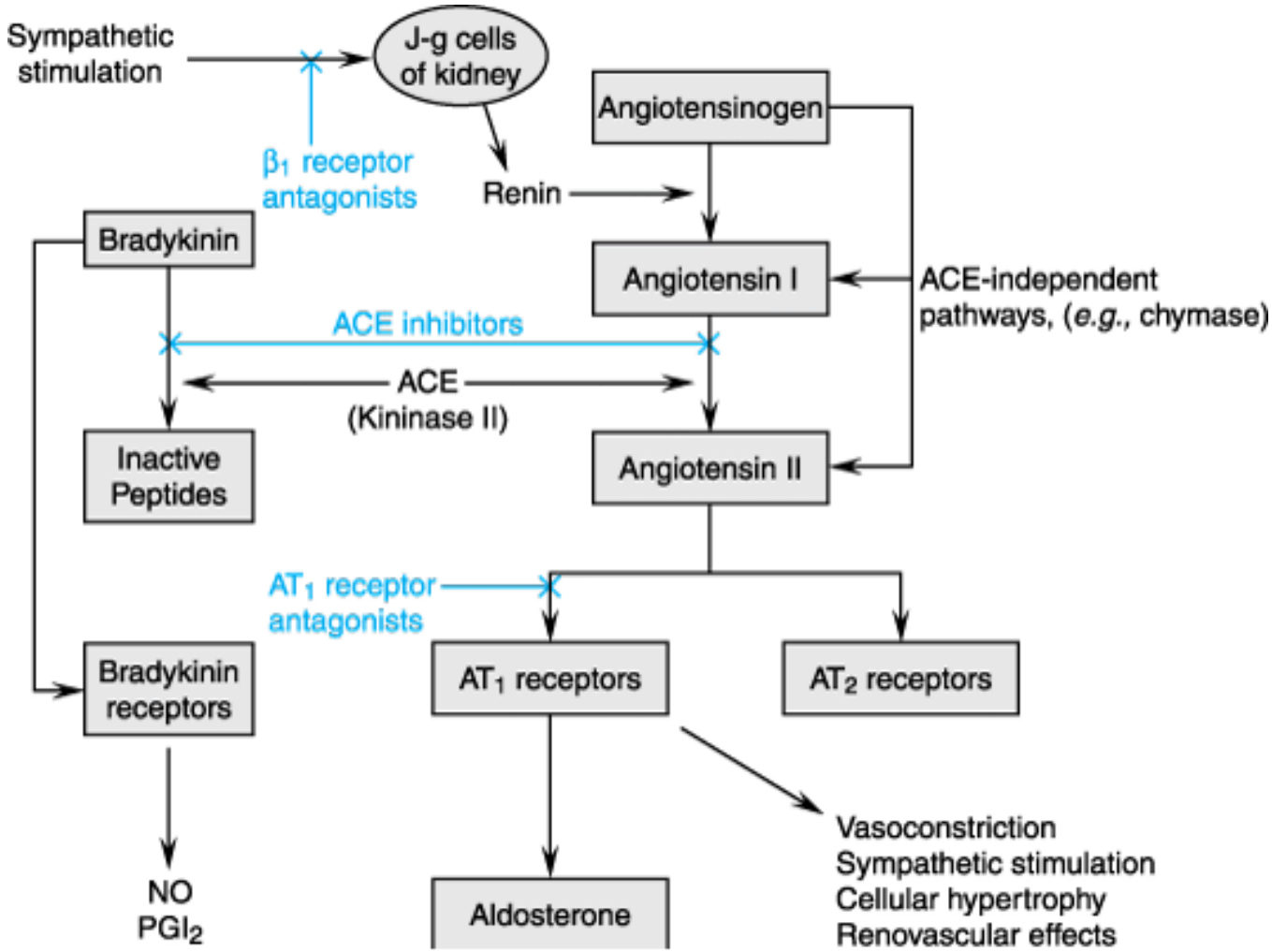


Figure 13.22 The major extrinsic neurohumoral compensatory mechanisms involved in congestive heart failure. (1) The initial event is a reduction in cardiac output. (2) Reflex sympathetic compensation can increase cardiac output, but (3) an associated increase in afterload can reduce cardiac output. The cascade of other events can lead to hypertrophy (4) owing to actions of angiotensin II on the heart, which increases cardiac output and Na+ retention. This may increase cardiac output (5) by raising preload and left ventricular end-diastolic pressure, but this may cause death by initiating pulmonary edema.

Renin – angiotensin system



Farmakoterapevtski pristop

- Klasični: usmerjenost v ključna končna pojava:
  - preobremenitev z volumnom krvi (ECF) $\Rightarrow$ diuretiki
  - disfunkcija srca (pešanje) $\Rightarrow$ pozitivna inotropna zdravila
- Novejši pristop $\Rightarrow$ cilji zdravljenja:
  - motena cirkulatorna dinamika
  - patološko remodeliranje miokarda

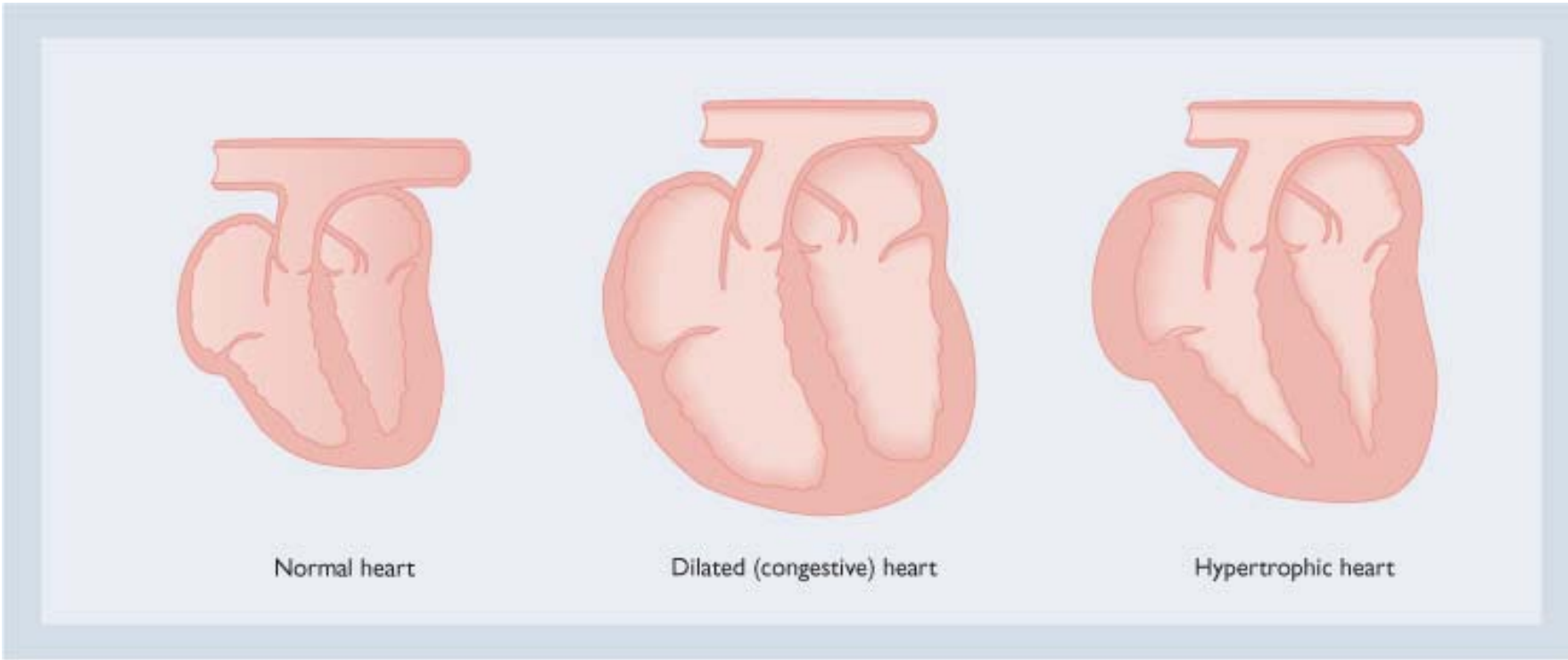
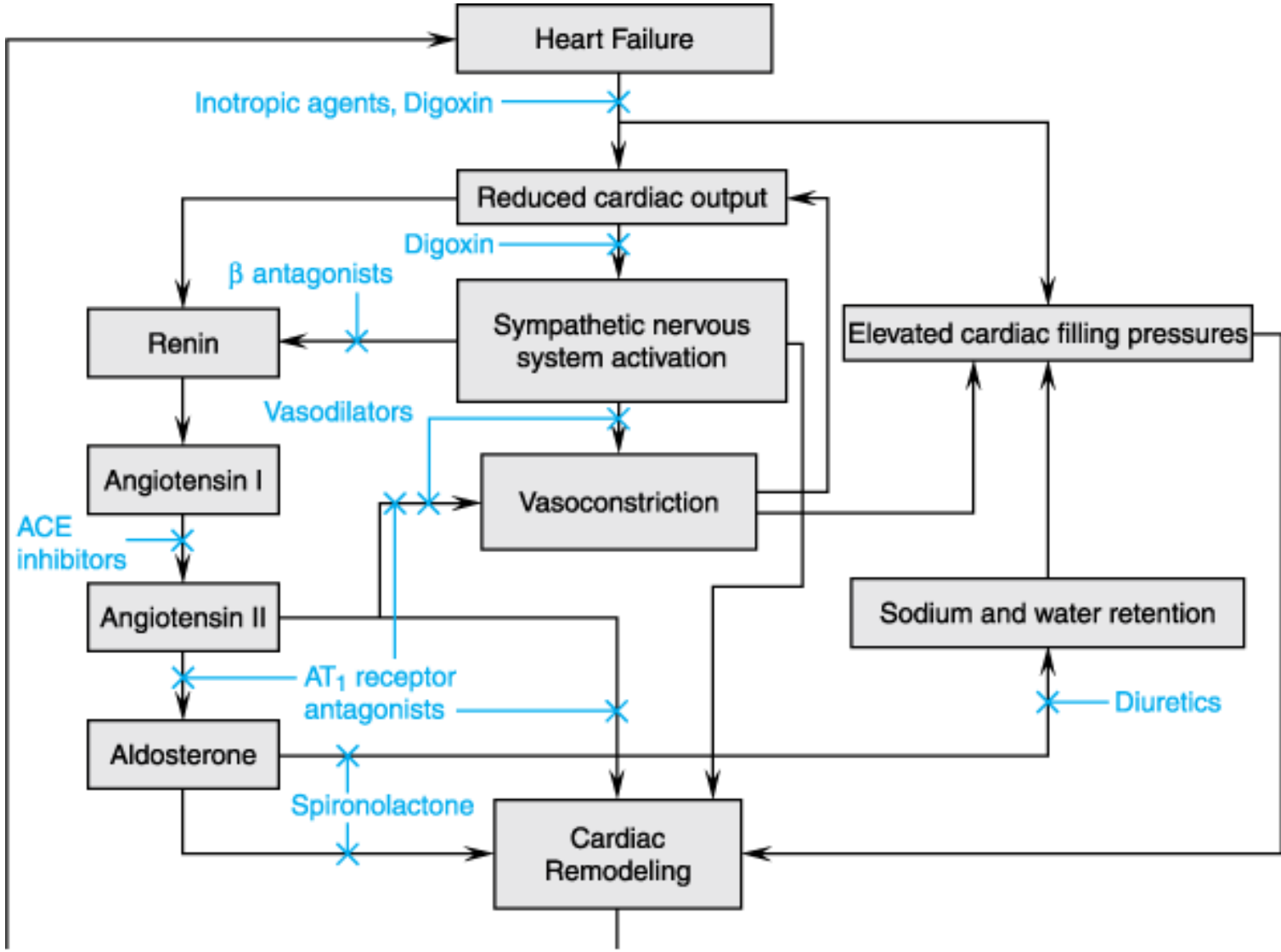


Figure 13.21 Types of cardiomyopathies involving both the right and left ventricle.

Mechanisms of heart failure and major sites of drug action.



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Pharmacotherapeutic approach to congestive heart failure

Problem	Approach
Fatigue	Rest, positive inotropes
Edema	Diet (salt restriction), diuretics, digitalis
Poor cardiac contractility	Positive inotropes
Dyspnea	Diuretics (thiazides/loop)
Congestion	Nitrovasodilators
Increased cardiac preload and afterload	Angiotensin-converting enzyme inhibitors, venodilators, vasodilators
Irreversible heart failure	Heart transplantation

Pozitivno inotropna zdravila

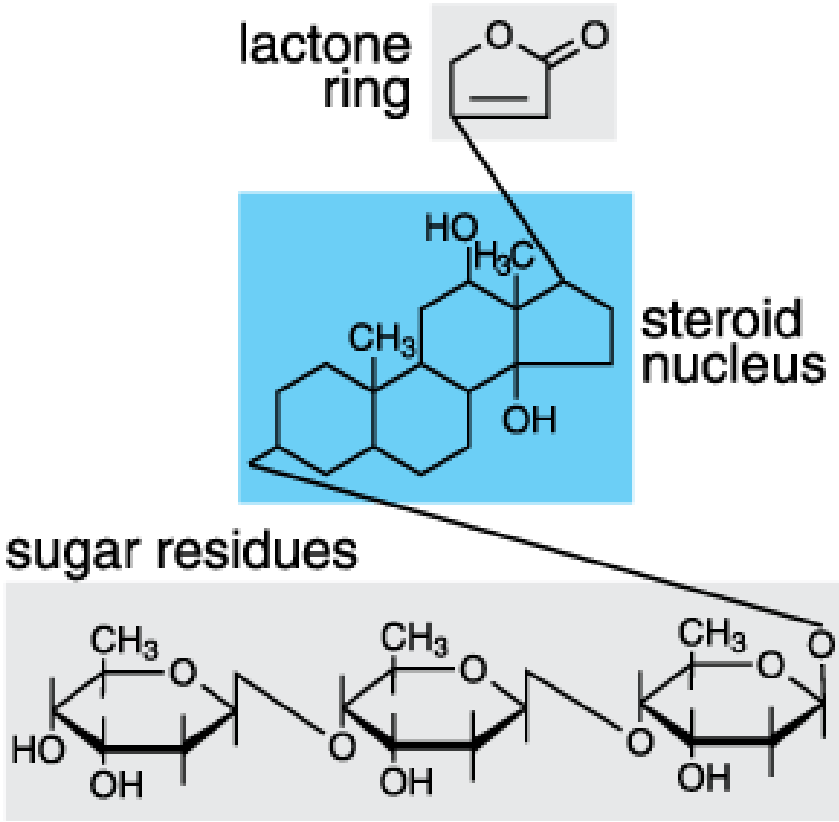
Izboljšanje kontraktilnosti miokarda:

- Kardiotonični glikozidi (npr. digoksin)
- Inhibitorji fosfodiesteraze (npr. inamrinon)
- $ß_1$ agonisti (npr. dobutamin)

Kardiotonični glikozidi (KG)

- Primarni učinek na srcu: Zaviranje Na^+,K^+-ATP-aze, najbolj očitno v miokardu
- Ekstrakardialni učinki:
  - GIT
  - OŽ (vagusova jedra, drugi centri)
  - ledvice

Structure of cardiotonic glycoside



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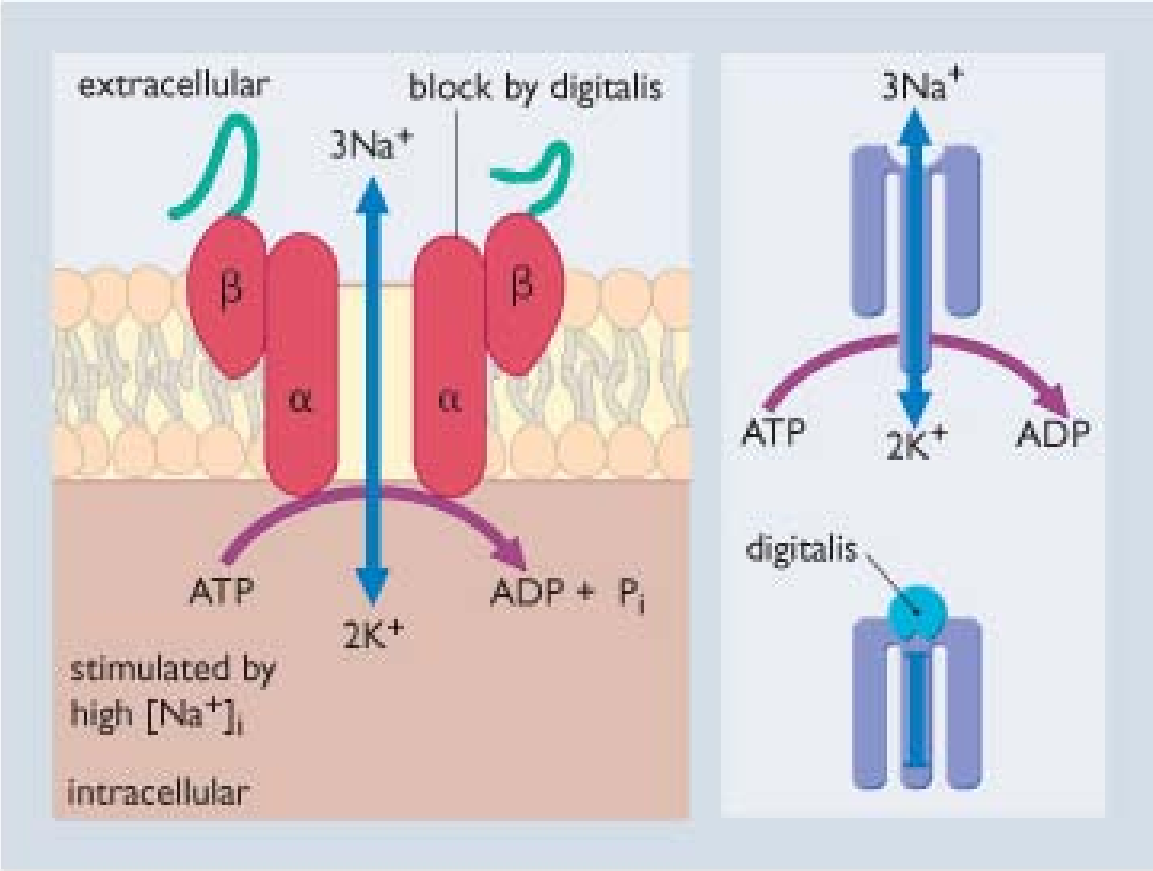
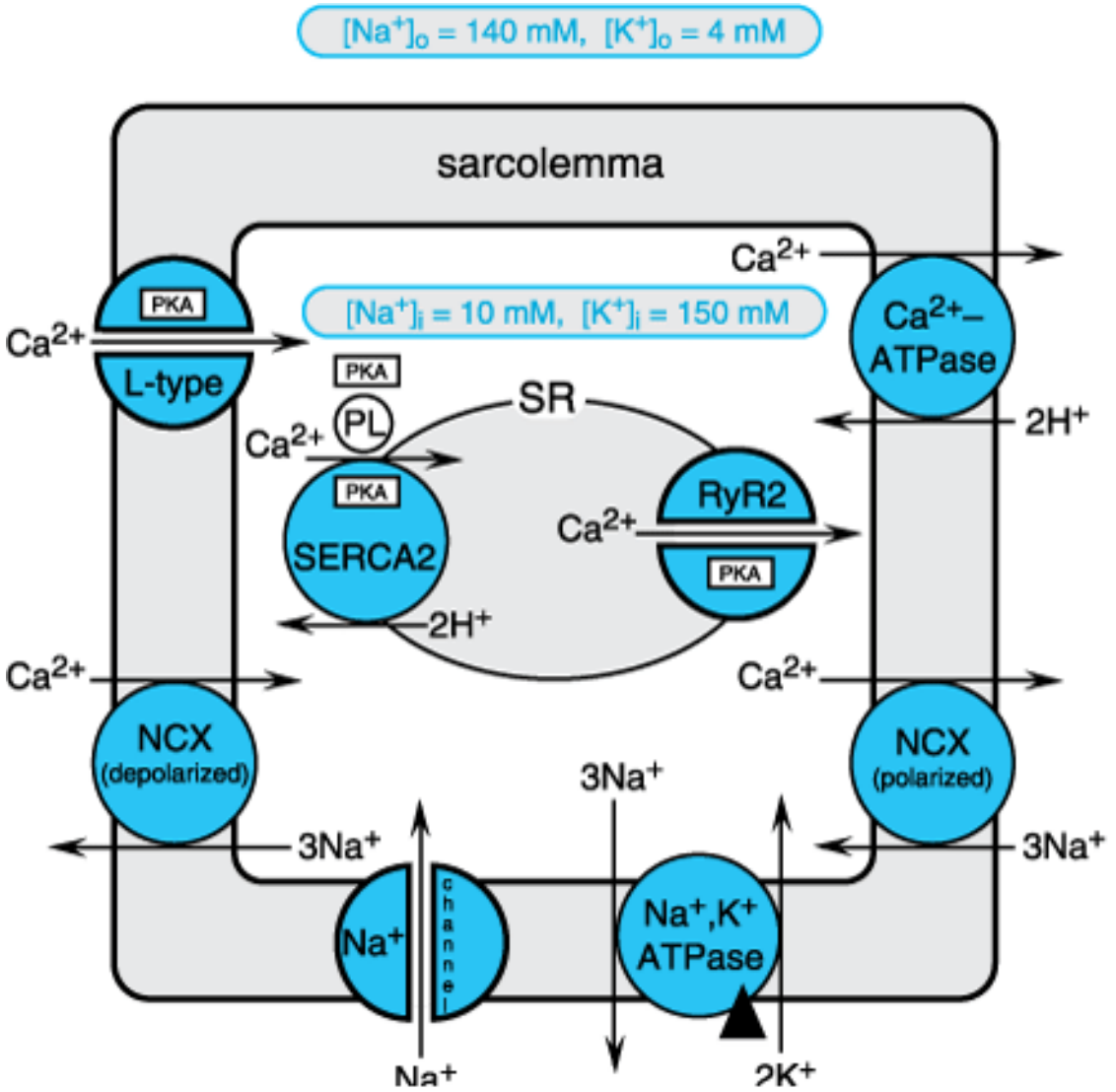


Figure 13.24 Mechanism of action of digitalis glycosides. The binding site for digitalis is on the extracellular aspect of the α-β heterodimer structure of the Na+/K+ ATPase enzyme. Inhibition of this enzyme raises intracellular Na+ concentration, which raises intracellular Ca2+, and mediates the positive inotropic actions of cardiac glycosides.

Sarcolemmal exchange of Na^+ and Ca^{2+} during cell depolarization and repolarization



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Učinki KG - n. vagus

Povečana aktivnost vagusa se najbolj kaže supraventrikularno in privede do:

- upočasnitve proženja v SA vozlu,
- upočasnitve prevajanja v AV vozlu (podaljšan interval PR),
- skrajšanja atrijskega akcijskega potenciala

Učinki KG - srce

- Neenakomerna vzdražnost miokarda – aritmije (AV blok, tahikardija iz AV vozla, ventrikularne ekstrasistole)

- Pri večjih koncentracijah KG doseže prosti Ca^{2+} toksične nivoje, pride do zasičenja prenašalca Ca^{2+} v sarkoplazemski retikulum (SR) $\Rightarrow$ oscilacije konc. prostega Ca^{2+} (Ca^{2+} inducira sproščanje Ca^{2+} iz SR) $\Rightarrow$ oscilacije membranskega potenciala (oscillatory afterpotentials).

$\Downarrow$

Aritmije, posamezne in multiple ventrikularne ekstrasistole

Neželeni učinki KG

- Ozko terapevtsko okno
- Izgube K^+ v miokardu $\Rightarrow$ aritmije (posebno nevarno ob uporabi nekaterih diuretikov)
- Aritmije ob kardioverziji

Ekstrakardialni neželeni učinki KG

- Vpliv na GIT (draženje v želodcu).
- Učinki na OŽ – stimulacija vagalnih aferentnih poti, kemoreceptorne cone $\Rightarrow$ nauzea, bruhanje, diareja in anoreksija.
- Drugi učinki na OŽ: motnje vida, glavobol, omotica, utrujenost in halucinacije – starejši bolniki
- Redko: eozinofilija, izpuščaj, ginekomastija (vpliv na hipotalamus ali estrogeno delovanje KG).

Zdravljenje toksičnih učinkov

- Oralno nadomeščanje K^+ (preprečevanje hipokaliemije)
- Antiaritmiki (prokainamid and phenytoin)
- Monoklonska protitelesa, ki vežejo KG.

Inhibitorji fosfodiesteraze (PDE)

- Inhibicija razgradnje cAMP poveča citosolno koncentracijo Ca^{2+}.
- Razgradnja cAMP inhibirana tudi v arterijskih in venskih miocitih $\Rightarrow$ vazodilatacija
- Inhibitorji PDE: $\Uparrow$ MV, $\Downarrow$ zagozditveni pritisk v pljučnih kapilarah, $\Downarrow$ PU (brez spremembe ν srca in AP).

Učinki inhibitorjev PDE pri PS

- Popravi se MV srca
- ⇑ utripni volumen
- ⇓ pritisk v desnem atriju in zagozditveni pritisk v pljučnih kapilarah
- Abnormalni jetrni testi in trombocitopenija
- Predstavnika: inamrinon in milrinon (močnejši analog inamrinona).

Antagonisti adrenoceptorjev $ß_1$ pri PS

- Mehanizem: antagonizem neugodnega remodeliranja miokarda $\Leftarrow \Uparrow$ tonus simpatika.
- Antagonisti adrenoceptorjev $ß_1 \Rightarrow$ preprečenje $\Downarrow$ števila (down regulation) adrenoceptorjev $ß_1$ (posledica $\Uparrow$ tonusa simpatika)
- Klinične študije: $\Downarrow$ smrtnost pri PS ob dolgotrajni uporabi antagonistov β.

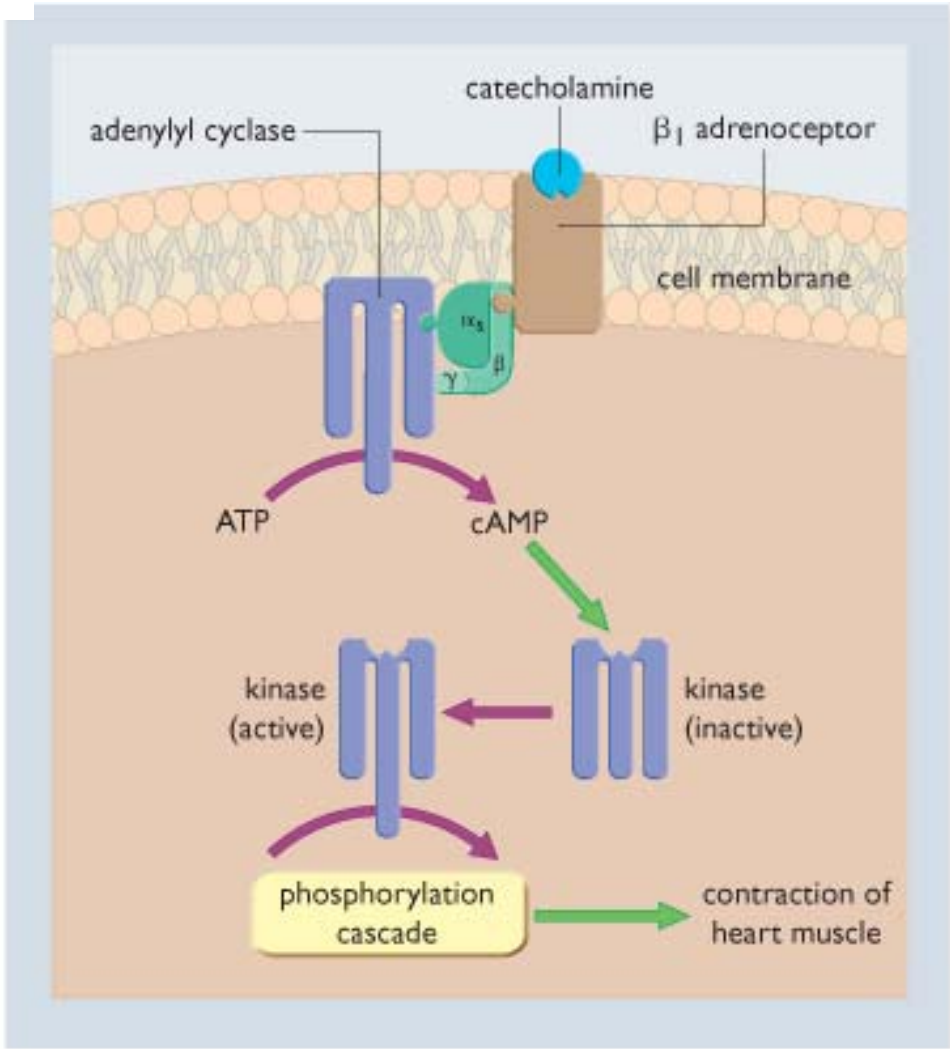
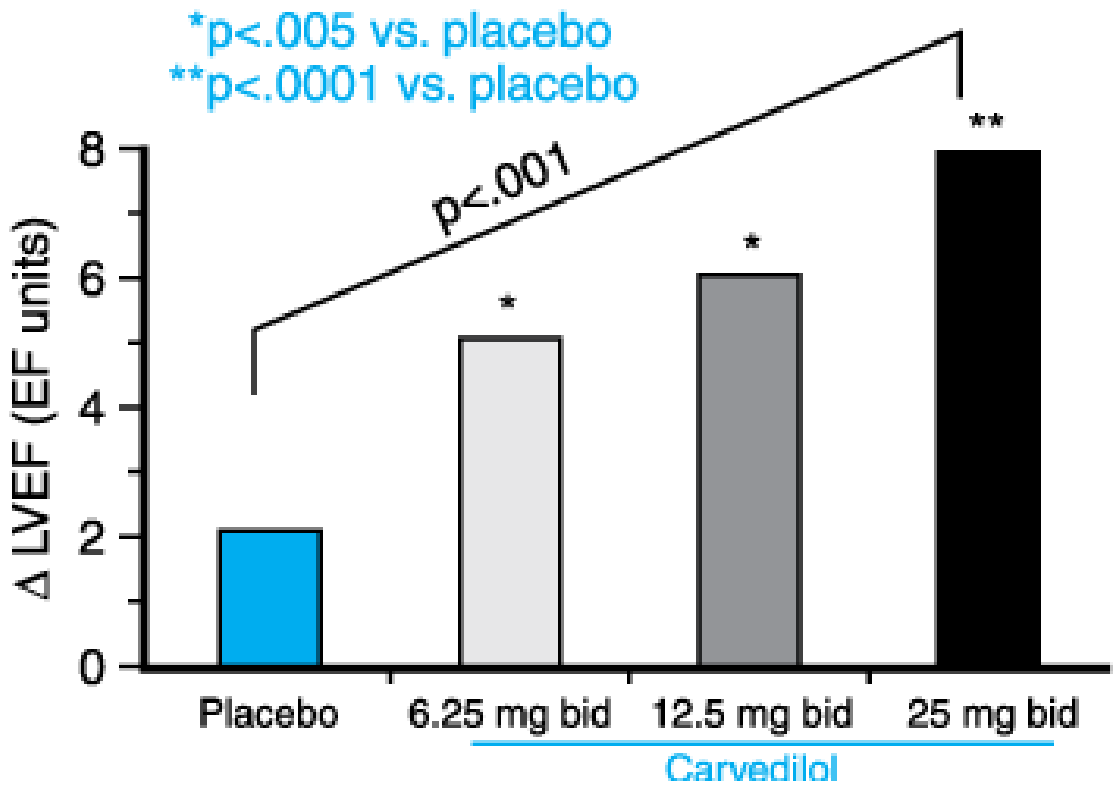


Figure 13.15 Molecular mechanism of action of beta;1 adrenoceptor antagonists. Stimulation of beta;1 adrenoceptors by catecholamines leads to activation of adenylyl cyclase and an elevation of cAMP. This process is inhibited by beta;1 adrenoceptor antagonists.

Dose-dependent effect of carvedilol on left ventricular ejection fraction.



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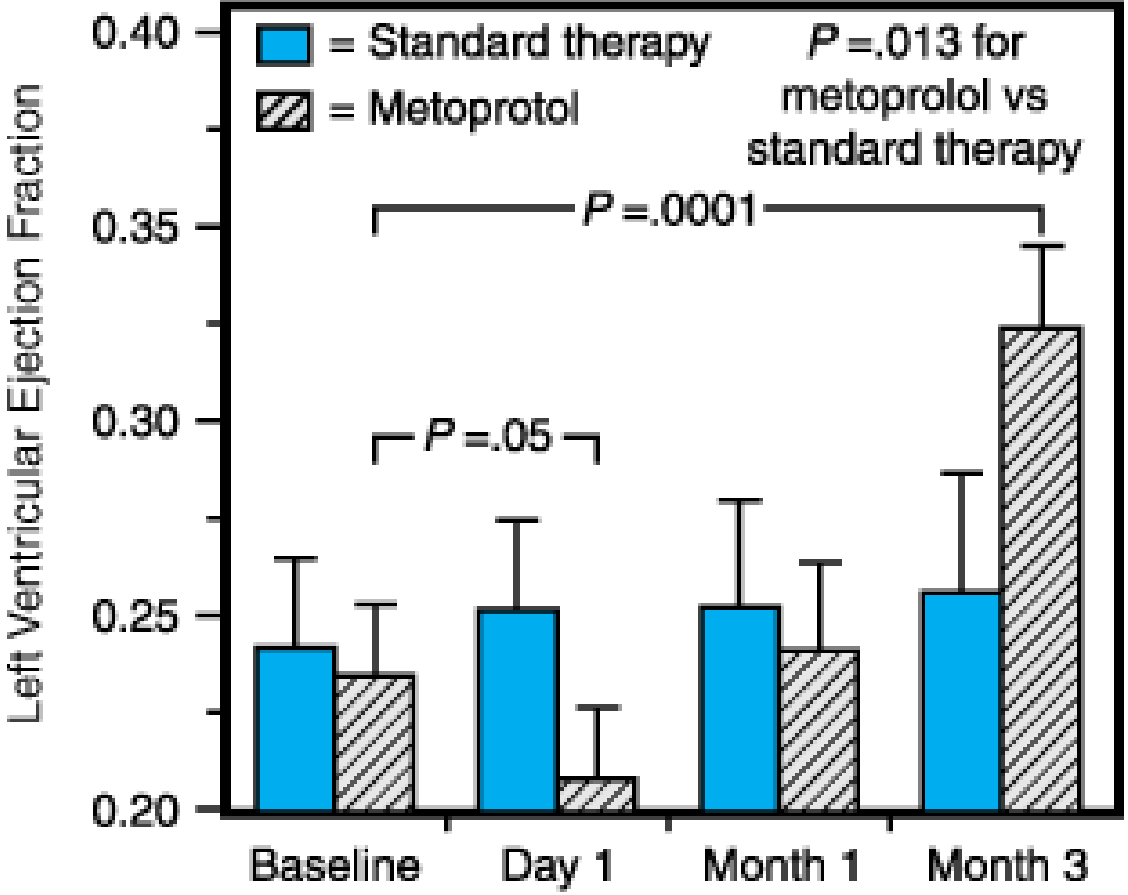


Time-dependent effects of metoprolol on left ventricular ejection fraction in patients with heart failure.

Še druga zdravila, ki se uporabljajo pri PS

- Inhibitorji angiotenzinske-konvertaze (ACE) (npr. kaptopril)
- Blokatorji angiotenzinskih receptorjev
- Antagonisti aldosterona
- Vazodilatatorji (npr. nitroprusid, hidralazin, minoksidil, nitroglicerin)
- β_1 agonisti
- Diuretiki (npr. tiazidi, furosemid)

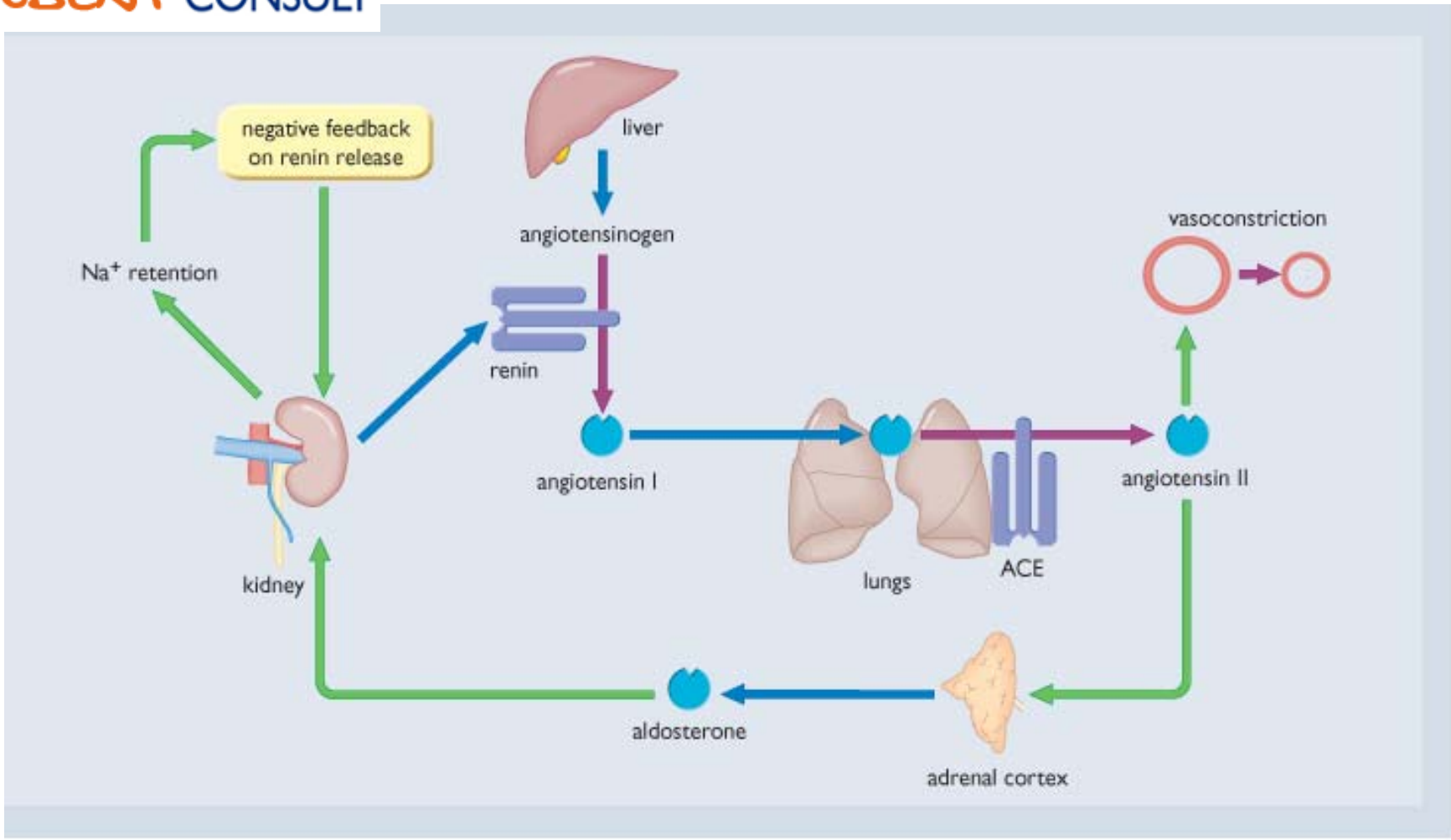


Figure 13.30 Renin-angiotensin-aldosterone system. Release of renin stimulates conversion of angiotensinogen (from the liver) to angiotensin I, which in turn is converted to angiotensin II under the influence of angiotensin-converting enzyme. Angiotensin II leads to vasoconstriction, release of aldosterone (adrenal cortex) and Na+ retention. The latter increases blood pressure but reduces renin release, so the system is a homeostatic process.

Inhibitorji ACE

- Najpomembnejša zdravila pri PS
- Različna prijemališča
- Večinoma predzdravila
- Malo stranskih učinkov (suh kašelj)
- Previdnost v nosečnosti (okvare ploda)

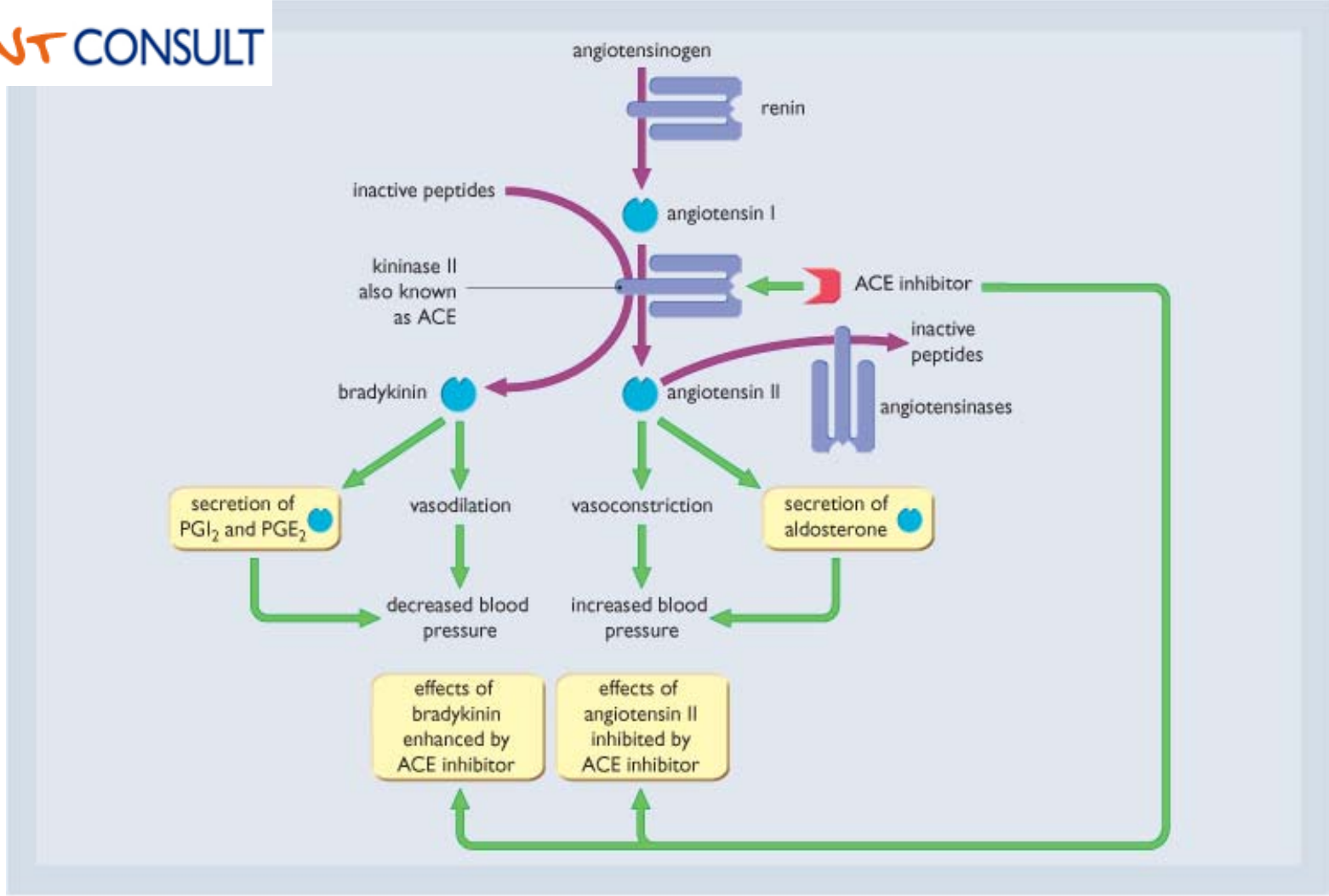


Figure 13.41 Effects of angiotensin-converting enzyme (ACE) inhibitors. ACE inhibitors reduce angiotensin II (vasoconstrictor) concentrations and elevate bradykinin (vasodilator) concentrations. The accumulation of bradykinin shown in the lower part of the figure results from the action of the ACE inhibitors on kininase II. Note, kininase II and ACE are actually the same enzyme (peptidyl-dipeptidase).

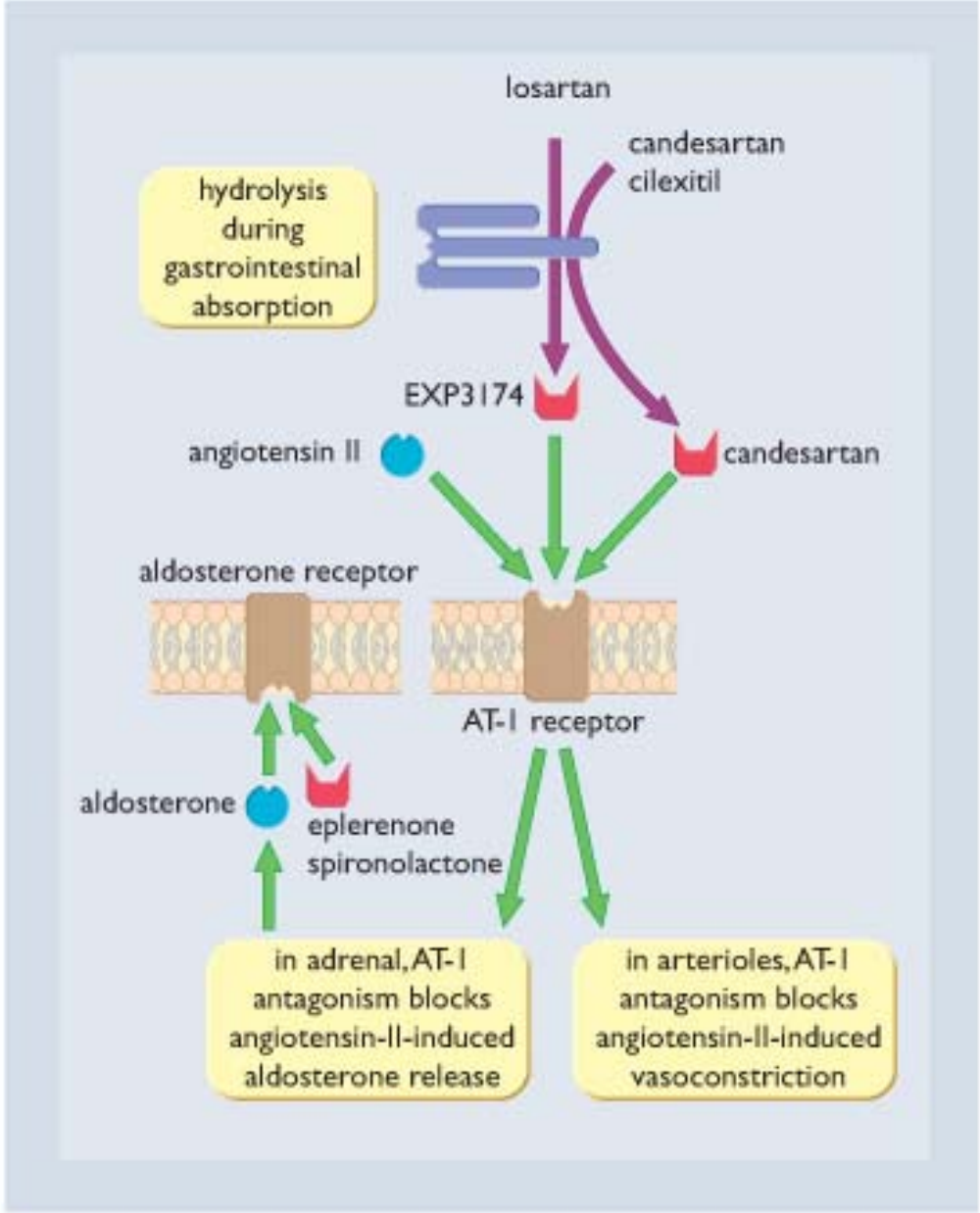
Table 33–2 Potential Roles of Aldosterone in the Pathophysiology of Heart Failure

MECHANISM	PATHOPHYSIOLOGICAL EFFECT
Increased Na^+ and water retention	Edema, elevated cardiac filling pressures
K^+ and Mg^{2+} loss	Arrhythmogenesis and risk of sudden cardiac death
Reduced myocardial norepinephrine uptake	Potentiation of norepinephrine effects: myocardial remodeling and arrhythmogenesis
Reduced baroreceptor sensitivity	Reduced parasympathetic activity and risk of sudden cardiac death
Myocardial fibrosis, fibroblast proliferation	Remodeling and ventricular dysfunction
Alterations in Na^+ channel expression	Increased excitability and contractility of cardiac myocytes

ACE inhibitors

Drug	Pro-drug ?	Main uses	Usual doses (mg/day) p.o	Elimination plasma half-life of active drug (h)	Elimination	Adverse effects
Captopril	No	Hypertension Congestive heart failure	6.25-300	1.7 (shorter than all other ACE inhibitors)	Renal	Hypotension, cough, and (rarely) agranulocytsis hepatic failure and lethal angiodema
Enalapril	Yes	Hypertension Congestive heart failure	2.5-40	11	Renal	
Lisinopril	No	Hypertension Congestive heart failure	10-40 2.5-10	12	Exclusively renal	
Cilazapril	Yes	Hypertension Congestive heart failure	1.25-20	30-50	Renal	
Ramipril	Yes	Hypertension Congestive heart failure	2.5-10 (1.25 in renal impairment)	85-190	Renal	
Quinapril	Yes	Hypertension Congestive heart failure	5-40	30-50	Renal	
Perindopril	Yes	Hypertension Heart failure	2-8	30-50	Renal	

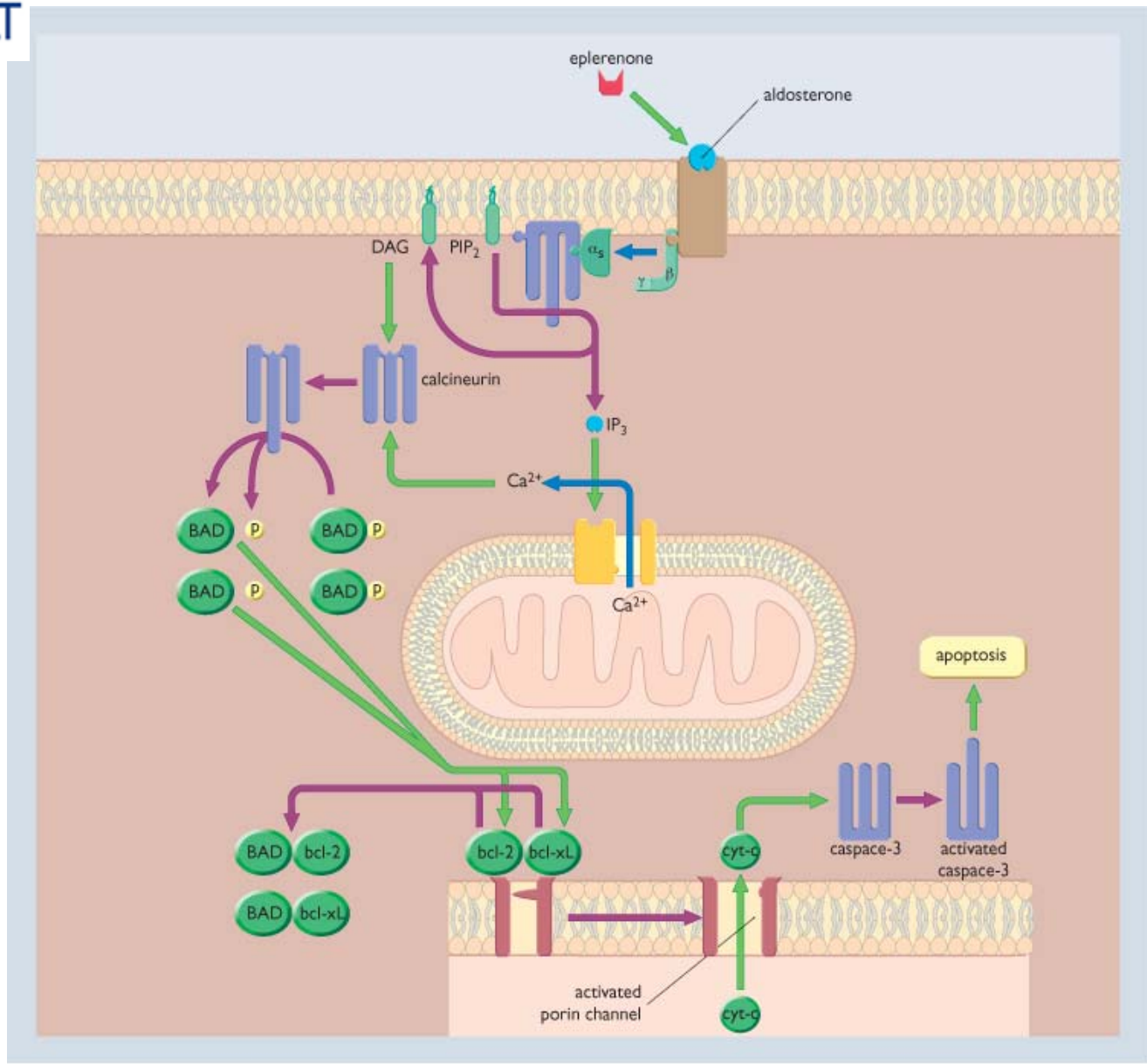
Figure 13.36 Losartan and candesartan are used to treat hypertension primarily as a consequence of angiotensin AT-1 receptor antagonist activity, by reducing blood levels of aldosterone and by dilating arterioles. Eplerenone treats hypertension by blocking aldosterone receptors.



Blokatorji aldosteronskih receptorjev

- Delovanje na membranske receptorje (hiter odgovor) na kardiomiocitih $\Rightarrow$ preprečenje z aldosteronom povzročene apoptoze
- Aktivacija teh receptorjev z aldosteronom povzroči:
  - Aktivacijo fosfolipaze C.
  - Hiter dvig intracelularne konc. Ca^{2+}.
  - Aktivacijo proteinske kinase C in kalcinevrina (od Ca^{2+}-odvisna fosfataza).
  - Defosforilacijo pro-apoptotičnega proteina BAD.
  - Mitohondrijsko depolarizacijo in sproščanje citohroma C.
  - Activacijo apoptotičnega encima kaspaze-3.
- Predstavnik eplerenon – selektivni inhibitor aldosteronskih receptorjev (SARA)

Figure 13.27 Postulated mechanism by which aldosterone causes apoptotic cell death and by which eplerenone inhibits this in the treatment of heart failure. Aldosterone receptor activation leads to activation of calcineurin, which dephosphorylates the protein BAD, which heterodimerizes with bcl-2 and bcl-xL. The heterodimers can no longer block the mitochondrial porin channel, allowing cytochrome c (cyt-c) to escape and activate the pro-apoptotic enzyme caspase-3. DAG, diacycloglycerol; PIP2 phosphotidylinositol; IP3 inositol-1,4,5-triphosphate.



Vazodilatatorji

- Različni mehanizmi delovanja:
  - Vpliv na gvanilatno ciklazo
  - Vpliv na K^+ kanale
  - Vpliv na i.c. koncentracijo Ca^{2+}
  - Vpliv na nastajanje PG (PGI)
- $\Downarrow$ diastoličnega pritiska $\Rightarrow$ izboljšanje fukcije srca
- Refleksna aktivacija simpatika (potreba po kombinaciji z drugimi zdravili)
- Hidralazin – uporaba skupaj z nitrati alternativa inhibitorjem ACE (sistemski lupus eritematodes)

Vasodilator drugs used to treat heart failure I

DRUG CLASS	EXAMPLES	MECHANISM	⇓ PRELOAD	⇓ AFTERLOAD
Organic nitrates	Nitroglycerin, isosorbide dinitrate	NO-mediated vasodilation	+++	+
Nitric oxide donors	Nitroprusside	NO-mediated vasodilation	+++	+++
Angiotensin-converting enzyme inhibitors	Captopril, enalapril, lisinopril	Inhibition of Ang II generation, decreased bradykinin degradation	++	++
Angiotensin receptor blockers	Losartan, candesartan	Blockade of AT1 receptors	++	++

Vasodilator drugs used to treat heart failure II

DRUG CLASS	EXAMPLES	MECHANISM	⇓ PRELOAD	⇓ AFTERLOAD
Phosphodiesterase inhibitors	Milrinone, inamrinone	Inhibition of cyclic AMP degradation	++	++
Direct-acting K+-channel agonist	Hydralazine	Unknown	+	+++
	Minoxidil	Hyperpolarization of vascular smooth muscle cells	+	+++
α_1 Adrenergic antagonists	Doxazosin, prazosin	Selective α_1 adrenergic receptor blockade	+++	++
Nonselective α-adrenergic antagonists	Phentolamine	Nonselective α-adrenergic receptor blockade	+++	+++

Vasodilator drugs used to treat heart failure III

DRUG CLASS	EXAMPLES	MECHANISM	⇓ PRELOAD	⇓ AFTERLOAD
Vasodilating β/α_1 adrenergic antagonists	Carvedilol, labetalol	Selective α_1 adrenergic receptor blockade	++	++
Ca^{2+} channel blockers	Amlodipine, nifedipine, felodipine	Inhibition of L-type Ca^{2+} channels	+	+++
β adrenergic agonists	Isoproterenol	Stimulation of vascular β_2 adrenergic receptors	+	++

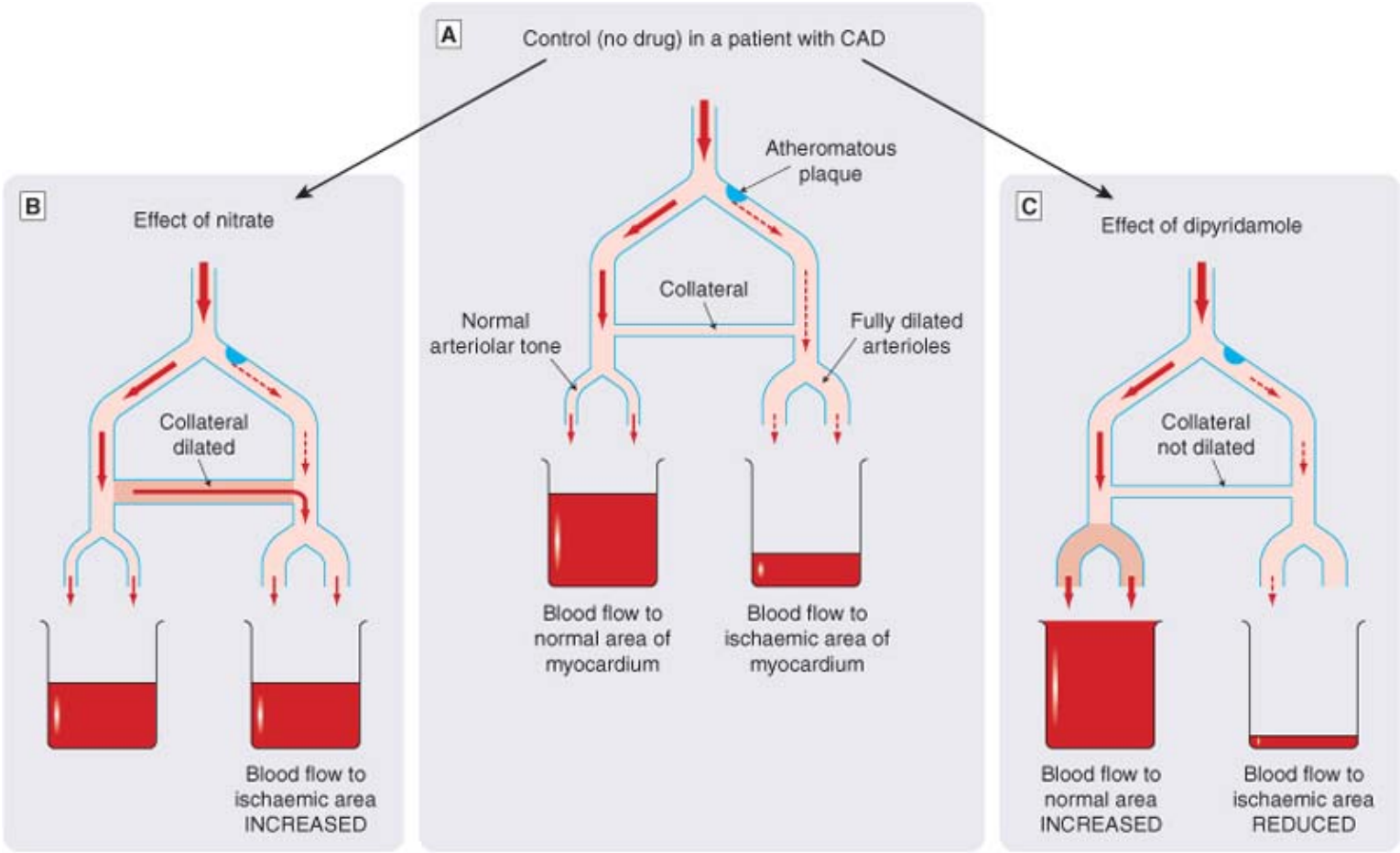


Figure 18-11 Comparison of the effects of organic nitrates and an arteriolar vasodilator (dipyridamole) on the coronary circulation. Control. Nitrates dilate the collateral vessel, thus allowing more blood through to the underperfused region (mostly by diversion from the adequately perfused area). Dipyridamole dilates arterioles, increasing flow through the normal area at the expense of the ischaemic area (in which the arterioles are anyway fully dilated). CAD, coronary artery disease.

Nesiritid

- Rekombinantni humani BNP
- i.v. uporaba pri bolnikih z akutnim dekompenziranim PS.
- Vezava na gvanilatno ciklazo v žilnih gladkih mišicah in v endotelnih celicah $\Rightarrow \Uparrow$ i.c. konc. cGMP $\Rightarrow$ relaksacija (podobno kot endogeni NO)

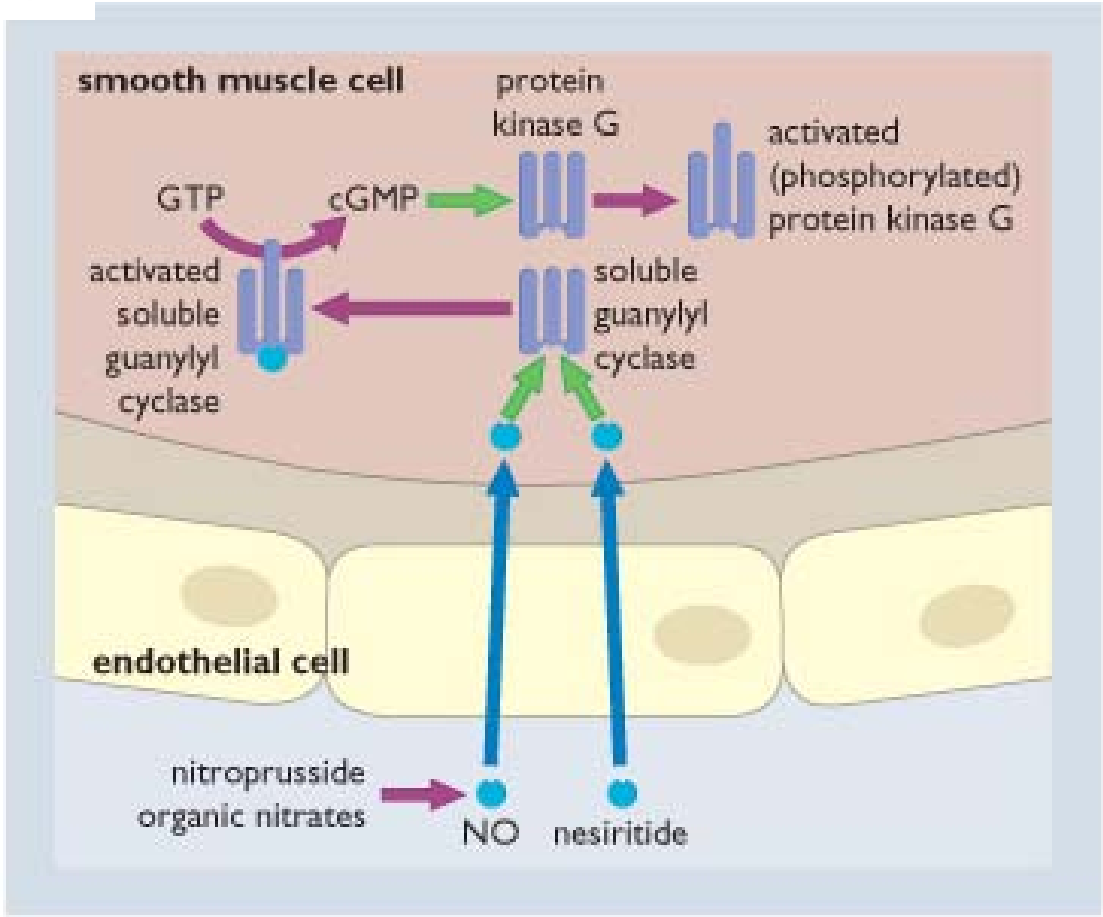


Figure 13.14 Molecular and cellular mechanisms of action of nitrate and nitrite vasodilators, nitric oxide (NO) and nesiritide. The primary molecular target, soluble guanylyl cyclase, is accessed by drug or NO diffusion between cells. The product, phosphorylated protein kinase, causes vascular smooth muscle relaxation by phosphorylating (and inactivating) myosin light chain kinase.

Levosimendan

- Novo, obetavno zdravilo
- Levosimendan $\Rightarrow \Uparrow$ občutljivost miokarda za kalcij
- Specifični učinku zdravila:
  1. Inhibicija fosfodiesteraze III
  2. Sensitiziranje miofilamentov troponina-C za kalcijeve ione;
  3. Stimulacija K_{ATP} kanalov v miokardu (glibenklamid inhibira ta učinek)
- Pozitiven inotropen in vazodilatatoren učinek
- Ni neugodnih učinkov povečane koncentracije Ca^{2+} (aritmije)

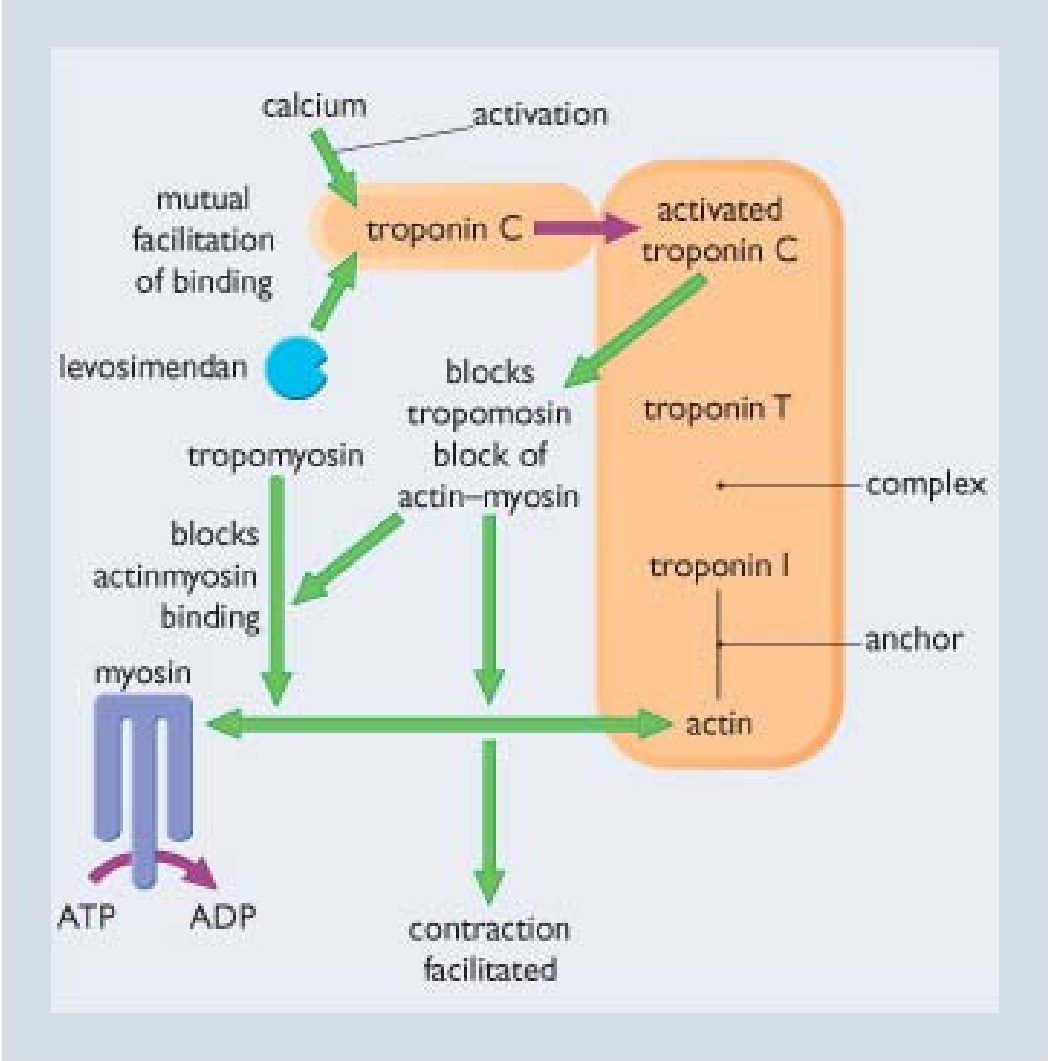


Figure 13.28 Proposed mechanism of action of levosimendan. Ca2+ and levosimendan bind to troponin C. This alters the conformation of troponin C such that its affinity for both Ca2+ and levosimendan is increased. This is the 'Ca2+ sensitizer' effect. Tropinin C is activated when Ca2+ binds to it. Activated troponin C prevents tropomyosin from blocking the binding of actin to myosin. This facilitates actin-myosin binding and generates the positive inotropic response.

Agonisti ß$_1$ adrenoceptorjev

- Dobutamin akutno izboljša parametre delovanja srca:
- ⇑ MV
- ⇓ MAP
- ⇓ PU
- ⇓ polnitev ventriklov
- Uporaba pri akutnem opešanju levega srca

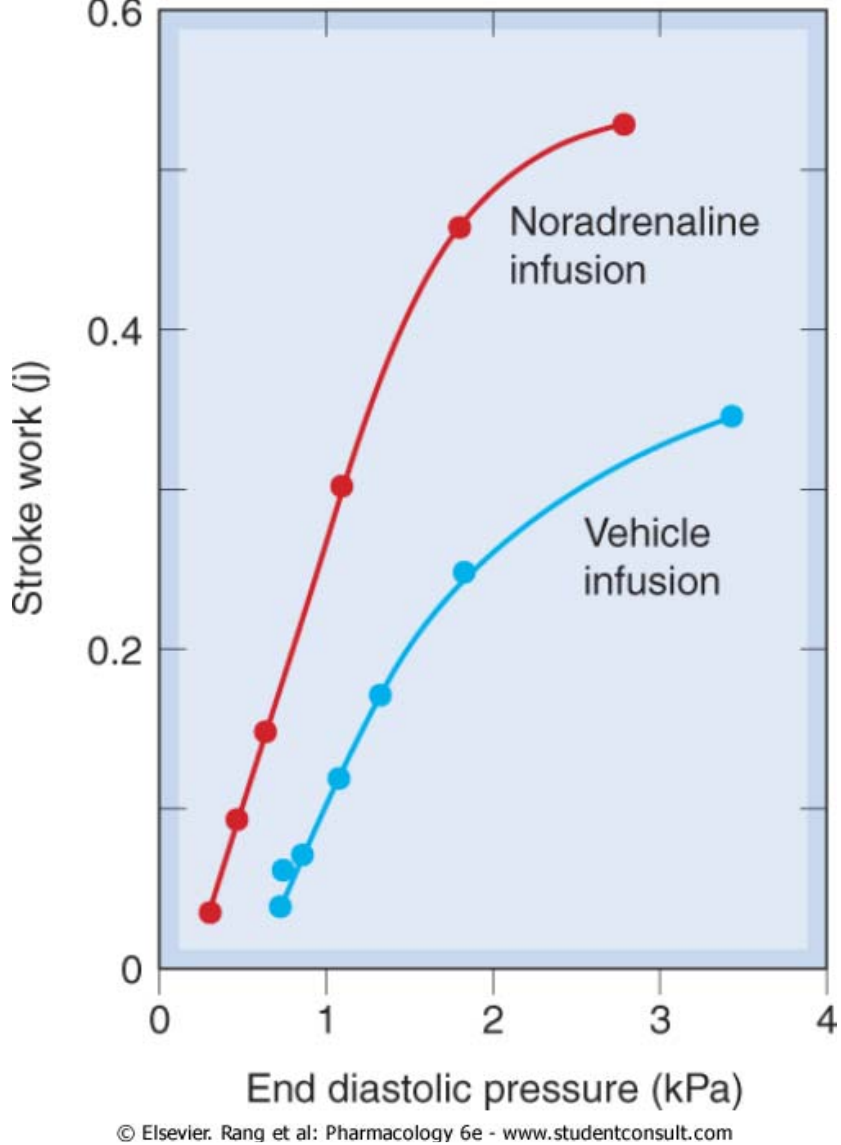
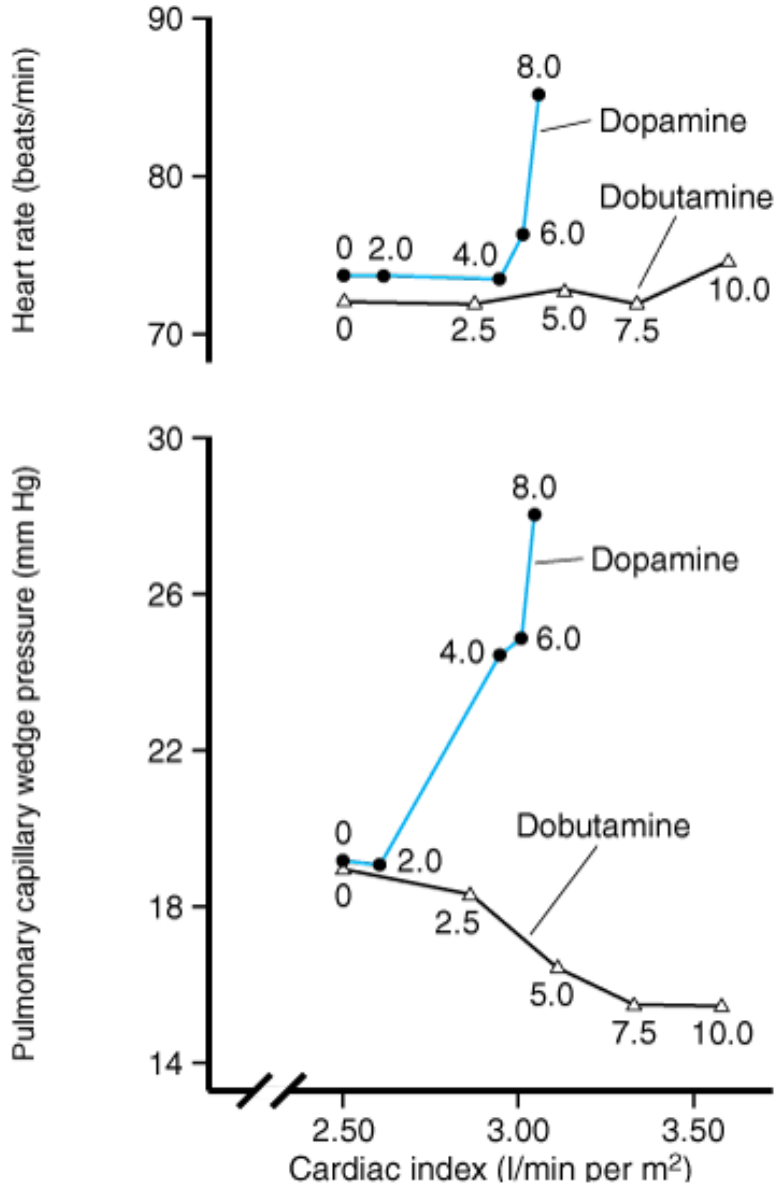


Figure 18-4 Ventricular function curves in the dog. Infusion of physiological saline increases blood volume and hence end-diastolic pressure. This increases stroke work ('extrinsic' control) by increasing the force of contraction of the heart. This relationship is called the Starling curve. Noradrenaline has a direct action on the heart ('intrinsic' control), increasing the slope of the Starling curve. (Redrawn from Sarnoff S J et al. 1960 Circ Res 8: 1108.)

Comparative hemodynamic effects of dopamine and dobutamine in patients with heart failure



Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

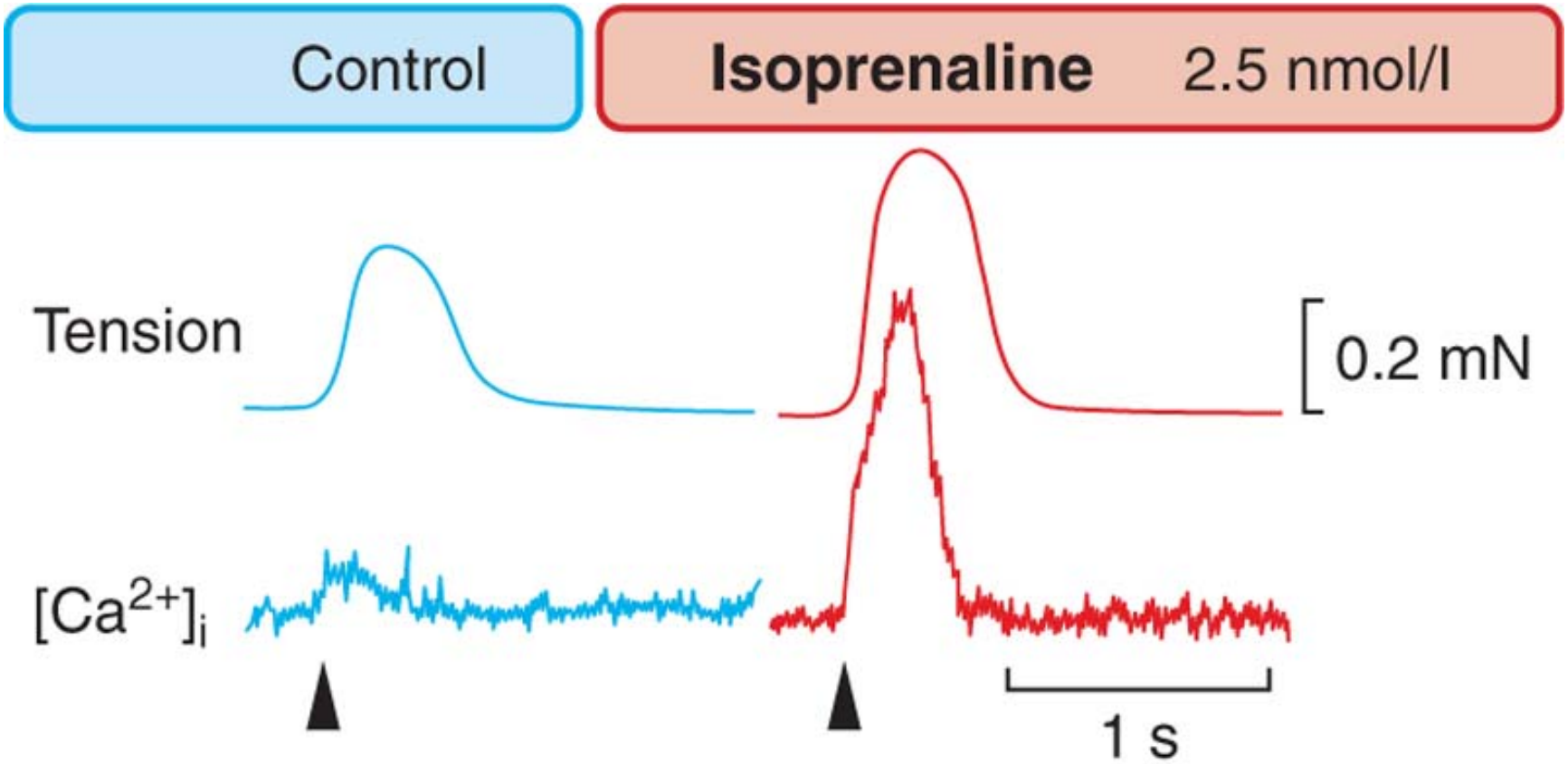
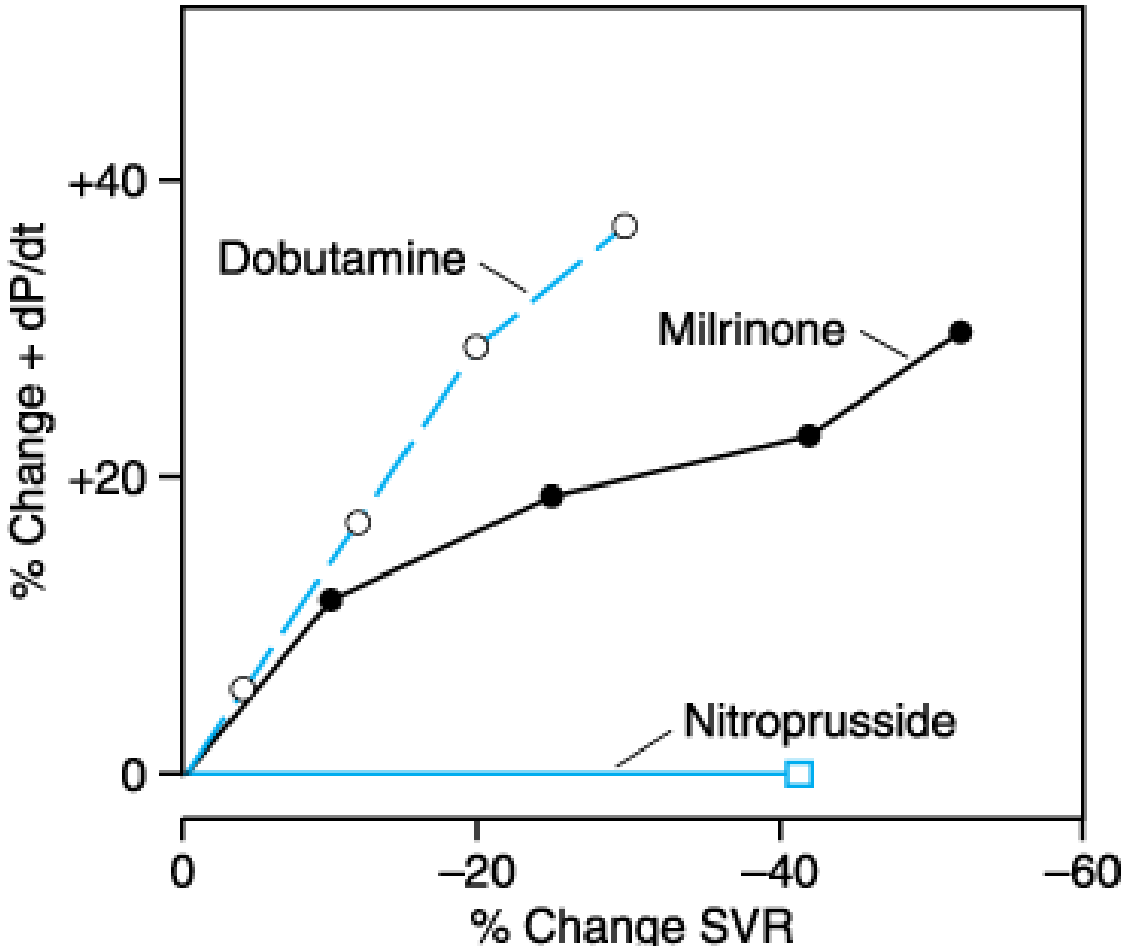


Figure 18-6 The calcium transient in frog cardiac muscle. A group of cells was injected with the phosphorescent Ca2+ indicator aequorin, which allows [Ca2+]i to be monitored optically. Isoprenaline causes a large increase in the tension and in the [Ca2+]i transient caused by an electrical stimulus (▴). (From Allen D G, Blinks J R 1978 Nature 273: 509.)

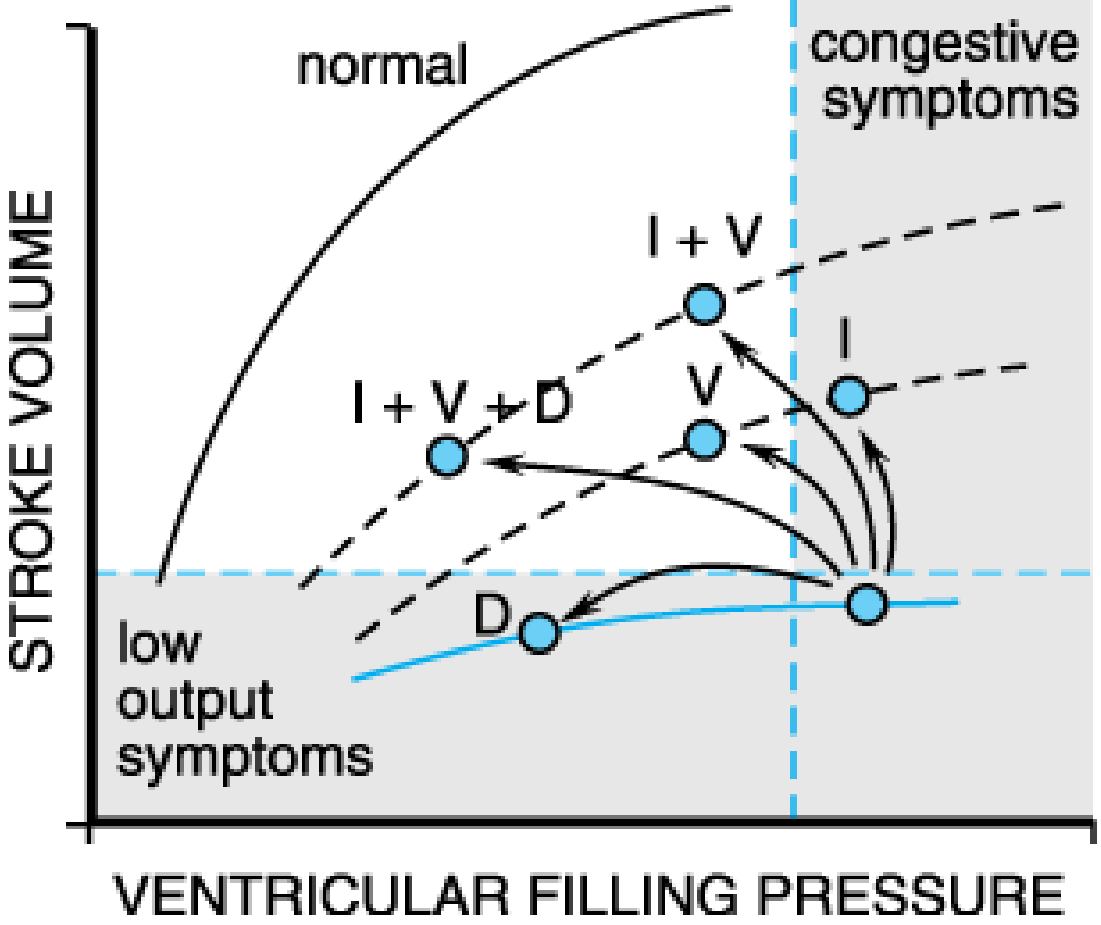
Adverse effects of drugs used in the treatment of congestive heart failure

- Cardiac glycosides have a narrow therapeutic index and may precipitate arrhythmias
- Short-term treatment with phosphodiesterase inhibitors can cause thrombocytopenia and arrhythmias
- ß1 agonists may precipitate tachyarrhythmias, and long-term use may worsen myocardial function
- Diuretics produce serious electrolyte imbalances such as hypokalemia, which may produce ventricular arrhythmias
- Angiotensin-converting enzyme (ACE) inhibitors produce few adverse effects, and generally only hypotension
- Nitrovasodilators, nesiritide and eplerenone have few adverse effects

Comparative effects of dobutamine, milrinone, and nitroprusside on left ventricular contractility and systemic vascular resistance



Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com



Hemodynamic responses to pharmacological interventions in heart failure.

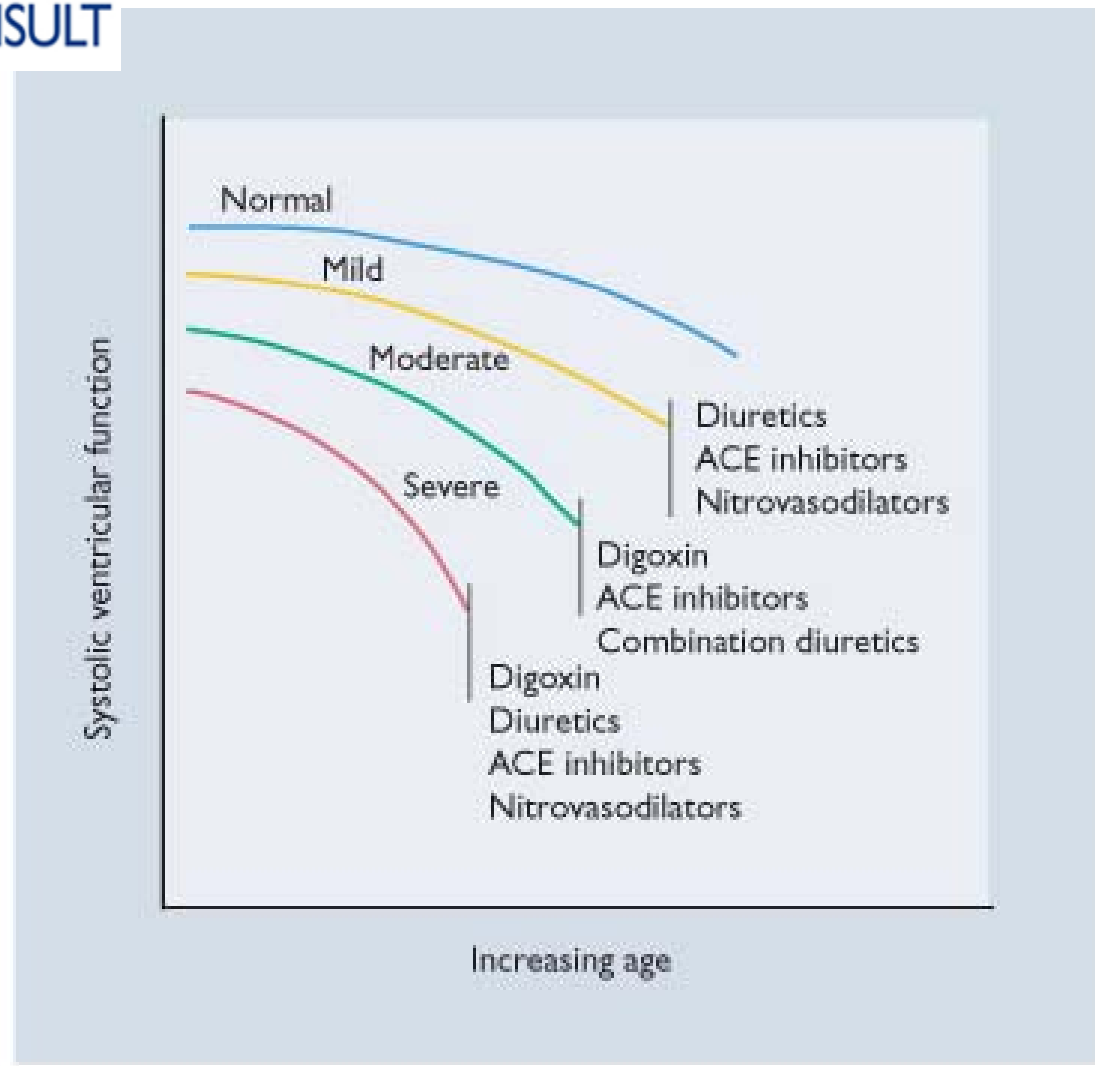
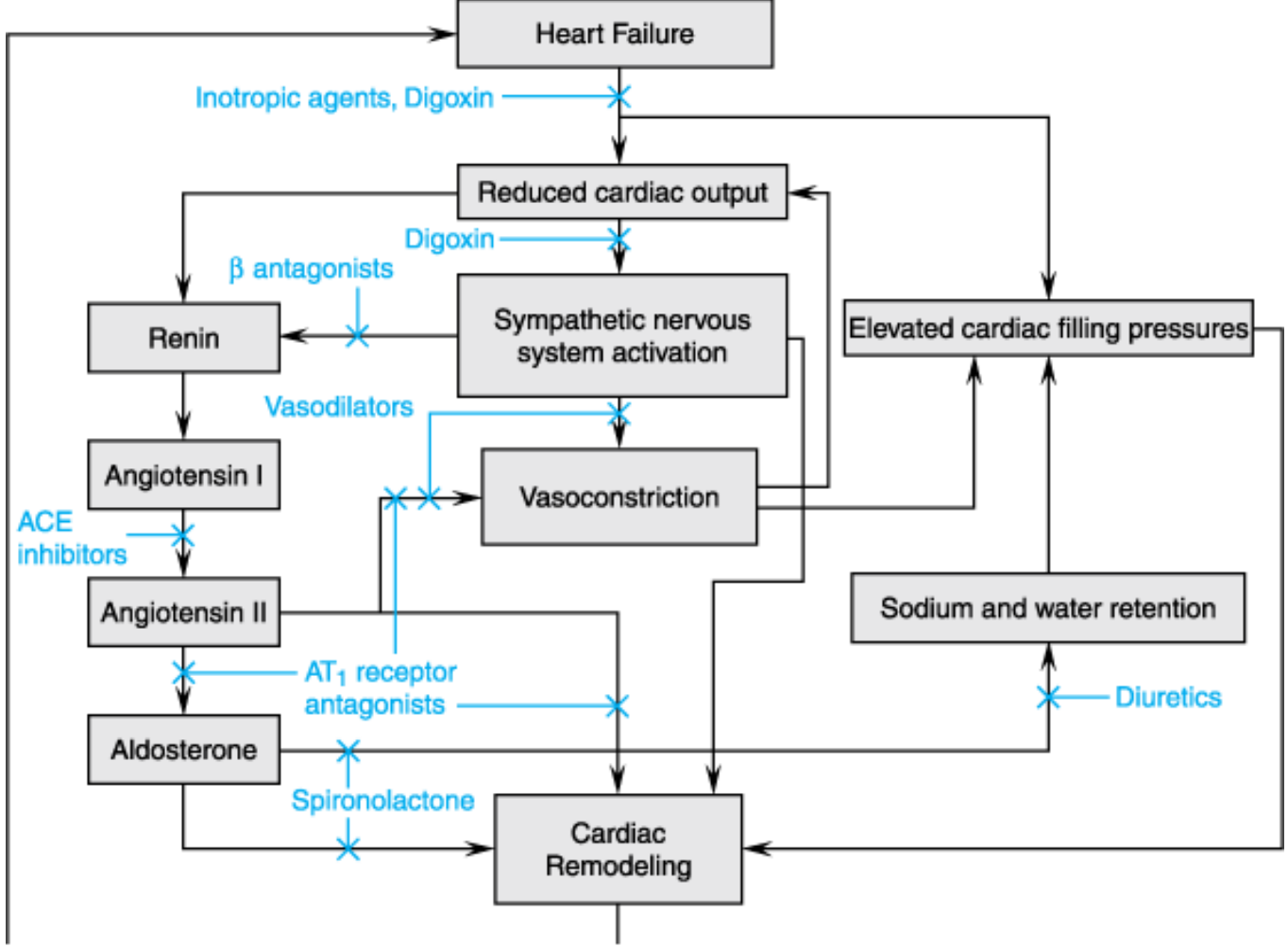


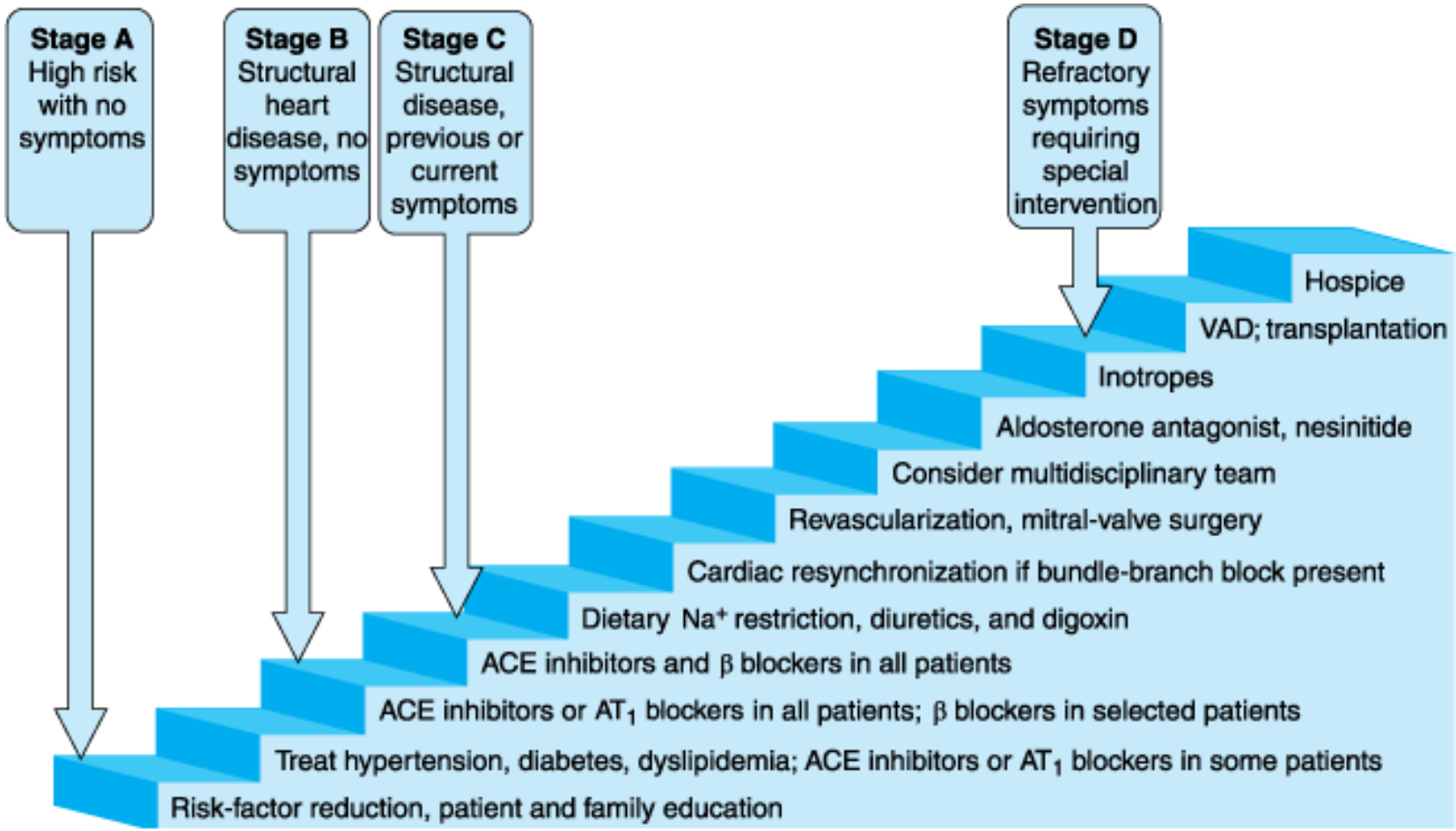
Figure 13.23 Drugs used in the treatment of the various stages of congestive heart failure. The slow decline in ventricular function with age is exacerbated by disease (ACE, angiotensin-converting enzyme).

Pathophysiological mechanisms of heart failure and major sites of drug action.



Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

Stages of heart failure



Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com