DEEPAK L. BHATT

Enhanced DIGITAL VERSION Included

OPIE'S CARDIOVASCULAR DRUGS

A COMPANION TO **BRAUNWALD'S**
HEART DISEASE

NINTH EDITION

ELSEVIER

Expert CONSULT | eBooks

Any screen. Any time. Anywhere.

Activate the eBook version of this title at no additional charge.

Expert Consult eBooks give you the power to browse and find content, view enhanced images, share notes and highlights—both online and offline.

Unlock your eBook today.

1. Visit **expertconsult.inkling.com/redeem**
2. Scratch off your code
3. Type code into "Enter Code" box
4. Click "Redeem"
5. Log in or Sign up
6. Go to "My Library"

It's that easy!

Scan this QR code to redeem your eBook through your mobile device:

Place Peel Off Sticker Here

ELSEVIER

For technical assistance:
email expertconsult.help@elsevier.com
call 1-800-401-9962 (inside the US)
call +1-314-447-8200 (outside the US)

OPIE'S CARDIOVASCULAR DRUGS

A COMPANION TO **BRAUNWALD'S HEART DISEASE**

OPIE'S CARDIOVASCULAR DRUGS

A COMPANION TO **BRAUNWALD'S HEART DISEASE**

NINTH EDITION

DEEPAK L. **BHATT**, MD, MPH
Executive Director of Interventional Cardiovascular Programs
Brigham and Women's Hospital
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

ELSEVIER

Elsevier
1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

OPIE'S CARDIOVASCULAR DRUGS: A COMPANION TO BRAUNWALD'S HEART DISEASE, NINTH EDITION

ISBN: 978-0-323673617

New illustrations by Dr Bernard Bulwer, Boston, MA.

Notice

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds or experiments described herein. Because of rapid advances in the medical sciences, in particular, independent verification of diagnoses and drug dosages should be made. To the fullest extent of the law, no responsibility is assumed by Elsevier, authors, editors or contributors for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

Previous editions copyrighted 2013, 2009, 2005, 2001, 1995, 1991, 1987, 1984.

Library of Congress Control Number: 2020944971

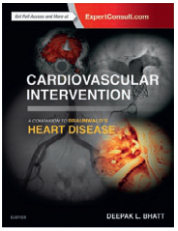
Publishing Director: Dolores Meloni
Content Strategist: Robin R. Carter
Content Development Specialist: Sara Watkins
Publishing Services Manager: Deepthi Unni
Project Manager: Beula Christopher
Design Direction: Ryan Cook

Printed in India

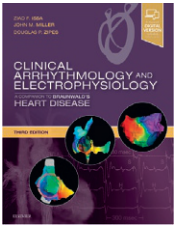
Last digit is the print number: 9 8 7 6 5 4 3 2 1

Contents

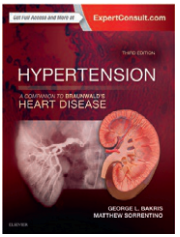
Braunwald's Heart Disease Family of Books



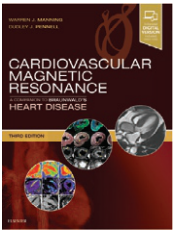
BHATT
Cardiovascular Intervention



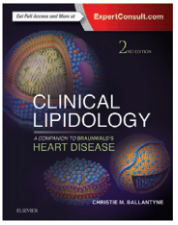
ISSA, MILLER, AND ZIPES
Clinical Arrhythmology and Electrophysiology



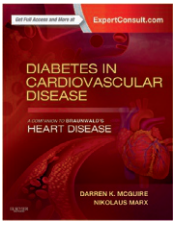
BAKRIS AND SORRENTINO
Hypertension



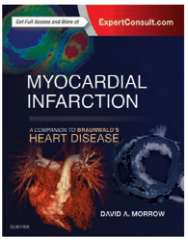
MANNING AND PENNELL
Cardiovascular Magnetic Reson



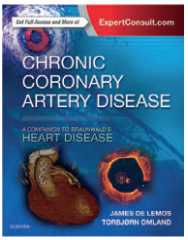
BALLANTYNE
Clinical Lipidology



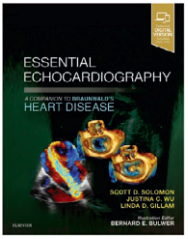
MCGUIRE AND MARX
Diabetes in Cardiovascular Disease



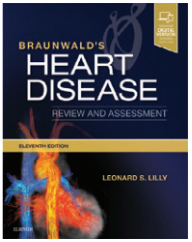
MORROW
Myocardial Infarction



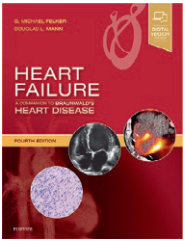
DE LEMOS AND OMLAND
Chronic Coronary Artery Disease



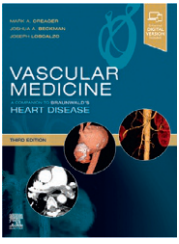
SOLOMON, WU, AND GILLAM
Essential Echocardiography



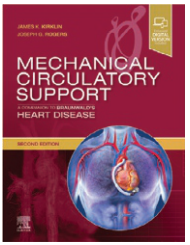
LILLY
Braunwald's Heart Disease Review and Assessment



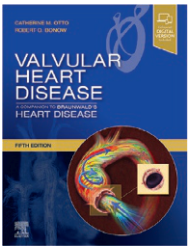
FELKER AND MANN
Heart Failure



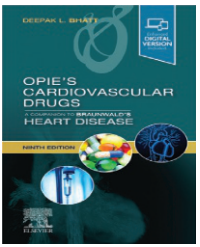
CREAGER
Vascular Medicine



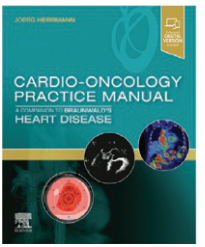
KIRKLIN AND ROGERS
Mechanical Circulatory Support



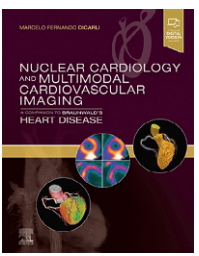
OTTO AND BONOW
Valvular Heart Disease



BHATT
Opie's Cardiovascular Drugs



HERRMANN
Cardio-Oncology Practice Manual



DICARLI
Nuclear Cardiology and Multimodal Cardiovascular Imaging

1

Drugs for Ischemic Heart Disease

WILLIAM E. BODEN

Introduction

The contemporary management of patients with ischemic heart disease demands a sound understanding of the pathophysiologic precipitants of both angina pectoris and myocardial ischemia from which the principles of pharmacotherapy can be applied and tailored to the specific causes underlying these perturbations of myocardial oxygen supply and demand. This chapter details several broad classes of drug therapies directed at both symptom relief and ameliorating the consequences of reduced coronary blood flow and myocardial supply-demand imbalances for which specific treatments are targeted, including the traditional agents (β-blockers, nitrates, calcium channel blockers) as well as newer, non-traditional antianginal agents such as ranolazine as well as agents (ivabradine, nicorandil, and trimetazidine) that are not available for use in the US, but are in use internationally. These drugs are discussed comprehensively for both acute and chronic coronary syndromes, with particular attention to drug selection, dosing considerations, drug interactions, and common side effects that may influence treatment considerations.

β-Blockers

Introduction

β-adrenergic receptor antagonist agents remain a therapeutic mainstay in the management of ischemic heart disease with the exception of variant angina or myocardial ischemia due to coronary vasospasm. β-blockade is still widely regarded as standard therapy in cardiology professional society guidelines for exertional angina, unstable angina, and for variable threshold angina (or mixed

angina), particularly where increases in heart rate and/or blood pressure (BP) (including the rate-pressure product rise that occurs during exercise or stress) results in an increase in myocardial oxygen consumption. β-blockers have an important role in reducing mortality when used as secondary prevention after acute myocardial infarction (MI), though outcomes data are lacking to support a beneficial role of β-blockers in ischemic heart disease patients without prior MI. And while β-blockers exert a markedly beneficial effect on outcomes in patients with heart failure, particularly in those with reduced EF, and have an important role as antiarrhythmic agents and to control the ventricular rate in chronic atrial fibrillation, as well as to adjunctively treat hypertension, the therapeutic applications of β-blockers in these other disease states will not be discussed in this chapter. Established and approved indications for β-blockers in the United States are shown in Table 1.1.

The extraordinary complexity of the β-adrenergic signaling system probably evolved millions of years ago when rapid activation was required for hunting and resisting animals, with the need for rapid inactivation during the period of rest and recovery. These mechanisms are now analyzed.[1]

Table 1.1

Indications for β-blockade and US FDA-approved drugs

Indications for β-blockade	FDA-approved drugs
1. Ischemic heart disease	
Angina pectoris	Atenolol, metoprolol, nadolol, propranolol
Silent ischemia	None
AMI, early phase	Atenolol, metoprolol
AMI, follow-up	Propranolol, timolol, metoprolol, carvedilol
Perioperative ischemia	Bisoprolol[a], atenolol[a]
2. Hypertension	
Hypertension, systemic	Acebutolol, atenolol, bisoprolol, labetalol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol
Hypertension, severe, urgent	Labetalol
Hypertension with LVH	Prefer ARB
Hypertension, isolated systolic	No outcome studies, prefer diuretic, CCB
Pheochromocytoma (already receiving alpha-blockade)	Propranolol
Hypertension, severe perioperative	Esmolol

Table 1.1

Indications for β-blockade and US FDA-approved drugs (Continued)

Indications for β-blockade	FDA-approved drugs
3. Arrhythmias	
Excess urgent sinus tachycardia	Esmolol
Tachycardias (sinus, SVT, and VT)	Propranolol
Supraventricular, perioperative	Esmolol
Recurrences of Afib, Afl	Sotalol
Control of ventricular rate in Afib, Afl	Propranolol
Digitalis-induced tachyarrhythmias	Propranolol
Anesthetic arrhythmias	Propranolol
PVC control	Acebutolol, propranolol
Serious ventricular tachycardia	Sotalol
4. Congestive heart failure	Carvedilol, metoprolol, bisoprolol[a]
5. Cardiomyopathy	
Hypertrophic obstructive cardiomyopathy	Propranolol
6. Other cardiovascular indications	
POTS	Propranolol low dose[a]
Aortic dissection, Marfan syndrome, mitral valve prolapse, congenital QT prolongation, tetralogy of Fallot, fetal tachycardia	All?[a] Only some tested[a]
7. Central indications	
Anxiety	Propranolol [a]
Essential tremor	Propranolol
Migraine prophylaxis	Propranolol, nadolol, timolol
Alcohol withdrawal	Propranolol,[a] atenolol[a]
8. Endocrine	
Thyrotoxicosis (arrhythmias)	Propranolol
9. Gastrointestinal	
Esophageal varices? (data not good)	Propranolol?[a] Timolol negative study[a]
10. Glaucoma (local use)	Timolol, betoxalol, carteolol, levobunolol, metipranolol

[a]Well tested but not FDA approved.
Afib, Atrial fibrillation; *Afl,* atrial flutter; *AMI,* acute myocardial infarction; *ARB,* angiotensin receptor blocker; *CCB,* calcium channel blocker; *FDA,* Food and Drug Administration; *LVH,* left ventricular hypertrophy; *POTS,* postural tachycardia syndrome; *PVC,* premature ventricular contraction; *SVT,* supraventricular tachycardia; *VT,* ventricular tachycardia.

Mechanism of Action

The β_1-adrenoceptor and signal transduction. Situated on the cardiac sarcolemma, the β_1-receptor is part of the adenylyl (= adenyl) cyclase system (Fig. 1.1) and is one of the group of G protein–coupled receptors. The G protein system links the receptor to adenylyl cyclase (AC) when the G protein is in the stimulatory configuration (G_s, also called Gαs). The link is interrupted by the inhibitory form (G_i or Gαi), the formation of which results from muscarinic stimulation following vagal activation. When activated, AC produces cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). The intracellular second messenger of β_1-stimulation is cAMP; among its actions is the "opening" of calcium channels to increase the rate and force of myocardial contraction (the positive inotropic effect) and increased reuptake of cytosolic calcium into the sarcoplasmic reticulum (SR; relaxing or lusitropic effect, see Fig. 1.1). In the sinus node the pacemaker current is increased (positive chronotropic effect), and the rate of conduction is accelerated (positive dromotropic effect). The effect of a given β-blocking agent depends on the way it is absorbed, the binding to plasma proteins, the generation of metabolites, and the extent to which it inhibits the β-receptor (lock-and-key fit).

β_2-receptors. The β-receptors classically are divided into the β_1-receptors found in heart muscle and the β_2-receptors of bronchial and vascular smooth muscle. If the β-blocking drug selectively interacts better with the β_1- than the β_2-receptors, then such a *β_1-selective blocker* is less likely to interact with the β_2-receptors in the bronchial tree, thereby giving a degree of protection from the tendency of nonselective β-blockers to cause pulmonary complications.

β_3-receptors. Endothelial β_3-receptors mediate the vasodilation induced by nitric oxide in response to the vasodilating β-blocker nebivolol (see Fig. 1.2).[2,3]

Secondary effects of β-receptor blockade. During physiologic β-adrenergic stimulation, the increased contractile activity resulting from the greater and faster rise of cytosolic calcium (Fig. 1.3) is coupled to increased breakdown of ATP by the myosin adenosine triphosphatase (ATPase). The increased rate of relaxation is linked to increased activity of the sarcoplasmic/endoplasmic reticulum calcium uptake pump. Thus, the uptake of calcium is enhanced with a more rapid rate of fall of cytosolic calcium, thereby accelerating relaxation. Increased cAMP also increases the phosphorylation of troponin-I, so that the interaction between the myosin heads and actin ends more rapidly. Therefore, the β-blocked heart not only beats more slowly by inhibition of the depolarizing currents

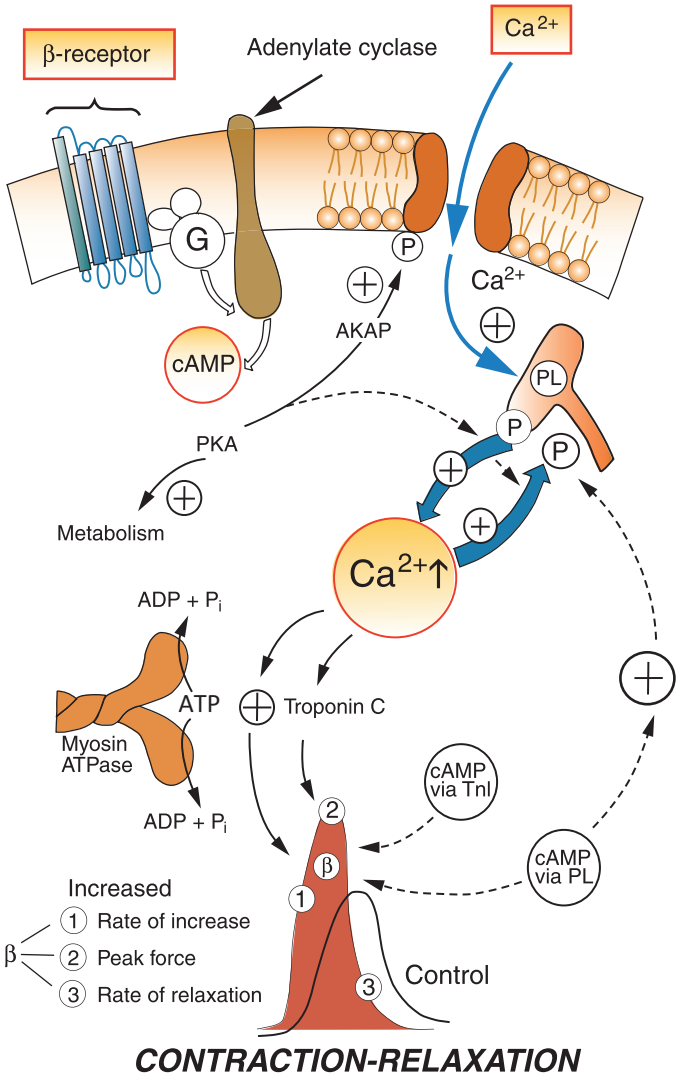


Fig. 1.1 See legend on opposite page

in the sinoatrial (SA) node but has a decreased force of contraction and decreased rate of relaxation. Metabolically, β-blockade switches the heart from using oxygen-wasting fatty acids toward oxygen-conserving glucose.[4] All these *oxygen-conserving properties* are of special importance in the therapy of ischemic heart disease. Inhibition of lipolysis in adipose tissue explains why gain of body mass may be a side effect of chronic β-blocker therapy.

Cardiovascular Effects of β-Blockade

β-blockers were originally designed by the Nobel prize winner Sir James Black to counteract the adverse cardiac effects of adrenergic stimulation. The latter, he reasoned, increased myocardial oxygen demand and worsened angina. His work led to the design of the prototype β-blocker, *propranolol*. By blocking the cardiac β-receptors, he showed that these agents could induce the now well-known inhibitory effects on the sinus node, atrioventricular (AV) node, and on myocardial contraction. These are the negative chronotropic, dromotropic, and inotropic effects, respectively (Fig. 1.4). Of these, it is especially bradycardia and the negative inotropic effects that are relevant to the therapeutic effect in angina pectoris and in patients with ischemic heart disease because these changes decrease the myocardial oxygen demand (Fig. 1.5). The inhibitory effect on the AV node is of special relevance in the therapy of supraventricular tachycardias (SVTs; see Chapter 9), or when β-blockade is used to control the ventricular response rate in atrial fibrillation.

Fig. 1.1, Cont'd β-adrenergic signal systems involved in positive inotropic and lusitropic (enhanced relaxation) effects. These can be explained in terms of changes in the cardiac calcium cycle. When the β-adrenergic agonist interacts with the β-receptor, a series of G protein-mediated changes lead to activation of adenylate cyclase and formation of the adrenergic second messenger, cyclic adenosine monophosphate *(cAMP)*. The latter acts via protein kinase A *(PKA)* to stimulate metabolism and to phosphorylate *(P)* the calcium channel protein, thus increasing the opening probability of this channel. More Ca^{2+} ions enter through the sarcolemmal channel, to release more Ca^{2+} ions from the sarcoplasmic reticulum (SR). Thus the cytosolic Ca^{2+} ions also increase the rate of breakdown of adenosine triphosphate (ATP) to adenosine diphosphate *(ADP)* and inorganic phosphate *(P_i)*. Enhanced myosin adenosine triphosphatase *(ATPase)* activity explains the increased rate of contraction, with increased activation of troponin-C explaining increased peak force development. An increased rate of relaxation (lusitropic effect) follows from phosphorylation of the protein phospholamban *(PL)*, situated on the membrane of the SR, that controls the rate of calcium uptake into the SR. *AKAP*, A-kinase-anchoring protein. (Figure © L. H. Opie, 2012.)

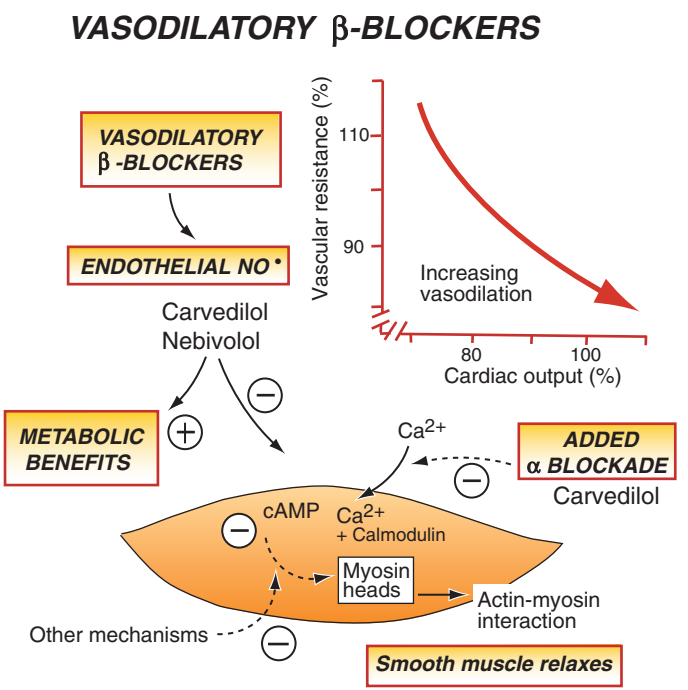


Fig. 1.2 **Vasodilatory mechanisms and effects.** Vasodilatory β-blockers tend to decrease the cardiac output less as the systemic vascular resistance falls. Vasodilatory mechanisms include α-blockade (carvedilol), formation of nitric oxide (nebivolol and carvedilol), and intrinsic sympathomimetic activity (ISA). ISA, as in pindolol, has a specific effect in increasing sympathetic tone when it is low, as at night, and increasing nocturnal heart rate, which might be disadvantageous in nocturnal angina or unstable angina. *cAMP,* Cyclic adenosine monophosphate; *NO,* nitric oxide. (Figure © L. H. Opie, 2012.)

Effects on coronary flow and myocardial perfusion. Enhanced β-adrenergic stimulation, as in exercise, leads to β-mediated coronary vasodilation. The signaling system in vascular smooth muscle again involves the formation of cAMP, but whereas the latter agent increases cytosolic calcium in the heart, it paradoxically decreases calcium levels in vascular muscle cells (see Fig. 1.6). Thus, during exercise, the heart pumps faster and more forcefully while coronary flow is augmented to meet the increased demand imposed by the increment in external workload. Conversely, while β-blockade

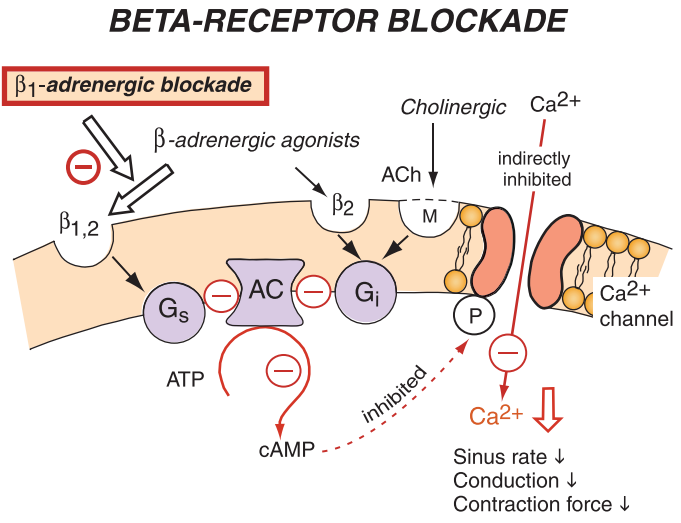


Fig. 1.3 The β-adrenergic receptor is coupled to adenyl (= adenylyl) cyclase *(AC)* via the activated stimulatory G-protein, G_s. Consequent formation of the second messenger, cyclic adenosine monophosphate *(cAMP)* activates protein kinase A (PKA) to phosphorylate *(P)* the calcium channel to increase calcium ion *(Ca^{2+})* entry. Activity of AC can be decreased by the inhibitory subunits of the acetylcholine *(ACh)*–associated inhibitory G-protein, G_i. cAMP is broken down by phosphodiesterase (PDE) so that PDE-inhibitor drugs have a sympathomimetic effect. The PDE is type 3 in contrast to the better-known PDE type 5 that is inhibited by sildenafil (see Fig. 2.6). A current hypothesis is that the β_2–receptor stimulation additionally signals via the inhibitory G-protein, G_i, thereby modulating the harm of excess adrenergic activity. (Figure © L. H. Opie, 2012.)

should have a coronary vasoconstrictive effect with a rise in coronary vascular resistance, the longer diastolic filling time resulting from a decreased heart rate during exercise leads to more nutritive coronary blood flow and better diastolic myocardial perfusion.

Pharmacokinetic Properties of β-Blockers

Plasma half-lives. Esmolol, given intravenously, has the shortest of all half-lives at only 9 minutes. Esmolol may therefore be preferable in unstable angina and threatened infarction when hemodynamic changes may call for withdrawal of β-blockade.

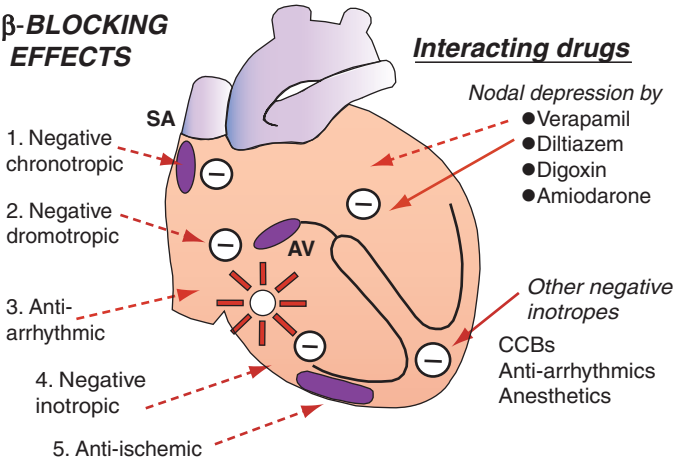


Fig. 1.4 Cardiac effects of β-adrenergic blocking drugs at the levels of the sinoatrial *(SA)* node, atrioventricular *(AV)* node, conduction system, and myocardium. Major pharmacodynamic drug interactions are shown on the right. (Figure © L. H. Opie, 2012.)

The half-life of propranolol (Table 1.2) is only 3 hours, but continued administration saturates the hepatic process that removes propranolol from the circulation; the active metabolite 4-hydroxypropranolol is formed, and the effective half-life then becomes longer. The biological half-life of propranolol and metoprolol (and all other β-blockers) exceeds the plasma half-life considerably, so that twice-daily dosages of standard propranolol are effective even in angina pectoris. Clearly, the higher the dose of any β-blocker, the longer the biologic effects. Longer-acting compounds such as nadolol, sotalol, atenolol, and slow-release propranolol (Inderal-LA) or extended-release metoprolol (Toprol-XL) should be better for hypertension and effort angina.

Protein binding. Propranolol is highly bound, as are pindolol, labetalol, and bisoprolol. Hypoproteinemia calls for lower doses of such compounds.

First-pass hepatic metabolism. First-pass liver metabolism is found especially with the highly lipid-soluble compounds, such as propranolol, labetalol, and oxprenolol. Major hepatic clearance is also found with acebutolol, nebivolol, metoprolol, and timolol. First-pass metabolism varies greatly among patients and alters the

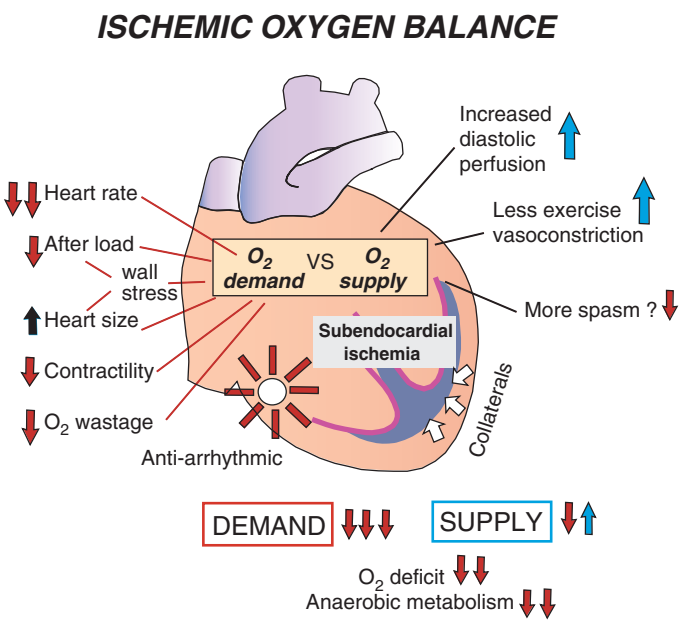


Fig. 1.5 Effects of β-blockade on ischemic heart. β-blockade has a beneficial effect on the ischemic myocardium, unless there is vasospastic angina when spasm may be promoted in some patients. Note unexpected proposal that β-blockade diminishes exercise-induced vasoconstriction. (Figure © L. H. Opie, 2012.)

dose required. In liver disease or low-output states the dose should be decreased. First-pass metabolism produces active metabolites with, in the case of propranolol, properties different from those of the parent compound. Metabolism of metoprolol occurs predominantly via cytochrome (CY) P450 2D6–mediated hydroxylation and is subject to marked genetic variability.[5] Acebutolol produces large amounts of diacetolol, and is also cardioselective with intrinsic sympathomimetic activity (ISA), but with a longer half-life and chiefly excreted by the kidneys (Fig. 1.7). Lipid-insoluble hydrophilic compounds (atenolol, sotalol, nadolol) are excreted only by the kidneys (see Fig. 1.7) and have low brain penetration. In patients with renal or liver disease, the simpler pharmacokinetic patterns of lipid-insoluble agents make dosage easier. As a group, these agents have low protein binding (see Table 1.2).

Pharmacokinetic interactions. Those drugs metabolized by the liver and hence prone to hepatic interactions are metoprolol,

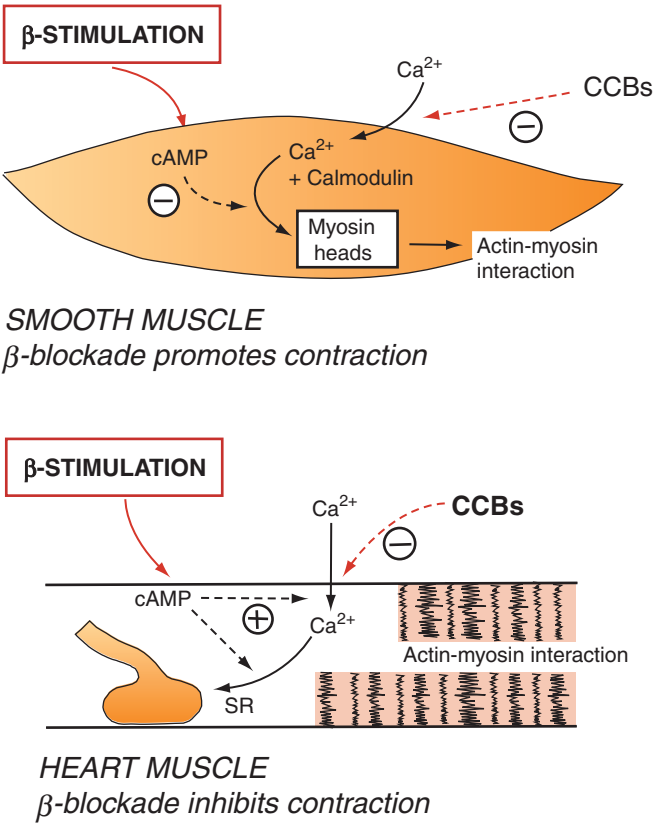


Fig. 1.6 Proposed comparative effects of β-blockade and calcium channel blockers *(CCBs)* on smooth muscle and myocardium. The opposing effects on vascular smooth muscle are of critical therapeutic importance. *cAMP,* Cyclic adenosine monophosphate; *SR,* sarcoplasmic reticulum. (Figure © L.H. Opie, 2012.)

carvedilol, labetalol, and propranolol, of which metoprolol and carvedilol are more frequently used. Both are metabolized by the hepatic CYP2D6 system that is inhibited by paroxetine, a widely used antidepressant that is a selective serotonin reuptake inhibitor. To avoid such hepatic interactions, it is simpler to use those β-blockers not metabolized by the liver (see Fig. 1.7). β-blockers, in turn, depress hepatic blood flow so that the blood levels of lidocaine increase with greater risk of lidocaine toxicity.