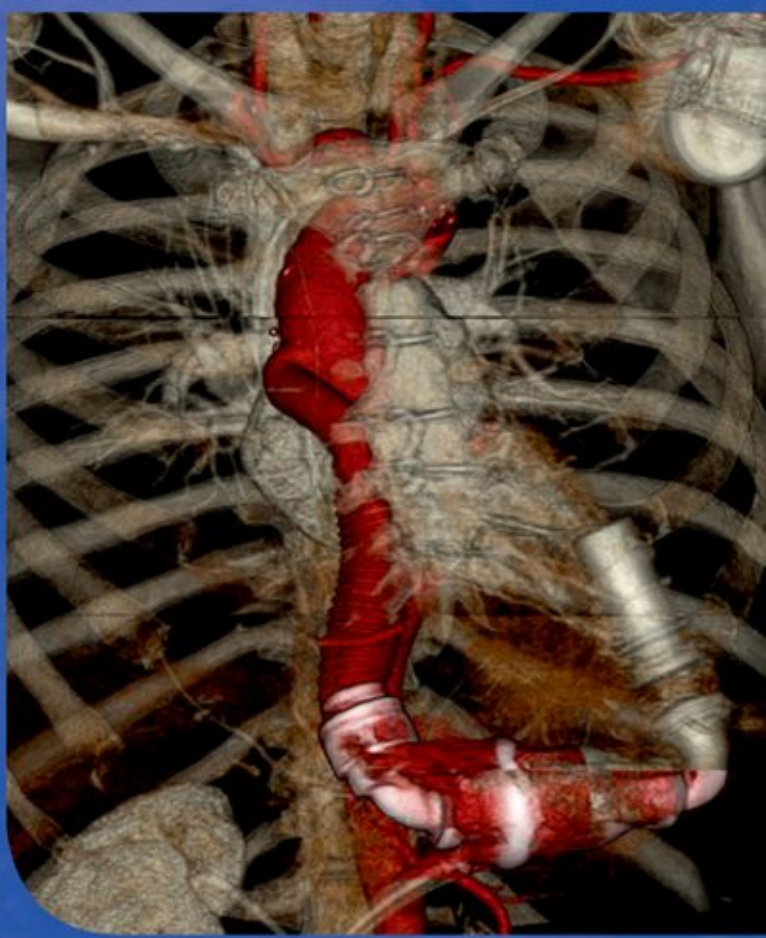
OXFORD TEXTBOOKS IN CARDIOLOGY

Oxford Textbook of Advanced Heart Failure and Cardiac Transplantation

Edited by
Michael J. Domanski
Mandeep R. Mehra
Marc A. Pfeffer



With Foreword by
Eugene Braunwald

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Foreword

During the last half century there have been extraordinary advances in the diagnosis and management of many forms of heart disease. A variety of drugs, devices, surgical and catheter-based interventions have resulted in dramatic reductions of morbidity and mortality of many cardiovascular disorders. For example, in the early 1960s, the one year mortality in patients with acute myocardial infarction who reached the hospital was about 50% and has been reduced to 10% since then. Surgical and catheter-based interventions have prolonged the lives of most patients with valvular and congenital heart disease. Hypertension can now be controlled with pharmacotherapy in the majority of patients. Patients at high risk of sudden cardiac death can be identified and this outcome can be prevented in many patients.

Concomitant with these spectacular advances, there has been a progressive and alarming increase in the prevalence of heart failure, which has become the most frequent diagnosis of hospital admission in Medicare patients. The development of heart failure has actually become the price of successful treatment of heart disease, and for many patients this price has been high indeed. How can this seeming paradox be explained? While the life of patients with most forms of heart disease has certainly been prolonged and its quality improved, with some exceptions the underlying condition is rarely cured. For example, while most patients with acute myocardial infarction now survive for years after the event, they often develop additional episodes of myocardial infarction which "chip away" at their remaining viable myocardium leading to left ventricular dysfunction and ultimately to heart failure. Similar scenarios play out in patients with hypertension, who might have died as a consequence of a hemorrhagic stroke in 1960, but who now develop heart failure later in life as a consequence of prolonged and progressive ventricular hypertrophy despite receiving antihypertensive drugs. While the development and more widespread use of implanted cardiac defibrillators has reduced sudden cardiac death, this treatment has increased the prevalence of patients who survive to develop failure of the myocardial pump. Co-morbidities such as diabetes mellitus, obesity, atrial fibrillation, chronic obstructive lung disease and severely reduced renal function, which are common in the elderly, increase the risk of heart failure in patients with the aforementioned underlying cardiac disorders.

Fortunately, there has been progress in the treatment of one form of heart failure—that which occurs in patients with reduced ejection fraction. However, while the prognosis in such patients has improved, this improvement is usually temporary, and after several years, the condition often progresses. Treatment of patients with heart failure and preserved ejection fraction as well as of patients with acute decompensated heart failure has improved relatively little in the last few decades. As a consequence, many patients with a history of heart failure enter a phase commonly known as advanced heart failure. This pre-morbid condition is the subject of this excellent book, edited by Michael Domanski, Marc Pfeffer, and Mandeep Mehra, three acknowledged leaders of this field. They have been joined by a team of expert co-authors and have produced a volume which reviews the fundamental pathobiology and pathophysiology of advanced heart failure, including right heart failure. It then goes on to describe and assess diagnostic procedures, pharmacologic and device management, and treatment with mechanical circulatory support and cardiac transplantation.

This well written, carefully edited book will be of great interest to clinicians faced with the challenge of caring for the growing number of patients with advanced heart failure. It will be of particular value to trainees who will join the ranks of specialists in advanced heart failure. It is this next generation who, in addition to providing care to these patients, will advance this importance branch of cardiology, and this book will help them on their journey.

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Abbreviations

ABIM	American Board of Internal Medicine
AC	adenylyl cyclase
AC	arrhythmogenic cardiomyopathy
ACC	American College of Cardiology
ACE	angiotensin converting enzyme
ACEI	angiotensin converting enzyme inhibitor
ACHD	adult congenital heart disease
ACLS	adult cardiac life support
ACR	acute cellular rejection
ACT	activated clotting time
ADCC	antibody-dependent cellular cytotoxicity
ADHF	acute decompensated heart failure
ADL	activities of daily living
AF	atrial fibrillation
AHA	American Heart Association
AHG	anti-human globulin
AMPK	AMP-sensitive kinase
AMR	antibody-mediated rejection
ANS	autonomic nervous system
APC	antigen presenting cells
AR	aortic regurgitation
ARB	angiotensin receptor blocker
ARVC	arrhythmogenic right ventricular cardiomyopathy
AS	aortic stenosis
ASD	atrial septal defect
ASE	American Society of Echocardiography
ASO	arterial switch operation
AT	atrial tachycardia
ATG	anti-thymocyte globulin
ATP	anti-tachycardia pacing
ATR	atrial tachycardia remodeling
AUC	area under the curve
AV	atrioventricular
AVA	aortic valve area
AVM	arteriovenous malformations
AVR	aortic valve replacement
AZA	azathioprine
BiVAD	biventricular assist device
BiVP	biventricular pacing
BMI	body mass index
BMV	balloon mitral valvotomy
BNP	brain natriuretic peptide
BR	breathing reserve
BTT	bridge to transplant
BUN	blood urea nitrogen
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CARE	cholesterol and recurrent events
CARP	cardiac ankyrin repeat protein
CAV	cardiac allograft vasculopathy
cCTGA	congenitally corrected transposition of the great arteries
CDC	complement-dependent cytotoxicity
CHD	congenital heart disease
CHF	congestive heart failure
CI	cardiac index
CICR	calcium-induced calcium release
CIED	cardiovascular implantable electronic devices
CK	creatine kinase
CMR	cardiac magnetic resonance
CMV	cytomegalovirus
CNI	calcineurin inhibitor
CO	cardiac output
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CPET	cardiopulmonary exercise testing
CREB	CAMP response binding
CRT	cardiac resynchronization therapy
CS	coronary sinus
CSA	cyclosporine
CTD	connective tissue disease
CTEPH	chronic thromboembolic pulmonary hypertension
CTL	cytotoxic T lymphocyte
CTPH	chronic thromboembolic pulmonary hypertension
CTRD	cardiac transplant research database
CVP	central venous pressure
CXR	chest radiograph
DAMPS	damage-associated molecular patterns
DAVID	dual-chamber and vvi implantable defibrillator
DC	dendritic cell
DCD	donation after circulatory death
DENSE	displacement encoding with stimulated echoes
DSA	donor-specific antibodies
DSE	dobutamine stress-echocardiography

EBV	Epstein–Barr virus
ECG	electrocardiography
ECMO	extracorporeal membrane oxygenation
EDV	end-diastolic volume
EEPV	end-ejection pressure/volume
EF	ejection fraction
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EMB	endomyocardial biopsy
EPR	external pressure reference
ER	endoplasmic reticulum
ERA	endothelial receptor antagonist
ESC	European Society of Cardiology
ESV	end-systolic volume
EVR	everolimus
FAC	fractional area change
FC	functional class
FDA	food and drug administration
FDG	fluorodeoxyglucose
FFA	free fatty acid
FHF	first heart field
FI	fluid index
FSV	forward stroke volume
FVC	forced vital capacity
GALT	gut-associated lymphoid tissue
GCM	giant cell myocarditis
GEP	gene expression profiling
GFR	glomerular filtration rate
GI	gastrointestinal
GLS	global longitudinal strain
GPCR	G-protein-coupled receptors
H&E	hematoxylin and eosin (strain)
HBV	hepatitis B virus
HCV	hepatitis C virus
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HIT	heparin-induced thrombocytopenia
HLA	human leukocyte antigen
HMR	heart-to-mediastinum ratio
HPV	human papillomavirus
HRS	Heart Rhythm Society
HRV	heart rate variability
HTLV	human T-lymphotropic virus
IABP	intra-aortic balloon pump
ICD	implantable cardioverter defibrillator
ICU	intensive care unit
IDC	interdigitating dendritic cell
IHM	implantable hemodynamic monitors
INR	international normalized ratio
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
IPAH	idiopathic pulmonary arterial hypertension
IR	insulin resistance
IRIS	immediate risk stratification improves survival
ISHLT	International Society for Heart and Lung Transplantation
ITAMS	immune-receptor tyrosine based activation motifs
IVC	inferior vena cava
IVUS	intravascular ultrasound
JNK	jun N-terminal kinases
JVP	jugular venous pressure
KIR	killer immunoglobulin-like receptors
LA	left atrium
LAD	left anterior descending
LAO	left anterior oblique
LAP	left atrial pressure
LAS	lung allocation score
LBBB	left bundle branch block
LDH	lactate dehydrogenase
LFT	liver function test
LGE	late gadolinium enhancement
LIMA	left internal mammary artery
LM	lateral marginal
LV	left ventricle
LVAD	left ventricular assist device
LVEDP	left ventricular end-diastolic pressure
LVEDV	left ventricular end-diastolic volume
LVEF	left ventricular ejection fraction
LVFP	left ventricular filling pressure
LVH	left ventricular hypertrophy
LVOT	left ventricular outflow tract
LVP	left ventricular pacing
MAC	membrane attack complex
MAP	mean arterial pressure
MAPK	mitogen-activated protein kinase
MBL	mannose-binding lectin
MCS	mechanical circulatory support
MCV	middle cardiac vein
MHC	major histocompatibility complex
MI	myocardial infarction
MMF	mycophenolate mofetil
MPI	myocardial performance index
MPT	mitochondrial permeability transitions
MR	mitral regurgitation
MRS	magnetic resonance spectroscopy
MS	mitral stenosis
MSCT	multislice CT
MUGA	Multi Gated Acquisition Scan
MV	minute ventilation
MVR	mitral valve repair/replacement
MVV	maximum voluntary ventilation
NAION	nonarteritic anterior ischemic optic neuropathy
NAT	nucleic acid testing
NEM	necrotizing eosinophilic myocarditis
NFAT	nuclear factor of activated transcription
NHLBI	National Heart, Lung, and Blood Institute
NHR	nighttime heart rate
NIH	National Institutes of Health
NODM	new-onset diabetes mellitus
NPV	negative predictive value
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
OPCAB	off-pump coronary artery bypass
PA	pulmonary artery
PAC	pulmonary artery catheter
PAD	peripheral arterial disease
PAH	pulmonary arterial hypertension

PAM	patient advisory module
PAP	pulmonary artery pressure
PAWP	pulmonary arterial wedge pressure
PBMC	peripheral blood mononuclear cell
PCI	percutaneous coronary intervention
PCR	polymerase chain reaction
PCWP	pulmonary capillary wedge pressure
PDA	patent ductus arteriosus
PDA	posterior descending artery
PDGF	platelet-derived growth factor
PE	pulmonary embolism
PEA	peak endocardial acceleration
PEEP	positive end-expiratory pressure
PEP	pre-ejection period
PET	positron emission tomography
PFT	pulmonary function test
PH	pulmonary hypertension
PI	pulmonic insufficiency
PI	pulsatility index
PKA	*protein kinase A*
PKC	*protein kinase C*
PMA	phorbol myristate acetate
PND	paroxysmal nocturnal dyspnea
PPH	primary pulmonary hypertension
PR	pulmonary regurgitation
PRA	panel reactive antibody
PRES	posterior reversible encephalopathy syndrome
PS	pulmonic stenosis
PTLD	post-transplantation lymphoproliferative disorder
PVC	premature ventricular contraction
PVI	pulmonary vascular impedance
PVOD	pulmonary venous occlusive disease
PVR	pulmonary vascular resistance
QOL	quality of life
RA	right atrium
RAAS	renin–angiotensin–aldosterone system
RAP	right atrial pressure
RAVI	right atrial volume index
RBBB	right bundle branch block
RBC	red blood cells
RCA	right coronary artery
RCT	randomized controlled trial
RER	respiratory exchange ratio
RHC	right heart catheterization
RIMA	right internal mammary artery
RIP	receptor-interacting protein
RLC	regulatory light chain
ROC	receiver operating characteristic
RV	right ventricle
RVA	right ventricular apex
RVAD	right ventricular assist device
RVDP	right ventricular diastolic pressure
RVEF	right ventricular ejection fraction
RVFW	right ventricular free wall
RVMI	right ventricular myocardial infarction
RVOT	right ventricular outflow tract
RVSP	right ventricular systolic pressure
RVSWI	right ventricular stroke work index
RVWS	right ventricular wall stress
SAI	systolic area index
SCD	sudden cardiac death
SDI	systolic dyssynchrony index
SERCA	sarcoplasmic reticulum calcium ATPase
SFI	standard fluorescent intensity
SHF	second heart field; systolic heart failure
SM	sensor module
SMVT	sustained monomorphic ventricular tachycardia
SPECT	single photcon emission CT
SPI	solid-phase immunoassays
SR	sarcoplasmic reticulum; sinus rhythm
SSRI	selective serotonin reuptake inhibitor
STAR	speckle tracking and resynchronization
STE	speckle tracking echocardiography
STS	Society of Thoracic Surgeons
SV	stroke volume
SVC	superior vena cava
SVR	systemic vascular resistance
SVT	supraventricular tachycardia
SWI	stroke work index
TAC	transverse aortic constriction
TAH	total artificial heart
TAP	transporter associated with antigen processing
TAPSE	tricuspid annular plane systolic excursion
TARP	total atrial refractory period
TAVR	transcatheter aortic valve replacement
TCE	threshold-crossing event
TCR	T cell receptor
TDI	tissue Doppler imaging
TEE	transesophageal echocardiography
TNF	tumor necrosis factor
TOF	tetralogy of Fallot
TOR	target of rapamycin
TP	tachycardia pacing
TPG	transpulmonary gradient
TPR	total pulmonary resistance
TR	tricuspid regurgitation
TRP	transient receptor potential
TTE	transthoracic echocardiography
TV	tricuspid valve
TVM	tissue velocity mapping
UNOS	United Network for Organ Sharing
VA	ventricular arrhythmias
VAD	ventricular assist device
VCF	velocity of circumferential fiber
VEGF	vascular endothelial growth factor
VER	ventricular evoked response
VF	ventricular fibrillation
VIP	vasoactive intestinal peptide
VS	ventricular sensing
VSD	ventricular septal defect
VT	ventricular tachycardia
WHO	World Health Organization
WMA	wall motion abnormality

CHAPTER 1

Advanced heart failure in perspective

Marc A. Pfeffer MD PhD, Michael J. Domanski MD, and Mandeep R. Mehra MD

Introduction

Heart failure encompasses an extremely broad clinical syndrome which, despite its diverse etiologies, can uniformly lead to marked limitations in functional capacity with reduced quality and quantity of life. The syndrome is characterized by a constellation of signs and symptoms which are expressions of excessive intravascular volume and/or inadequate tissue perfusion.[1] Although multiple disorders of respiratory and renal function can also contribute to some of these signs and symptoms, an overarching inability of the heart to maintain adequate pump function without utilizing reserve mechanisms is fundamental for the diagnosis of heart failure.[2]

The reduction in the pump function of the heart may occur as the consequence of any of a multitude of abnormalities which distort the tightly coordinated aspects of the normally highly efficient cardiac performance. Impaired ventricular emptying (systolic dysfunction) is commonly characterized in clinical practice by reduced left ventricular ejection fraction. At the molecular level, this may result from any combination of either an intrinsic myofibrillar contractile defect (genetic or acquired) or loss of effective contractile mass from myocardial infarction, or myocarditis. However, disturbances in many other aspects of cardiac performance required for effective integrated cardiac function such as abnormal relaxation (lusitropy), inadequate coronary perfusion, electrical–mechanical dyssynchrony, arrhythmias, valvular stenosis or insufficiency, or commonly, combinations of these disorders that sufficiently impair the exquisitely integrated cardiac performance can result in the signs and symptoms of heart failure (Figure 1.1).

An evaluation during exercise may elicit more subtle abnormalities of cardiac function not apparent at rest to better delineate the connection of the heart to the clinical diagnosis of heart failure.[3] Even in the absence of an overt abnormality of cardiac structure of function, under extreme circumstances such as those produced by malignant hypertension or pheochromocytoma,[4,5,6,7] highly excessive loading conditions can exceed normal reserve capacity of the ventricle resulting in the transient appearance of heart failure in the context of intrinsically normal myocardial function. Many of the etiological pathways that precede the clinical appearance of symptomatic heart failure can be attributed to a less intense but more sustained hyperfunctional state imposed on the myocardium.[8]

An expanding number of genetic mutations encoding for a variety of cytoskeletal and mitochondrial abnormalities are being identified as causal factors for several dilated cardiomyopathies.[9] However, less well understood complex polygenetic environmental temporal interactions must currently be invoked for the vast majority of clinical heart failure, which is commonly preceded by hypertension and or coronary artery disease. The established concept of an initial adaptive (physiologic) hypertrophy where structural alterations are initially associated with an increased capacity to sustain these excessive workloads but can eventually lead to pathologic hypertrophy with an exhaustion of compensatory reserve and more overt cardiac dysfunction continues to be supported by longitudinal data.[8,10,11] In both experimental animal models and human studies a consistent temporal pattern has emerged that prolonged hyperfunction of a cardiac chamber can result in altered genotypic expression (shift towards a fetal or neonatal pattern) with a subsequent alteration in several cascades of signaling pathways that have been frequently identified in hypertrophied myocytes.[12,13,14] If sustained, these unfavorable molecular shifts lead to perturbations in calcium cycling, altered properties of β-adrenergic receptors, mitochondria, and key sarcomeric proteins (actin, myosin, titin), which have each been associated with the reduced contractile function observed in pathologic hypertrophy.[15,16,17,18] Imbalances in the signaling pathways for cell growth, cell death (apoptosis, necrosis, proteotoxicity), maladaptive autophagy, as well as the newly appreciated capacity to regenerate and repair, also appear to play important roles in the molecular mechanisms associated with this deterioration of cardiac performance[12,19,20,21] as well as perturbations of the histological balances in the relative tissue composition between myoctes, interstitial connective, and vascular elements.[22]

On a more macroscopic structural basis, sustained impairments in cardiac performance are also generally associated with enlargements of cardiac chambers often termed adverse ventricular remodeling. As opposed to acute distention, where the volume of the ventricle is increased due to raised filling pressure (operating on a higher portion of the pressure–volume curve), chronic dilatation or remodeling represents an actual structural change wherein the pressure–volume curve is shifted to the right with higher cavity volumes at the same filling pressure.[23] Distention is an effective short-term means of raising stroke volume by the Frank–Starling mechanism. Ventricular remodeling can also be considered as a mechanism of facilitating the restoration of stroke volume in the setting of loss of contractile function, since a structurally larger

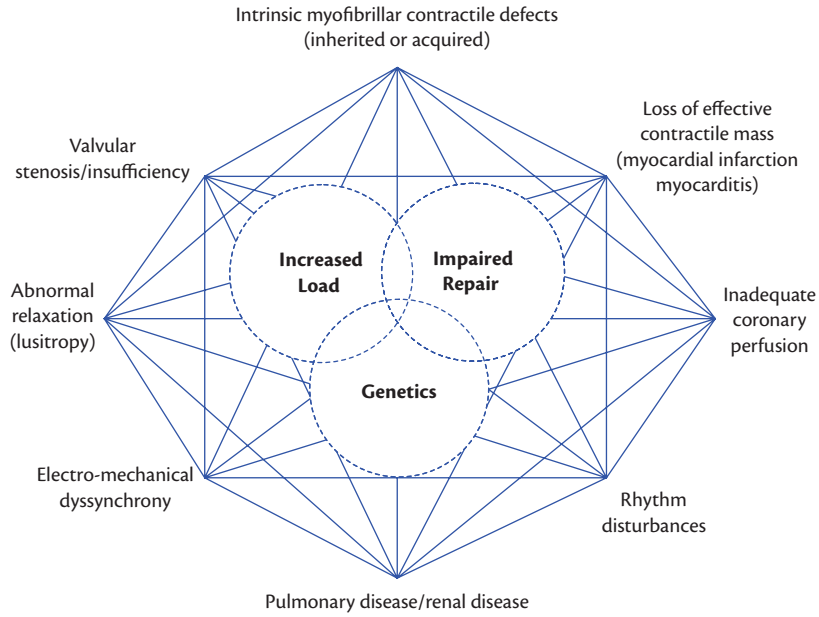

Fig. 1.1 Mosaic representation of the multifaceted aspects of cardiac performance that can contribute to cardiac dysfunction.

ventricular cavity requires less fractional shortening to eject a normal stroke volume.[24] However, based on the Laplace relationship, as a consequence of the larger radius, there is an important pathophysiologic offsetting increase in wall stress.[25] Some degree of structural ventricular enlargement may be considered as an adaptive mechanism to compensate for the loss of effective contractile tissue. The progressive nature of ventricular remodeling (a vicious cycle of enlargement begetting higher wall stress and more remodeling) makes this structural change maladaptive in the long run.[26,27,28]

Although the presence of abnormalities in any of the highly integrated aspects of cardiac performance or structure can be anticipated to result in heart failure, the converse is also true that similar findings can be present in asymptomatic individuals. Moreover, the degree of the cardiac performance abnormality is a limited predictor of symptoms or functional state.[29] Despite statistical associations between quantitative measures of cardiac function such as left ventricular ejection fraction (LVEF) and functional limitations (symptoms or exercise capacity) within large cohorts, these correlations are at best only modest.[30,31,32,33] Indeed, almost all of the abnormalities of cardiac performance can be identified to some extent in individuals with minimal or no symptoms. Just as experienced physicians are no longer surprised by patients with clinically important coronary or valvular heart disease who appear to have normal functional capacity, on an individual level, the finding of reduced LVEF or marked chamber enlargement does not in itself provide sufficient insight to permit a reliable estimate of functional status. Consider that some patients with heart failure and preserved ejection fraction (HFpEF) can be markedly symptomatic and limited, whereas a person with asymptomatic left ventricular dysfunction may have an excellent functional capacity despite an abnormal cardiac function and geometry. Acknowledging these limitations of structural and functional determinations on the assessment of functional capacity on an individual basis, in population studies the extent of these abnormalities have been consistently associated with a heightened risk for developing symptomatic heart failure and/or cardiovascular death.[34,35]

Crossing the clinical threshold from asymptomatic to symptomatic

NYHA classification system

Notwithstanding mechanistically diverse etiologies and the array of abnormalities of cardiac function as well as structure, it is the presence and magnitude of signs and symptoms that bestow some uniformity on both the diagnosis and prognosis across this broad syndrome encompassed by the clinical term heart failure. Since the diagnosis of heart failure covers such a broad range of severity from the compensated ambulatory fully functional to the bedridden mechanically supported patient, more refinement in categorization is needed. The time-honored New York Heart Association (NYHA) classification system was introduced in 1928 as a way of providing a description of an individual's physical limitations during the performance of daily activities.[36] The NYHA classification has consistently proven its value as a major instrument to not only assess disease severity but also provide important information regarding prognosis. The deceptively simple classification (class I, no symptoms or limitations; class II, mild shortness of breath during ordinary activities slightly limiting ordinary activities; class III, marked limitations with even less than ordinary activities but comfortable at rest; and class IV, severe limitations experiencing symptoms even at rest), continues to be an extremely useful and powerful tool to communicate disease severity for both the individual patient as well as cohorts in clinical trials, epidemiologic surveys, and administrative databases. Indeed, in everyday clinical parlance across the globe during exchange of clinical coverage and sign-out rounds, the description of a patient with heart failure is generally preceded by the designation of their NYHA class.

The very nature of the NYHA classification indicates that within the diagnosis of heart failure, there is a wide range of functional

limitations. It is also well recognized that the NYHA class provides an important indicator of the likelihood for subsequent fatal and nonfatal heart failure events. All other factors being similar, a patient with NYHA class I or II would be anticipated to have a better life expectancy and fewer nonfatal heart-failure-related serious events than a comparable patient with more substantial limitations (NYHA III and IV).[37,38,39,40]

Experienced physicians, however, appreciate and understand the limitations of the subjective NYHA functional class and other symptom-based classification systems. An individual patient's status may fluctuate considerably. Fortunately, symptoms can frequently be mitigated with increases in physical capacity. Conversely, clinical condition can progressively or abruptly deteriorate. The NYHA classification figures prominently in all of the major stratification scores systems of heart failure prognosis,[37,38,39,40] and continues as the main severity categorization for the most recent European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic heart failure.[41]

AHA/ACC guidelines

The American Heart Association/American College of Cardiology (AHA/ACC) guideline for the diagnosis and management of heart failure in adults, introduced in 2001, provided a new contextual framework to characterize this spectrum of heart failure and its treatments.[42] This four-stage (A, B, C, D) classification underscores the progressive nature of heart failure and additionally provides an important stage specific framework to consider opportunities for therapeutic interventions to lower the odds of both developing heart failure or progressing to the higher morbidity and mortality heart failure (Figure 1.2). This system was introduced in the setting of heart failure practice guidelines to improve the utilization of evidence-based approaches to prevent as well as manage heart failure. As such, it offers recommendations for therapies and goals in relation to disease severity and prognosis. The recommendations of the guidelines represent an attempt to better optimize the intensity of treatment considering risk/benefit assessments.[43,44]

Stages A and B designate those without signs and symptoms of heart failure and define "at-risk" populations. Although patients in these two stages would not be diagnosed as having heart failure, by highlighting two asymptomatic stages (A, at high risk for heart failure without structural heart disease; B, structural heart disease without signs or symptoms of heart failure), the task force committee appropriately emphasized that to a large extent heart failure should be considered a preventable disease. However, an effective population-based preventive strategy would require both improvements in detection of at-risk individuals along with greater implementation of proven deterrent approaches.[43]

For those at the lowest risk—stage A—the recommendations focus on nonpharmacologic lifestyle measures such as smoking cessation and, where appropriate, addressing obesity and encouraging more physical activity. These general wellness-promoting actions are of minimal risk as well as cost and are generally prudent approaches to lower the chances of developing heart failure (as well as atherosclerotic diseases). Identifying and effectively treating hypertension, diabetes, and lipid disorders are the earliest recommendations for long-term pharmacologic therapy, which for individuals in stage A, represent preventive measures for heart failure.[45,46,47,48,49,50,51,52]

The designation of stage B (structural heart disease but without signs or symptoms of heart failure) requires additional imaging

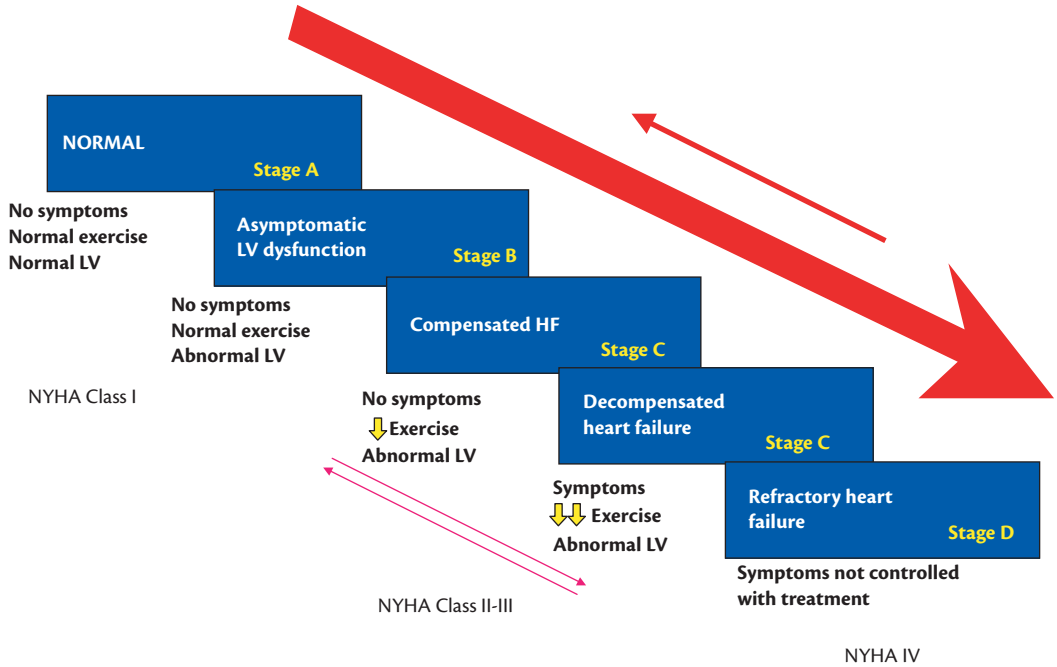

Fig. 1.2 Schematic depiction of the progression of heart failure using the ACC/AHA Guidelines for the Evaluation and Management of Heart Failure in the Adult. This adaptation superimposes NYHA functional class on the stages to emphasize that stages A and B represent asymptomatic conditions.

Adapted from Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldmanmd AM, Francis GS, et al. ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure).

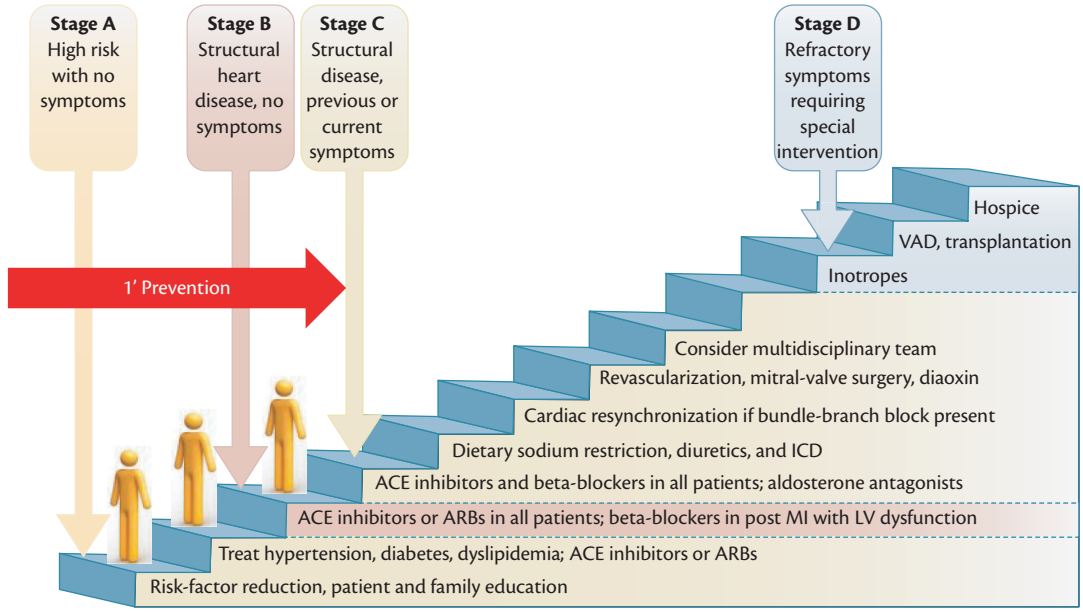

Fig. 1.3 Opportunities to prevent heart failure in AHA/ACC stages A and B.
Adapted from Jessup M, Brozena S. Heart failure. N Engl J Med 2003;348(20):2007–18.

or electrocardiographic evidence of a cardiac abnormality that augments the risk of developing heart failure. To a large extent, the justification for this additional screening for cardiac structural involvement stems from the results of both Studies Of Left Ventricular Dysfunction (SOLVD) Prevention and the Survival And Ventricular Enlargement (SAVE) trials, which both demonstrated that the strategy to identify and treat even asymptomatic persons with reduced LVEF with an angiotensin-converting enzyme inhibitor (ACEI), was effective in preventing the clinical appearance of heart failure and reducing mortality.[53,54] In the updated guidelines,[55] the higher risk of both heart failure and sudden unexpected death in stage B compared to A, coupled with clinical trial data demonstrating that interventions (ACEI, β-blockers and for some an implantable cardioverter defibrillator) can lower their risk of dying or progressing to developing symptomatic heart failure (stage C), further justified the additional screening of asymptomatic individuals to identify for the initiation of these long-term preventive interventions (Figure 1.3, red arrow).[56,57,58,59,60,61,62,63,64,65,66]

Crossing the threshold to heart failure (stage B to C)

Once the signs and symptoms that lead to the clinical diagnosis of heart failure are manifest, the risks for further clinical deteriorations and death escalate greatly. The marked negative prognostic impact of this crossing of the clinical threshold from asymptomatic ventricular dysfunction to symptomatic heart failure was also clearly demonstrated by the SOLVD investigators. The SOLVD program simultaneously conducted two of the pioneering randomized clinical trials comparing the differences in survival with use of an ACEI to placebo in subjects with reduced LVEF (<35%).[53,67] Enrollment into the SOLVD Treatment arm was predicated on physician-designated presence of symptomatic heart failure whereas in the concurrently conducted SOLVD Prevention, the entry criterion was the absence of a clinical diagnosis of heart failure. Since by design all patients had low LVEF, symptomatic status was the major difference between those enrolled in the Prevention and Treatment arms of SOLVD. The 1-year mortality rate in the asymptomatic left ventricular dysfunction Prevention group of approximately 4%, though much higher than anticipated from the general age- and sex-matched population, was still decisively better than for those classified as symptomatic. Indeed, the 12% annualized mortality rate of the Treatment cohort was nearly threefold higher than that of the low LVEF asymptomatic subjects in the Prevention arm of SOLVD (Figure 1.4).

This greatly heightened risk of death associated with the clinical manifestations of heart failure continues to be apparent within multiple recent clinical trials of diverse populations, even those not selecting subjects with reduced LVEF. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the 1761 participants that developed incident heart failure had a

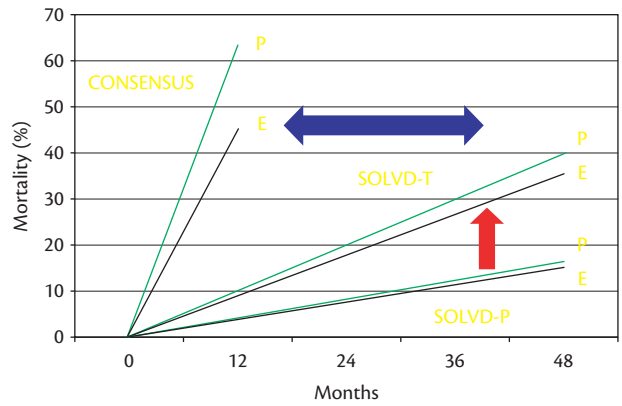

Fig. 1.4 Survival rate differences in asymptomatic people with left ventricular dysfunction[53] compared to symptomatic patients with same range of ejection fraction[67] indicated by the red arrow. Survival rate differences in trials of symptomatic heart failure patients are indicated by the blue arrow.[67,96]

nearly threefold risk of death compared to the other 31 043 with hypertension who did not, even with adjustments for several important demographic factors.[47] Similarly, within the population of patients with a prior myocardial infarction without a history of heart failure, enrolled in the Cholesterol And Recurrent Events (CARE) trial, the risk of death amongst 243 patients (6.3%) who developed heart failure during the 5 years of observation was eightfold higher than in the CARE patients who did not manifest heart failure.[68]

Survivors of a myocardial infarction (MI) represent an expanding reservoir of stage B candidates to develop incident heart failure (stage C). In the Framingham cohort, a history of a prior MI was associated with a 10-fold higher risk of manifesting heart failure.[69] Although hospital mortality of elderly patients (>65 years) experiencing a first myocardial infarction has declined in the last decade, over three-fourths of them develop heart failure or die within the subsequent 5 years.[70,71]

Even transient heart failure during an acute MI worsens prognosis. The clinical recognition of pulmonary congestion (rales) promptly emerged, in the early coronary care unit experiences, as one of the most important clinical discriminators for greater risk of death.[72,73] In the setting of an acute MI, even the transient appearance of clinical signs or symptoms consistent with pulmonary congestion (Killip 2 and higher) greatly augmented the risk of death or development of heart failure (Figure 1.5).[74] This worrisome intersection between MI and heart failure continues in the modern era and across the entire range of acute coronary syndromes.[75]

Measurements of circulating biomarkers, particularly the cardiac-derived markers of wall stress such as natriuretic peptides and troponin, as an indicator of myocyte necrosis have already added to the discriminative models for predicting the development of heart failure and death.[76,77,78,79,80] However, unlike LVEF, data demonstrating that the ascertainment of these biomarkers would lead to the detection of previously unidentified individuals who would derive benefits from a specific therapy are currently needed to justify this additional screening of asymptomatic individuals.[81]

Stage C: Structural heart disease with prior or current symptoms of heart failure

Though much of the burden of heart failure can be prevented or deferred, the reality is that symptomatic heart continues to be the dominant cardiovascular problem in elderly people.[82] Each year in the United States alone, over half a million new patients cross the threshold from stage B to C to become part of the 5 million living with the clinical diagnosis of symptomatic heart failure, double the prevalence of only 25 years ago.[83,84]

Although heart failure is seen in all age groups, it becomes increasingly, almost exponentially, more prevalent with advancing age (Figure 1.6).[82] In the Rotterdam study of a general population, heart failure was diagnosed in 1% individuals aged between 55 and 64 years, 3% from age 65 to 74 years, 7% from age 75 to 84 years, and over 10% for patients 85 years or age and over.[85] A US study of heart failure prevalence showed a similar increase with age, affecting more than 20% of those over 80 years of age. At 40 years of age, 1 in 9 men and 1 in 6 women can be anticipated to develop symptomatic heart failure (stage B to C) over their subsequent lifespan.[86]

Heart failure is therefore often considered a disease of aging attributed to the convergence of a number of contributing age-related disease processes such as coronary artery disease (more survivors of MI), hypertension, diabetes, and obesity. As a result of both its prevalence in the aging population and impact on the risk

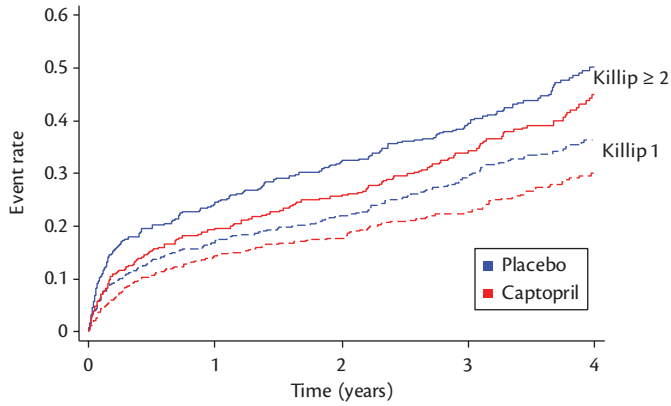

Fig. 1.5 Survival following myocardial infarction in those with (Killip ≥2) and without (Killip 1) pulmonary congestion, from the SAVE study.[54,74] The reduction in risk of death with randomization to captopril was observed in both groups.
Adapted from Moye LA, Pfeffer MA, Wun C, Davis BR, Geltman E, Hayes D, et al. Uniformity of captopril benefit in the SAVE study: Subgroup Analysis. European Heart Journal (1994);15(Suppl B):2-8 by permission of Oxford University Press.

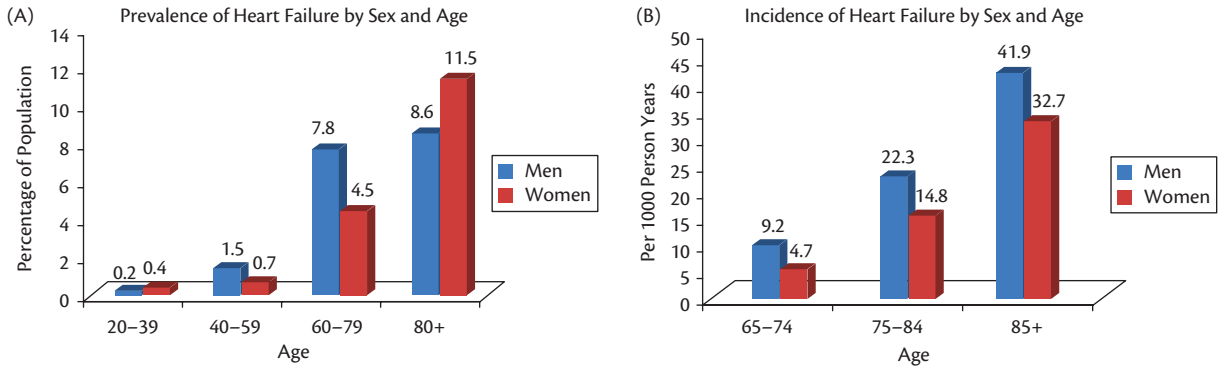

Fig. 1.6 Influence of age on prevalence (A) and incidence (B) of heart failure.
Adapted from Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart Disease and Stroke Statistics—2013 Update: A Report From the American Heart Association. Circulation 2013;127(1):e6-e245.

of developing heart failure, hypertension remains the most common underlying factor for heart failure on a population attributable basis.[87] Beyond the age of 70 years, heart failure is the most common reason for hospitalization.[84,88,89,90]

The devastating impact on prognosis, attending the development of heart failure symptoms, was well demonstrated by the classic population-based longitudinal cardiovascular epidemiologic studies. In the Framingham Heart Study, crossing the clinical threshold to the diagnosis of heart failure was associated with a 5-year mortality of ~50%.[91] Using a countrywide administrative database, Scottish investigators have shown that the 1-year mortality following a first hospitalization for heart failure, though improving, is still approximately 25%.[71] These, and many other comparisons of those with heart failure to their age- and sex-matched peers, provide powerful and consistent data regarding the medical and economic disease-related burdens across different countries.[41,92,93,94] However, within the diagnosis of heart failure, there is a well-recognized extremely broad spectrum of severity that must also be considered to gain fuller insights into the devastating personal as well as economic impacts of this clinical syndrome.[95] For example, in early clinical trials such as CONSENSUS,[96] the annualized mortality rate was approximately 50%, whereas in SOLVD-T[67] it was 10% (see Figure 1.4, blue arrow). Both groups are encompassed by stage C.

Despite this admittedly extensive range of severities under the unifying diagnosis of heart failure, the AHA/ACC Guidelines for the Diagnosis and Management of Heart Failure in Adults Committee choose to use only two stages to encompass all patients with symptomatic heart failure: C (structural heart disease with current or prior symptoms of heart failure) and D (refractory heart failure requiring specialized interventions) (see Figures 1.2 and 1.3). Fortunately, the vast majority of patients with symptomatic heart failure are classified in stage C rather than stage D. As with all prior stages, the goals of stage C are to build on prior strategies to prevent progression by adding appropriate use of evidenced-based therapies and devices to reduce symptoms and prolong survival. Over the past 30 years, compelling evidence from multiple high-quality randomized clinical outcome trials targeting these patients with reduced LVEF and symptomatic heart failure has resulted in proof that use of several classes of pharmacologic therapies and defibrillator/pacing devices can reduce episodes of clinical deterioration and/or prolong survival.[97] Several international societies have produced "practice guidelines" with evidence-graded recommendations.[41,43,94,98] The consistency of these authoritative documents and the relatively high number of grade 1A recommendations is a testament to the reliable evidence for improvements in clinical outcomes with multiple non-mutually-exclusive interventions (Chapter 8). Translating these discoveries into clinical practice has made a measurable positive impact.[43,99]

Stage D: Refractory symptoms requiring special intervention

Clinical status is of course not stagnant and apparently stable patients with heart failure may improve or experience a worsening of their symptoms. Often the adverse episodes or either chronic or acute decompensation can be addressed by adjustments in medical regimens. However, not infrequently, the consequences of either pulmonary congestion and/or hypoperfusion are so severe

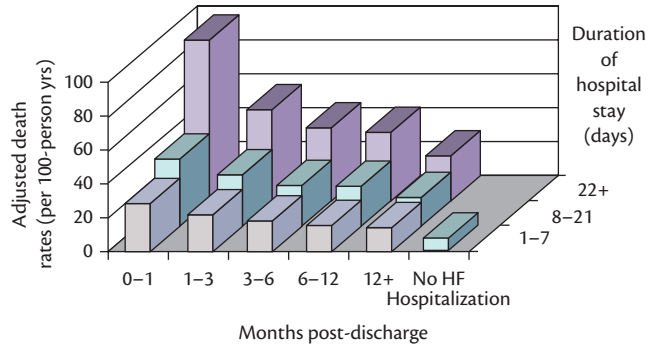

Fig. 1.7 The hazard of death is highest after a recent hospitalization for heart failure, and is exacerbated in those with a more prolonged stay compared to patients who are not hospitalized.
Data from the CHARM program: Braunwald E. The management of heart failure: the past, the present, and the future. Circulation: Heart Failure 2008;1(1):58–62.

and overall clinical status becomes so fragile that hospitalization is warranted. This inpatient care is considered necessary to provide the level of observation needed during this precarious period for the frequent medication adjustments made to manage symptoms and attempt to restore the patient to their prior baseline ambulatory activities. As the leading discharge diagnosis in the Medicare population, such heart failure-related hospitalizations are common.[84,88,89] These episodes of clinical deterioration requiring hospitalization are, unfortunately, much more than a bump in the road since they represent important clinical demarcations with lasting consequences (Figure 1.7).[100] Readmission and 30-day, all-cause, risk-standardized mortality rates are estimated at 24.56% and 11.17%, respectively.[101] Even within the hospitalized category, there are those who succumb to pump failure death, those patients who are managed with adjustments in their medications (stage C), and others who require ventilator and/or mechanical circulatory support to maintain adequate perfusion (stage D).

Refractory symptoms requiring special intervention (stage D) designates the most advanced severity of the AHA/ACC heart failure spectrum (see Figure 1.3). Terms like advanced, decompensated, recalcitrant, NYHA IV, end-stage, and refractory can all be used as descriptive adjectives before the words heart failure to effectively connote the extent, gravity, and precariousness of this most serious clinical condition. Others had previously highlighted that a significant minority of patients continue to do poorly despite conventional therapy; Adams and Zannad used a combination of poor functional status (NYHA III–IV), low LVEF (<30%) and limited exercise capacity (peak oxygen consumption <14 ml kg^{-1} min^{-1}) to identify and define an advanced heart failure cohort.[102] The study group of the Heart Failure Association of the ESC incorporated physical signs of congestion/poor perfusion, additional objective measurements, along with a history of a recent hospitalization for heart failure in their definition of advanced chronic heart failure.[41] Both definitions clearly indicate that these adverse conditions defining advanced heart failure must exist despite attempts to use and optimize proven therapies.

The AHA/ACC chose to incorporate the terms "refractory" and "requiring specialized interventions" to characterize this most worrisome of its categories of heart failure.[42,55] This important but fortunately small minority of patients who do not respond to the usual measures to alleviate their symptoms remain markedly

symptomatic despite escalations in their medical therapy. Indeed, in many instances the disease progression is so severe that previous life-prolonging therapies are no longer hemodynamically tolerated and must be discontinued (Chapter 8). Many of these individuals cannot be safely cared for in the home setting and require extraordinary measures and support. That there is no absolute or uniformly accepted definition for this most severe category of heart failure is reminiscent of the citation from US Supreme Court Justice Potter Stewart "I know it when I see it" regarding hard-core pornography (Jacobellis v. Ohio, 378 U.S. 184, 1964).[103] For these patients with stage D heart failure, it may be more appropriate to add "and did not respond favorably to conventional therapies" to the justice's famous quote. Regardless of the precise definition of stage D heart failure, it is estimated that this group represents 2–5% of the symptomatic heart failure population in the US, which translates into approximately 200 000 individuals with advanced heart failure, and this number is anticipated to continue to grow.[82,84,104,105] The most recent ACCF/AHA guidelines offer some useful clinical features to identify these stage D patients (Table 1.1).[55]

This most challenging and fragile group of advanced heart failure patients disproportionately experiences the greatest healthcare burdens on individual, familial, and societal levels. An expanding number of healthcare providers have devoted their professional efforts to address the multiple challenges posed by these patients with stage D heart failure. The care for these most severely ill patients far exceeds that which can be expected to be offered by even the most capable and conscientious individual practitioner. Addressing these expanding needs has spawned new multidisciplinary teams. Consider how the advent of cardiac transplantation led major referral centers to garner the collective skills, expertise, and experience required to offer that resource-intensive service to "a significant minority" of highly selected patients. Subspecialists within cardiac surgery, cardiology, immunology, infectious diseases, nursing, and social services aligned within the selected institutions made the commitment to provide this extraordinary level of collective expertise and resources to offer cardiac transplantation.[106] It rapidly became apparent that the numbers of cardiac transplants performed at these specialized centers grossly underestimated the extent of the full clinical services rendered. Referrals to these multidisciplinary heart failure groups went beyond screening of potential transplant candidates. These self-selected teams rendered their specialized collective care to an expanding pool of advanced heart failure patients, many of whom were unlikely to become cardiac transplant recipients. As the patient populations being treated and the clinical services offered expanded, "advanced heart failure" rather than "transplant cardiology" became a better descriptor of the escalating medical activities of these affinity groups. Innovations in electrophysiological devices with randomized trials generating convincing evidence for morbidity and mortality benefits with the appropriate use of cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillators (ICDs) fostered even greater collaborations with additional subspecialists (Chapters 9, 10, 11).[107,108,109,110,111] As the services of these groups specializing in the care of patients with advanced heart failure expanded, their referral base broadened well beyond potential candidates for cardiac transplantation.

An even clearer distinguishing feature of institutions committed to the care of patients with advanced heart failure was made by those centers that added the capability of offering relatively long-term mechanical circulatory support for the most hemodynamically compromised patients to their therapeutic armamentarium. The demonstration of improvements in both the quantity and quality of life with use of a pulsatile left ventricular assist device (LVAD) compared to optimized intensive medical therapy offered a strong impetus for the consolidation of the intense human and physical resources needed to effectively provide these highly specialized services.[112] The use of the LVAD as "destination therapy" for refractory patients, even those not considered candidates for cardiac transplantation, greatly expanded the population served by these advanced heart failure units. The more recent demonstration of further improvements in patient outcomes with the newer generation of nonpulsatile LVADs afforded even greater evidence for offering mechanical support for expanded number of stage D heart failure patients and the clinical workloads of these specialized centers.[113] The accompanying growth in services and referrals underscored that offering this level of care to patients with advanced heart failure requires an institutional team commitment exceeding what even the most talented and dedicated individual physicians could offer.

Table 1.1 INTERMACS criteria which further discriminate patients with advanced heart failure beyond NYHA class

INTERMACS level	NYHA class	Shorthand
1	IV	"Crash and burn"
2	IV	"Sliding fast" on inotropes
3	IV	"Stable" on continuous inotropes
4	Ambulatory IV	Symptoms at rest
5	Ambulatory IV	"Housebound" Comfortable at rest, symptoms with minimal activity
6	IIIB	"Walking wounded" Meaningful activity limited
7	III	Advanced class III

Adapted from reference 115 (Stevenson LW, Pagani FD, Young JB, et al. INTERMACS profiles of advanced heart failure: the current picture. J Heart Lung Transplant 2009;28(6):535–41.)

Advanced heart failure/heart transplantation as a distinct subspecialty

Patients with stage C heart failure are commonly encountered in medical practice and are most often treated by cardiologists, internists, or other healthcare providers. For this vast majority of heart failure patients, a physician well versed in the applicable guidelines with a background of knowledge and experience common to cardiovascular medicine training programs is appropriate and suitable.[114] However, the stage D patients, the 1–2% "refractory" individuals who remain incapacitated despite reasonable attempts with conventional therapies, are generally best served by the team approach offered at specialized advanced heart failure centers. Investigators cooperating on the Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) report have offered a classification profile as a modern expansion for the NYHA class III–IV heart failure patients into seven categories.[115] As with the AHA/ACC stages, this "profiling" attempts to improve selection for the

Box 1.1 Clinical features useful for the identification of patients with stage D heart failure[55]

- Repeated (≥2) hospitalizations or Emergency Department visits for heart failure in the past year
- Progressive deterioration in renal function—e.g., rise in blood urea nitrogen (BUN) and creatinine
- Weight loss without other cause (e.g., cardiac cachexia)
- Intolerance to angiotensin converting enzyme (ACE) inhibitors due to hypotension and/or worsening renal function
- Intolerance to β-blockers due to worsening heart failure or hypotension
- Frequent systolic blood pressure <90 mmHg
- Persistent dyspnea with dressing or bathing requiring rest
- Inability to walk one block on the level ground due to dyspnea or fatigue
- Recent need to escalate diuretics to maintain volume status, often reaching daily furosemide equivalent dose >160 mg/day and/or use of supplemental metolazone therapy
- Progressive decline in serum sodium, usually to <133 mEq/L
- Frequent ICD shocks

expanding therapeutic approaches including mechanical circulatory support (Box 1.1). Titrating conventional therapies, deciding which patients are likely to benefit from revascularization, valve surgery, mechanical circulatory assistance, heart transplantation, and/or other "advanced" therapies including end-of-life care: all these are sensitive to individual patient preferences, requiring a definable body of knowledge, skills, and experience that are not generally sufficiently encountered even during a fellowship in cardiovascular medicine.[116]

As particular knowledge and experience is needed for the practice of interventional cardiology or electrophysiology, there is an analogous, though different, specialized body of knowledge and training needed to properly care for these fragile patients with advanced heart failure. The leadership of the Heart Failure Society of America provided the rationale, outlined the proficiencies, and advocated for this new subspecialty.[117] In the US, the American Board of Internal Medicine (ABIM) recognized this need for core competencies and training by formally establishing Advanced Heart Failure/Cardiac Transplantation as a subspecialty of Cardiovascular Diseases in 2010.[118,119]

With or without the imprint of the ABIM and whether or not other national organizations offer similar accreditation, the new challenges of providing and improving health care to the expanding population of patients with truly advanced heart failure has already led to important realignments of resources as well as training. Regardless of a certification process, there is general recognition and agreement that advanced heart failure is a clinical field of specialization which requires additional training and expertise beyond the experiences afforded in standard cardiology programs. This textbook is directed to this cadre of healthcare workers who have or are making this extraordinary commitment to dedicate their professional careers to improve the care and prognosis of patients with advanced heart failure.

References

1. Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009;119(14):1977–2016.
2. Braunwald E, Ross Jr J, Sonnenblick E. Heart failure. In: Braunwald E, Ross Jr. J, Sonnenblick E, ed., Mechanisms of Contraction of the Failing Heart. Boston: Little, Brown; 1976, pp. 309–56.
3. Lele SS, Macfarlane D, Morrison S, et al. Determinants of exercise capacity in patients with coronary artery disease and mild to moderate systolic dysfunction: Role of heart rate and diastolic filling abnormalities. Eur Heart J 1996;17(2):204–12.
4. Dunn FG, De Carvalho JGR, Kem DC, et al. Pheochromocytoma crisis induced by saralasin. N Engl J Med 1976;295(11):605–7.
5. Szakacs JE CA. L-Norepinephrine myocarditis. Am J Clin Pathol 1958;30(5):425–34.
6. Van Vliet PD, Burchell HB, Titus JL. Focal myocarditis associated with pheochromocytoma. N Engl J Med 1966;274(20):1102–8.
7. Desai AS, Chutkow WA, Edelman E, et al. A crisis in late pregnancy. N Engl J Med 2009;361(23):2271–7.
8. Meerson FZ. Compensatory hyperfunction of the heart and cardiac insufficiency. Circ Res 1962;10(3):250–8.
9. McNally EM, Golbus JR, Puckelwartz MJ. Genetic mutations and mechanisms in dilated cardiomyopathy. J Clin Invest 2013;123(1):19–26.
10. Houser SR, Margulies KB, Murphy AM, et al. Animal models of heart failure: a scientific statement from the American Heart Association. Circ Res 2012;111(1):131–50.
11. Pfeffer MA, Pfeffer JM. Ventricular enlargement and reduced survival after myocardial infarction. Circulation 1987;75(5 Pt 2):IV93–7.
12. Hill JA, Olson EN. Cardiac plasticity. N Engl J Med 2008;358(13):1370–80.
13. Force T, Hajjar R, Del Monte F, et al. Signaling pathways mediating the response to hypertrophic stress in the heart. Gene Expr 1999;7(4–6):337–48.
14. van Berlo JH, Maillet M, Molkentin JD. Signaling effectors underlying pathologic growth and remodeling of the heart. J Clin Invest 2013;123(1):37–45.
15. van Der Velden J, Klein LJ, Zaremba R, et al. Effects of calcium, inorganic phosphate, and pH on isometric force in single skinned cardiomyocytes from donor and failing human hearts. Circulation 2001;104(10):1140–6.
16. Herman DS, Lam L, Taylor MR, et al. Truncations of titin causing dilated cardiomyopathy. N Engl J Med 2012;366(7):619–28.
17. Owen AA, Spinale FG. Myocardial basis for heart failure: role of the cardiac interstitium. In: Mann DL, ed., Heart Failure: A Companion to Braunwald's Heart Disease, 2nd ed. Philadelphia: Elsevier; 2010, pp. 73–84.
18. Marks AR. Calcium cycling proteins and heart failure: mechanisms and therapeutics. J Clin Invest 2013;123(1):46–52.
19. Willis MS, Patterson C. Proteotoxicity and cardiac dysfunction—Alzheimer's disease of the heart? N Engl J Med 2013;368(5):455–64.
20. Olivetti G, Abbi R, Quaini F, et al. Apoptosis in the failing human heart. N Engl J Med 1997;336(16):1131–41.
21. De Meyer GR, De Keulenaer GW, Martinet W. Role of autophagy in heart failure associated with aging. Heart Fail Rev 2010;15(5):423–30.
22. Sano M, Minamino T, Toko H, et al. p53-induced inhibition of Hif-1 causes cardiac dysfunction during pressure overload. Nature 2007;446(7134):444–8.

23. Borlaug BA, Kass DA. Invasive hemodynamic assessment in heart failure. Heart Fail Clin 2009;5(2):217–28.
24. Pfeffer MA, Braunwald E. Ventricular remodeilng after myocardial infarction. Experimental observations and clinical implications. Circulation 1990;81:1162–72.
25. Sandler H, Dodge HT. Left ventricular tension and stress in man. Circ Res 1963;13:91–104.
26. Grossman W, Jones D, McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 1975;56(1):56–64.
27. Hood WP, Rackley CE, Rolett EL. Wall stress in the normal and hypertrophied human left ventricle. Am J Cardiol 1968;22(4):550–8.
28. Fletcher PJ, Pfeffer JM, Pfeffer MA, Braunwald E. Left ventricular diastolic pressure-volume relations in rats with healed myocardial infarction. Effects on systolic function. Circ Res 1981;49(3):618–26.
29. Engler R, Ray R, Higgins CB, et al. Clinical assessment and follow-up of functional capacity in patients with chronic congestive cardiomyopathy. Am J Cardiol 1982;49(8):1832–7.
30. Aleksova A, Sabbadini G, Merlo M, et al. Natural history of dilated cardiomyopathy: from asymptomatic left ventricular dysfunction to heart failure—a subgroup analysis from the Trieste Cardiomyopathy Registry. J Cardiovasc Med 2009;10(9):699–705.
31. Rihal CS, Nishimura RA, Hatle LK, et al. Systolic and diastolic dysfunction in patients with clinical diagnosis of dilated cardiomyopathy. Relation to symptoms and prognosis. Circulation 1994;90(6):2772–9.
32. Pandhi J, Gottdiener JS, Bartz TM, et al. Comparison of characteristics and outcomes of asymptomatic versus symptomatic left ventricular dysfunction in subjects 65 years old or older (from the Cardiovascular Health Study). Am J Cardiol 2011;107(11):1667–74.
33. Yeboah J, Rodriguez CJ, Stacey B, et al. Prognosis of individuals with asymptomatic left ventricular systolic dysfunction in the multi-ethnic study of atherosclerosis (MESA). Circulation 2012;126(23):2713–19.
34. McDonagh TA, Morrison CE, Lawrence A, et al. Symptomatic and asymptomatic left-ventricular systolic dysfunction in an urban population. Lancet 1997;350(9081):829–33.
35. Wang TJ, Evans JC, Benjamin EJ, et al. Natural history of asymptomatic left ventricular systolic dysfunction in the community. Circulation 2003;108(8):977–82.
36. Criteria Committee of the New York Heart Association. Diseases of the Heart and Blood Vessels: Nomenclature and Criteria for Diagnosis, 6th edition, Boston: Little, Brown, 1928.
37. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation 2006;113(11):1424–33.
38. Senni M, Parrella P, De Maria R, et al. Predicting heart failure outcome from cardiac and comorbid conditions: The 3C-HF score. Int J Cardiol 2013;163(2):206–11.
39. Pocock SJ, Ariti CA, McMurray JJ, et al. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. Eur Heart J 2013;34(19):1404–13.
40. Aaronson KD, Schwartz JS, Chen T-M, et al. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. Circulation 1997;95(12):2660–7.
41. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33(14):1787–847.
42. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA Guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). Circulation 2001;104(24):2996–3007.
43. Hunt SA, Abraham WT, Chin MH, et al. 2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the International Society for Heart and Lung Transplantation. J Am Coll Cardiol 2009;53(15):e1–90.
44. Bonow RO, Ganiats TG, Beam CT, et al. ACCF/AHA/AMA-PCPI 2011 performance measures for adults with heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures and the American Medical Association-Physician Consortium for Performance Improvement. Circulation 2012;125(19):2382–401.
45. Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. JAMA 2003;289(19):2534–44.
46. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008;358(18):1887–98.
47. Davis BR, Kostis JB, Simpson LM, et al. Heart failure with preserved and reduced left ventricular ejection fraction in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. Circulation 2008;118(22):2259–67.
48. Kjekshus J, Pedersen TR, Olsson AG, Faergeman O, Pyorala K. The effects of simvastatin on the incidence of heart failure in patients with coronary heart disease. J Card Fail 1997;3(4):249–54.
49. Scirica BM, Morrow DA, Cannon CP, et al. Intensive statin therapy and the risk of hospitalization for heart failure after an acute coronary syndrome in the PROVE IT-TIMI 22 study. J Am Coll Cardiol 2006;47(11):2326–31.
50. de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA 2004;292(11):1307–16.
51. Khush KK, Waters DD, Bittner V, et al. Effect of high-dose atorvastatin on hospitalizations for heart failure: subgroup analysis of the Treating to New Targets (TNT) study. Circulation 2007;115(5):576–83.
52. Strandberg TE, Holme I, Faergeman O, et al. Comparative effect of atorvastatin (80 mg) versus simvastatin (20 to 40 mg) in preventing hospitalizations for heart failure in patients with previous myocardial infarction. Am J Cardiol 2009;103(10):1381–5.
53. SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327:685–91.
54. Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 1992;327:669–77.
55. Yancy CW, Jessup M, Bozkurt B. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;128(16):e240–327.
56. Jong P, Yusuf S, Rousseau MF, et al. Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. Lancet 2003;361(9372):1843–8.
57. Arnold JM, Yusuf S, Young J, et al. Prevention of heart failure in patients in the Heart Outcomes Prevention Evaluation (HOPE) study. Circulation 2003;107(9):1284–90.
58. Fox KM; EUROPA Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet 2003;362(9386):782–8.
59. Lewis EF, Solomon SD, Jablonski KA, et al. Predictors of heart failure in patients with stable coronary artery disease: a PEACE study. Circ Heart Fail 2009;2(3):209–16.
60. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet 2001;357(9266):1385–90.
61. Colucci WS, Kolias TJ, Adams KF, et al. Metoprolol reverses left ventricular remodeling in patients with asymptomatic systolic

dysfunction: the reversal of ventricular remodeling with Toprol-XL (REVERT) trial. Circulation 2007;116(1):49–56.
62. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346(12):877–83.
63. He J, Ogden LG, Bazzano LA, et al. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch Intern Med 2001;161(7):996–1002.
64. Schocken DD, Benjamin EJ, Fonarow GC, et al. Prevention of heart failure: a scientific statement from the American Heart Association Councils on Epidemiology and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; and Functional Genomics and Translational Biology Interdisciplinary Working Group. Circulation 2008;117(19):2544–65.
65. Butler J, Kalogeropoulos A, Georgiopoulou V, et al. Incident heart failure prediction in the elderly: the health ABC heart failure score. Circ Heart Fail 2008;1(2):125–33.
66. Jessup M, Brozena S. Heart failure. N Engl J Med 2003;348(20):2007–18.
67. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325(5):293–302.
68. Lewis EF, Moye LA, Rouleau JL, et al. Predictors of late development of heart failure in stable survivors of myocardial infarction. J Am Coll Cardiol 2003;42(8):1446–53.
69. Velagaleti RS, Pencina MJ, Murabito JM, et al. Long-term trends in the incidence of heart failure after myocardial infarction. Circulation 2008;118(20):2057–62.
70. Ezekowitz JA, Kaul P, Bakal JA, et al. Declining in-hospital mortality and increasing heart failure incidence in elderly patients with first myocardial infarction. J Am Coll Cardiol 2009;53(1):13–20.
71. Jhund PS, Macintyre K, Simpson CR, et al. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. Circulation 2009;119(4):515–23.
72. Wolk MJ, Scheidt S, Killip T. Heart failure complicating acute myocardial infarction. Circulation 1972;45(5):1125–38.
73. Norris RM, Bensley KE, Caughey DE, Scott PJ. Hospital mortality in acute myocardial infarction. Br Med J 1968;3(5611):143–6.
74. Moye LA, Pfeffer MA, Wun C, et al. Uniformity of captopril benefit in the SAVE study: Subgroup Analysis. Eur Heart J 1994;15(Suppl B):2–8.
75. Steg PG, Dabbous OH, Feldman LJ, et al. Determinants and prognostic impact of heart failure complicating acute coronary syndromes: observations from the Global Registry of Acute Coronary Events (GRACE). Circulation 2004;109(4):494–9.
76. Sabatine MS, Morrow DA, de Lemos JA, et al. Evaluation of multiple biomarkers of cardiovascular stress for risk prediction and guiding medical therapy in patients with stable coronary disease. Circulation 2012;125(2):233–40.
77. Omland T, Sabatine MS, Jablonski KA, et al. Prognostic value of B-Type natriuretic peptides in patients with stable coronary artery disease: the PEACE Trial. J Am Coll Cardiol 2007;50(3):205–14.
78. Dunn FG, Ichikawa I, Pfeffer JM, et al. Renal and systemic hemodyanic effects of synthetic atrial natriuretic peptide in the anesthetized rat. Circ Res 1986;59:237–46.
79. deFilippi CR, de Lemos JA, Christenson RH, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. JAMA 2010;304(22):2494–502.
80. Velagaleti RS, Gona P, Larson MG, et al. Multimarker approach for the prediction of heart failure incidence in the community. Circulation 2010;122(17):1700–6.
81. Ky B, French B, Levy WC, et al. Multiple biomarkers for risk prediction in chronic heart failure. Circ Heart Fail 2012;5(2):183–90.
82. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. Circulation 2013;127(1):e6–245.
83. Heidenreich PA, Trogdon JG, Khavjou OA, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation 2011;123(8):933–44.
84. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail 2013;6(3):606–19.
85. Bleumink GS, Knetsch AM, Sturkenboom MCJM, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure: The Rotterdam Study. Eur Heart J 2004;25(18):1614–19.
86. Lloyd-Jones DM, Larson MG, Leip EP, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. Circulation 2002;106(24):3068–72.
87. Levy D, Larson MG, Vasan RS, et al. THe progression from hypertension to congestive heart failure. JAMA 1996;275(20):1557–62.
88. Chen J, Normand ST, Wang Y, Krumholz HM. National and regional trends in heart failure hospitalization and mortality rates for medicare beneficiaries, 1998–2008. JAMA 2011;306(15):1669–78.
89. Zannad F, Agrinier N, Alla F. Heart failure burden and therapy. Europace 2009;11 Suppl 5:v1–9.
90. Dunlay SM, Shah ND, Shi Q, et al. Lifetime costs of medical care after heart failure diagnosis. Circ Cardiovasc Qual Outcomes 2011;4(1):68–75.
91. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med 2002;347(18):1397–402.
92. Laribi S, Aouba A, Nikolaou M, et al. Trends in death attributed to heart failure over the past two decades in Europe. Eur J Heart Fail 2012;14(3):234–9.
93. Cowie MR, Fox KF, Wood DA, et al. Hospitalization of patients with heart failure. A population-based study. Eur Heart J 2002;23(11):877–85.
94. McKelvie RS, Moe GW, Cheung A, et al. The 2011 Canadian Cardiovascular Society heart failure management guidelines update: focus on sleep apnea, renal dysfunction, mechanical circulatory support, and palliative care. Can J Cardiol 2011;27(3):319–38.
95. Moser DK, Yamokoski L, Sun JL, et al. Improvement in health-related quality of life after hospitalization predicts event-free survival in patients with advanced heart failure. J Card Fail 2009;15(9):763–9.
96. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the COoperative North Scandinavian ENalapril SUrvival Study (CONSENSUS). N Engl J Med 1987;316(23):1429–35.
97. Braunwald E. Heart failure. JACC Heart Fail 2013;1(1):1–20.
98. Heart Failure Society of America, Lindenfeld J, Albert NM, et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. J Card Fail 2010;16(6):e1–194.
99. Braunwald E. The management of heart failure: the past, the present, and the future. Circ Heart Fail 2008;1(1):58–62.
100. Solomon SD, Dobson J, Pocock S, et al. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. Circulation 2007;116(13):1482–7.
101. Krumholz HM, Lin Z, Keenan PS, et al. Relationship between hospital readmission and mortality rates for patients hospitalized with acute myocardial infarction, heart failure, or pneumonia. JAMA 2013;309(6):587–93.
102. Adams KF, Jr., Zannad F. Clinical definition and epidemiology of advanced heart failure. Am Heart J 1998;135(6 Pt 2 Su):S204–15.
103. Jacobellis v. Ohio, 378 U.S. 184.
104. Ammar KA, Jacobsen SJ, Mahoney DW, et al. Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community. Circulation 2007;115(12):1563–70.
105. Costanzo MR, Mills RM, Wynne J. Characteristics of "Stage D" heart failure: insights from the Acute Decompensated Heart Failure

National Registry Longitudinal Module (ADHERE LM). Am Heart J 2008;155(2):341–9.
106. DiBardino DJ. The history and development of cardiac transplantation. Tex Heart Inst J 1999;26(3):198–205.
107. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352(3):225–37.
108. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350(21):2140–50.
109. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352(15):1539–49.
110. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361(14):1329–38.
111. Tang AS, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 2010;363(25):2385–95.
112. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med 2001;345(20):1435–43.
113. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009;361(23):2241–51.
114. Schou M, Gustafsson F, Videbaek L, et al. Extended heart failure clinic follow-up in low-risk patients: a randomized clinical trial (NorthStar). Eur Heart J 2013;34(6):432–42.
115. Stevenson LW, Pagani FD, Young JB, et al. INTERMACS profiles of advanced heart failure: the current picture. J Heart Lung Transplant 2009;28(6):535–41.
116. Allen LA, Stevenson LW, Grady KL, et al. Decision making in advanced heart failure: a scientific statement from the American Heart Association. Circulation 2012;125(15):1928–52.
117. Konstam MA, Executive Council of the Heart Failure Society of America. Heart failure training: a call for an integrative, patient-focused approach to an emerging cardiology subspecialty. J Am Coll Cardiol 2004;44(7):1361–2.
118. Konstam MA, Jessup M, Francis GS, et al. Advanced heart failure and transplant cardiology: a subspecialty is born. J Am Coll Cardiol 2009;53(10):834–6.
119. <http://www.abim.org/specialty/advanced-heart-failure-transplant-cardiology.aspx>.

CHAPTER 2

Cell biology of heart failure

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Introduction

Though the syndrome of congestive heart failure (CHF) can arise from a variety of different pathologic circumstances, this syndrome is always characterized by (indeed defined by) deterioration of cardiac pump function. Cardiac myocytes are the only cells in the heart capable of the cyclic active force generation and relaxation required for the pump function of the heart. Based on current estimates, the normal adult human left ventricle (LV) is comprised of more than 4 billion cardiac myocytes.[1] In many etiologies of heart failure, there is a reduction in this normal number of cardiac myocytes within the heart. This reduction may occur via a sudden ischemic event triggering myocardial necrosis or via alternative cell death pathways, such as apoptosis and autophagy, resulting from chronic pathologic stress. In addition to quantitative changes of cardiac myocytes (generally reductions), the syndrome of heart failure is consistently associated with qualitative changes in the cardiac myocytes.

Pathologic myocardial remodeling describes the multifaceted process in which gross changes in the morphology of the heart are accompanied by a variety of ultimately maladaptive changes at the tissue, cellular, and subcellular levels in response to disease-associated changes in biomechanical and biochemical stimuli. At the organ level, characteristics of remodeling typically include increases in myocardial mass, changes in the ratio of wall thickness to chamber volume, and other shape changes that can affect pump function, energy utilization, and the risk of unfavorable clinical sequelae including valvular dysfunction, heart failure, arrhythmias, and thromboembolism. In patients with LV systolic dysfunction, pathologic remodeling typically includes an increase in LV chamber volume, a transition from the normal elliptical shape of the LV to a more globular, spherical shape, and a decreased ejection fraction (LVEF). At the cellular level, the myocytes become longer and changes in calcium handling and β-adrenergic signaling cause changes in contractility and reductions in contractile reserve. These pathologic abnormalities in cellular morphology and function are also associated with, and often driven by, changes in intracellular signaling and energy metabolism. In many instances, adaptations to chronic biomechanical and neurohumoral stress or changes in availability of key substrates elicit activation of one or more cell death pathways that may further propagate the myocardial dysfunction and heart failure syndrome.

Though there is ongoing debate about which changes might be adaptive versus maladaptive, the qualitative changes in cardiac myocytes in failing hearts ultimately involve virtually every aspect of cell biology and profoundly impact both organ-level remodeling and the pump function of failing hearts. To better elucidate these important processes and the therapeutic opportunities they provide, this chapter describes the triggers, phenomena, and mechanisms associated with the transitions away from normal cardiac myocyte structure and function during pathologic remodeling of the heart. In many cases these transitions involve an increase in cell and organ size, referred to as pathologic hypertrophy. This chapter considers morphologic adaptations of cardiac myocytes, the regulation of cardiac contractility, cardiac metabolism, and alternative cell death pathways activated in failing hearts. In each section, we consider both normal biology and the molecular determinants and signaling pathways contributing to pathologic adaptations, and highlight opportunities for salutary therapeutic interventions. Finally, we highlight the reversibility of cardiac myocyte hypertrophy and dysfunction that has been demonstrated in in recent years. These reverse remodeling phenomena demonstrate the substantial plasticity of the severely failing heart, provide insights into factors driving and sustaining pathologic adaptations and attest to the potential benefit of therapeutic interventions targeting the failing heart.

Cardiac myocyte hypertrophy

Normal cardiac myocyte morphology

The billions of cardiac myocytes and other cell types within the heart, the cardiac conduction system, the full coronary vascular tree, and the extracellular matrix are arranged in a complex, three-dimensional structure that is well-suited to the primary function of the heart, namely contraction and relaxation to promote efficient pumping of blood to the lungs (RV) and other organs (LV). Within this complex structure, individual cardiac myocytes are arranged as an integrated syncytium such that each myocyte is in contact with several other myocytes, other cell types, multiple capillaries and an extracellular matrix that helps maintain structural integrity and coordinated contraction. As illustrated in Figure 2.1,[2] cardiac myocytes are generally rod-shaped striated cells with surface irregularities that form step-offs at the locations of contact with other cardiac myocytes. Within an individual adult heart there is great variation among the size of the constituent cardiac myocytes, which range from 50 to over 200 μm in length, from 10 to 50 μm in width and from 7500 to over 40 000 μm^3 in volume.[3] Across a variety of mammalian species, the *average* length/width ratio of normal cardiac myocytes is fairly consistent, between 7/1

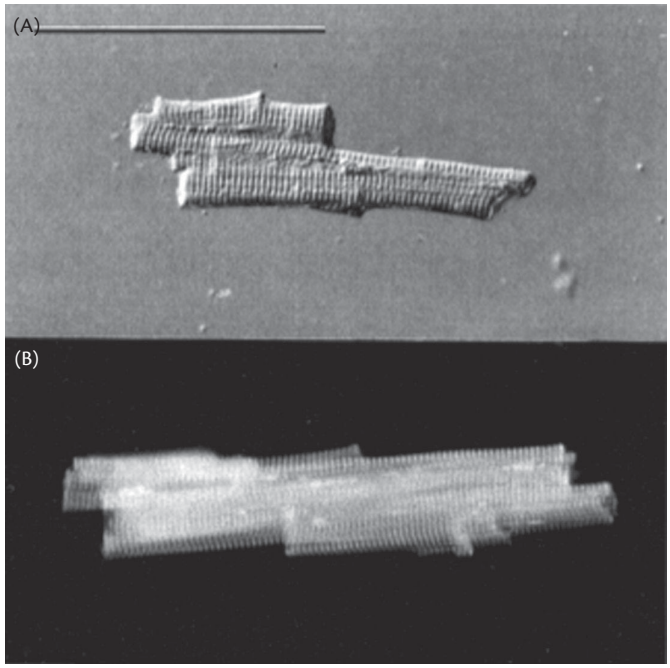

Fig. 2.1 (A) Typical isolated cardiac myocyte from a nonfailing human left ventricle. Nomarski optics; bar = 100 µm. (B) Isolated myocyte from the left ventricle of a patient with ischemic cardiomyopathy. Cell is labeled with rhodamine–phalloidin to show actin (same magnification as panel a).
Gerdes AM, Kellerman SE, Moore JA, Muffly KE, Clark LC, Reaves PY, Malec KB, McKeown PP, Schocken DD. Structural remodeling of cardiac myocytes in patients with ischemic cardiomyopathy. Circulation. 1992; 86(2):426–30.

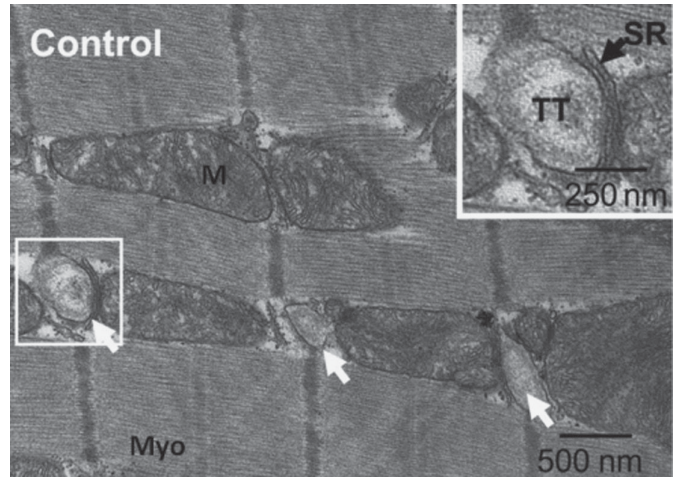

Fig. 2.2 Ultrastructural characterization of cardiac myocytes.
Zhang HB1, Li RC, Xu M, Xu SM, Lai YS, Wu HD, Xie XJ, Gao W, Ye H, Zhang YY, Meng X, Wang SQ. Ultrastructural uncoupling between T-tubules and sarcoplasmic reticulum in human heart failure. Cardiovasc Res. 2013 May 1;98(2):269–76.

and 9/1, despite wide differences in the number of cardiac myocytes within the heart. In addition, the cross-sections of most cardiac myocytes are elliptical rather than round. As shown in Figure 2.2,[4] ultrastructural characterization of cardiac myocytes[5] reveals that the striated appearance of cardiac myocytes is derived from a repeating pattern of sarcomeres that are defined by the partially overlapping thick and thin myofilaments responsible for muscle shortening and force generation. Myofibrils comprise nearly half of the volume of mature cardiac myocytes, and an additional 35% of the volume is occupied by mitochondria that provide the chemical energy required for cardiac pump function. Ultrastructural examination also reveals extensive invaginations, called T-tubules, in the myocyte cell surface that allow the plasma membrane, and voltage-gated ion channels, to have access to the interior of the cardiac myocytes. T-tubules, in turn, are closely approximated to the intracellular sarcoplasmic reticulum where large intracellular stores of Ca^{2+} are released and resequestered to activate and deactivate myofilament interactions, as discussed below.

Abnormal cardiac myocyte morphology

Though normal adult cardiac myocytes exhibit considerable variation in size and shape, there are characteristic changes observed in diseased hearts that contribute to cardiac remodeling at the whole-organ level. For example, cardiac myocytes from dilated failing human hearts due to either ischemic or nonischemic cardiomyopathy exhibit nearly a 50% increase in average myocyte length but only a 20% increase in average cell width and no significant change in average cell thickness.[3] As cardiac myocyte lengthening occurs, there is no change in average sarcomere length, indicating that sarcomeres are added in series to produce the increase in average myocyte length. Because disproportionate cardiac myocyte lengthening is a fundamental contributor to decreases in relative wall thickness, and associated increases in wall stress, the addition of sarcomeres in series represents a potential driving mechanism for progression of cardiac overload and dysfunction over time.

In contrast, in hearts with concentric hypertrophy with normal chamber size due to aortic stenosis or hypertension, there is no significant increase in average myocyte length, but myocyte cross-sectional area is nearly double what is observed in normal hearts.[6,7,8] However, when hypertensive rats progress to heart failure and decompensation with chamber dilation, length steadily increases in parallel with the increases in chamber volume.[6] Observing that the initial increase in relative wall thickness in response to sustained increases in systolic pressure loading effectively normalizes systolic wall stress, Grossman and colleagues speculated that this type of hypertrophy is adaptive.[9] However, this concept of adaptive hypertrophy is challenged by subsequent studies in which transgenic mice incapable of developing concentric hypertrophy exhibited improved cardiac function and better survival despite significantly greater wall stress following sustained pressure overload induced by aortic banding.[10]

Physiologic hypertrophic signaling in myocardium

Several different signaling pathways have been implicated in driving cardiac myocyte hypertrophy, but their relative contributions remain uncertain. Nevertheless, there is strong evidence that the hypertrophy of cardiac myocytes that occurs during maturation, pregnancy or following chronic exercise training, labeled "physiologic hypertrophy," involves signaling pathways that are distinct from those involved in the responses to pressure overload or myocardial infarction, labeled "pathologic hypertrophy," as illustrated in Figure 2.3.[11] Most importantly, at the organ level, cardiac function associated with physiologic hypertrophy is essentially normal, or even enhanced,[12] and associated with enhanced capacity for both oxidative and glycolytic metabolism that is distinct from

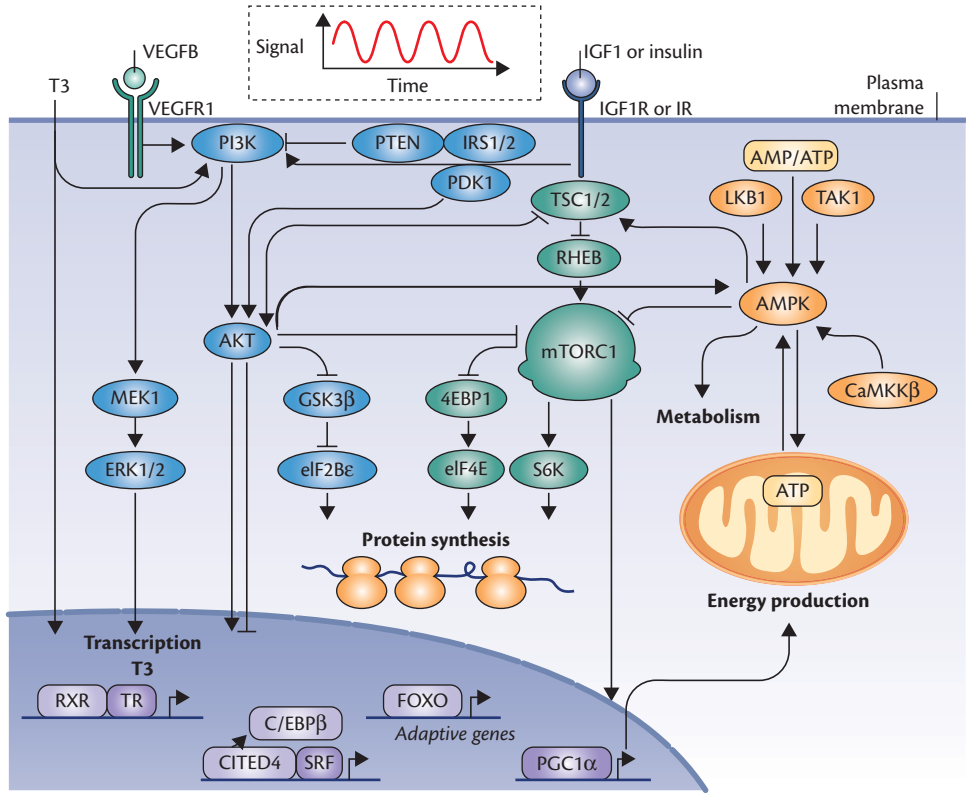

Fig. 2.3 Physiologic hypertrophy is an adaptive form of cardiac hypertrophy. The figure depicts central signaling pathways of physiologic hypertrophy discussed in the text. Physiologic hypertrophy is initiated by intermittent signals of triiodothyronine (T3), vascular endothelial growth factor B (VEGFB), insulin, and insulin-like growth factor 1 (IGF1), as illustrated by the oscillating curve. The growth hormones activate membrane-localized tyrosine kinase receptors (VEGF receptor 1 (VEGFR1), IGF1 receptor (IGF1R), or insulin receptor (IR)) and nuclear receptors (thyroid hormone receptor (TR)), which trigger intracellular signaling pathways specific to physiologic hypertrophy. These signaling pathways regulate the transcription of adaptive genes, protein synthesis, metabolism, and energy production. The growth signals centre on common signaling branches controlled by ERK1/2, PI3K, AKT, and mTOR complex 1 (mTORC1), whereas AMPK governs metabolic adaptive reprogramming. 4EBP1, eukaryotic translation initiation factor 4E-binding protein 1; C/EBPβ, CCAAT/enhancer binding protein-β; CaMKKβ, calcium/calmodulin-dependent protein kinase kinase-β; CITED4, CBP/p300 interacting transactivator 4; eIF2Bε, eukaryotic translation initiation factor 2Bε; FOXO, forkhead box O; GSK3β, glycogen synthase kinase 3β; IRS1/2, insulin receptor substrate 1 or 2; LKB1, liver kinase B1; PDK1, phosphoinositide-dependent protein kinase 1; PGC1α, peroxisome proliferator-activated receptor-γ coactivator 1α; RHEB, RAS homologue enriched in brain; RXR, retinoic acid receptor; S6K, S6 kinase; SRF, serum response factor; TAK1, transforming growth factor β-activated kinase 1; TSC1/2, tuberous sclerosis complex 1 or 2.

the impaired contractile reserve and increased dependence on glycolytic metabolism characteristic of pathologic myocardial hypertrophy.[13] The fact that maturation, exercise, and pregnancy trigger functional manifestations that are qualitatively different from those observed following pathologic stress indicates that there is a distinct set of physiologic sensing and signaling pathways involved with physiologic hypertrophy. As reviewed by Maillet et al., physiologic hypertrophy appears to be initiated by thyroid hormone, insulin, growth hormone, and insulin-like growth factor (IGF1),[11] with thyroid hormone and IGF1 most clearly involved with early postnatal maturational heart growth,[14,15] and insulin signaling involved with maintaining nonpathologic patterns of gene expression and metabolism.[11]

Growth hormone and IGF1 appear to be particularly important for exercise-induced, physiologic cardiac hypertrophy. In compelling studies using mouse models, Wilkins and colleagues demonstrated that IGF1 signaling through phosphoinositide 3-kinase and Akt mediate the physiologic cardiac hypertrophy associated with exercise.[11,16] Indeed, in transgenic mice, overexpression of the IGF1 receptor without exercise-induced cardiac hypertrophy was characterized by an increase in cardiac myocyte volume, absence of histopathology, and increased systolic function at 3 and 10 months of age.[17] Conversely, mice with IGF receptor deletion were resistant to exercise-induced hypertrophy.[18] In fact, IGF1 signaling is actively suppressed in response to pathologic stimuli such as chronic pressure overload and myocardial infarction.[11,16] These results strongly support the centrality of IGF1-dependent signaling to the physiologic growth of the heart.

Pathologic cardiac myocyte hypertrophy

A variety of factors can trigger pathologic cardiac myocyte hypertrophy with features that are distinct from the physiologic hypertrophy associated with exercise or pregnancy. The factors capable of triggering pathologic hypertrophy include biomechanical overload (either increased preload or afterload), neurohumoral mediators, and inflammation. Among neurohumoral mediators, those particularly implicated in triggering pathologic cardiac myocyte growth include catecholamines, angiotensin II, and endothelin. Among inflammatory cytokines most implicated in cardiac myocyte hypertrophy are interleukins IL-1β and IL-6 and tumor necrosis factor

alpha (TNFα).[19,20] In many clinical situations, these factors can coexist and overlap, with more than one alternative pathway being activated at the same time, such as when neurohumoral activation triggers vasoconstriction and increased afterload or inflammatory responses in addition to their direct effects on cardiac myocyte growth. Nevertheless, in the next few sections we will separately consider the mechanosensing and signaling involved with sustained biomechanical overload and the agonist-triggered signaling involved with sustained stimulation by neurohumoral or inflammatory mediators. Of note, several of these signaling pathways affect not only cell growth and cell shape, but also affect characteristic pathologic features of hypertrophied and failing cardiac myocytes including contractile dysfunction, abnormal gene expression, metabolic abnormalities, and the activation of cellular death pathways.

Transduction of biomechanical overload

The factor most consistently linked with pathologic cardiac myocyte hypertrophy in clinical settings is sustained biomechanical overload, such as occurs in patients with hypertension, valvular heart disease (inducing excessive preload and/or afterload), and antecedent myocardial infarction (MI). In the case of MI, the surviving myocytes are subjected to increased biomechanical stress as a consequence of expansion and extension of the infarction producing increased wall stress and the requirement of maintaining adequate pump function despite a substantial reduction in myocyte number. In general, the severity of biomechanical overload is correlated with the severity of pathologic hypertrophy manifested as increased myocardial mass at the organ level and increased cardiac myocyte size at the or cellular level.

There are multiple mechanosensing systems that may regulate physiologic and pathologic hypertrophy through direct load-sensing mechanisms within cardiomyocytes. For example, stretch-activated, transient receptor potential (TRP) ion channels that permit passage of calcium and other cations could trigger activation of calcium-dependent myocyte growth processes. In particular, the TRPC1 and TRPC6 isoforms have been directly implicated in regulating cardiac hypertrophy in response to mechanical stretch.[21,22] Accordingly, ligands for these receptors represent a potential target for regulating upstream responses to biomechanical overload. Because they are attached to both myocytes and the extracellular matrix components like fibronectin, collagen and laminin, integrins are another family of mechnosensing proteins that could mediate stretch-induced signaling in myocytes directly or via interactions with neighboring fibroblasts. Finally, several sarcomeric proteins are potential candidates for primary mechanosensing involved with growth signaling in cardiac myocytes, including muscle LIM protein (MLP), telethonin, myopalladin, palladin, actinin-associated LIM protein (ALP), cardiac ankyrin repeat protein (CARP), ankyrin, nebulette, obscurin, and titin. Of these, the giant molecule titin is a particularly interesting candidate because it directly regulates the distention of sarcomeres and binds many other sarcomeric proteins and regulators. In fact, recent reports indicate that titin mutations may account for as many as 25% of familial dilated cardiomyopathies.[23]

β-Adrenergic signaling in cardiac myocyte hypertrophy

Despite its essential role in augmenting cardiac output exercise and other acute physiologic stress settings, sympathetic activation and β-adrenergic signaling has distinctly pathologic effects on cardiac myocyte structure, function, and gene expression. β-Adrenergic receptors are a subclass of G-protein-coupled receptors that trigger activation of adenylyl cyclase, generation of cAMP, and phosphorylation of intracellular target proteins via protein kinase A (PKA)[24] Both in-vitro studies in isolated cardiac myocytes[25] and in-vivo studies employing transgenic mice with overexpression of the cardiac β1-adrenergic receptor,[26] Gs,[27] and PKA[28] demonstrate that this classical signaling cascade triggers growth of cardiac myocytes. Though the details of downstream events remains uncertain, there is strong evidence supporting the involvement of the cAMP response binding protein (CREB) and the cAMP response element modulator (CREM) as mediators of the gene expression changes producing cellular hypertrophy in response to sustained β-adrenergic signaling within cardiac myocytes.[24,29] The clinical importance of cardiac myocyte hypertrophy mediated through β_1-AR signaling is supported by the well-established cardioprotective effects of β-blockers. The salutary effects of the new class of biased β-arrestin agonists that block the classical adenyl cyclase/cAMP/PKA signaling downstream of the β1-AR, but agonize the cardioprotective β-arrestin-dependent transactivation of epidermal growth factor receptor (EGFR) signaling also support the pathogenic role of sustained catecholamine stimulation.[30]

Calcium-dependent signaling in cardiac myocyte hypertrophy

Another effect of chronic β_1-AR stimulation is an increase in intracellular Ca^{2+} that itself activates downstream signaling factors including calcineurin and calmodulin-dependent protein kinase II (CaMKII) (see Figure 2.1). Calcineurin is a protein phosphatase that dephosphorylates the nuclear factor of activated transcription (NFAT) to trigger its translocation to the nucleus where it is a potent activator of numerous prohypertrophic genes.[31] Interestingly, the same studies demonstrating that exercise induces IGF1-mediated physiologic hypertrophy also found that exercise is associated with *suppression* of calcineurin–NFAT signaling. Conversely, chronic pressure overload or MI induce calcineurin–NFAT activation with suppression of IGF1 signaling. Constitutive activation of calcineurin in transgenic mice produces massive cardiac hypertrophy,[16] whereas a mouse lacking a gene encoding the catalytic subunit of calcineurin (CnAβ) has substantially reduced hypertrophy in response to pressure overload or infusion of cathecholamines or angiotensin II.[32] From a therapeutic standpoint, adenovirus-mediated gene transfer of endogenous calcineurin inhibitors like Cabin/Cain that inhibit cardiac calcineurin activity likewise reduce hypertrophy in response to pressure overload without reducing aortic pressure.[33]

There is also increasing evidence implicating the multifunctional CaMKII as a central mediator in cardiac myocyte hypertrophy. As recently reviewed,[34] CaMKII is a serine–threonine kinase that has a wide variety of actions within the heart including effects on action potential waveshape and arrhythmogenesis, excitation–contraction coupling, transcriptional regulation of myocyte growth, and cardiac myocyte apoptosis pathways. Though there are several isoforms of CaMKII, the predominant form of CaMKII in myocardium appears to be CaMKIIδ. Because CaMKII is activated in response to signals generated through several different G-protein-coupled receptors (GPCRs), it has a key role in mediating the hypertrophic effects of humoral agents such as norepinephrine (NE), phenylephrine (PE), and endothelin (ET-1). This activation occurs through Ca^{2+} release from nuclear stores sensitive to inositol trisphosphate (InsP3).[35]

Both in-vitro data using neonatal rat myocytes and transgenic mouse models strongly support a pivotal role for CaMKII in mediating the effects of GPCR agonists on cardiac myocyte hypertrophy.[34] Moreover, rapid and sustained CaMKII activation via GPCR activation is also triggered by transverse aortic constriction (TAC) in mice suggesting that this pathway is involved in load-induced cardiac myocyte hypertrophy.[36] Further mechanistic studies have demonstrated that the hypertrophic effects of either CaMKIIδB or δC isoforms are mediated by transactivation of myocyte enhancer factor 2 (*MEF2*) gene expression and histone deacetylase 4 (HDAC4) translocation from nucleus to cytoplasm, indicating that either isoform can stimulate HDAC4 phosphorylation but only the CaMKIIδC isoform is involved with changes in cardiac myocyte Ca^{2+} handling.[37] In fact, preclinical studies employing pharmacologic inhibition of calmodulin/CaMKIIδB activity reported improved cardiac function in mice subjected to TAC in association with correction of the imbalance between NCX1 and SERCA2 that is otherwise observed in this model and in humans with severe heart failure.[38]

MAPK signaling in cardiac myocyte hypertrophy

Mitogen-activated protein kinase (MAPK) cascades are highly conserved intracellular signal transduction pathways with diverse developmental and regulatory functions in the heart. MAPKs are typically divided into four major subfamilies, namely extracellular signal-regulated kinases (ERK1/2), c-Jun N-terminal kinases (JNK), p38 MAP kinases, and ERK5 kinase. As shown in Figure 2.4,[39] for each subfamily there is a three-tiered kinase cascade in which a MAPK kinase kinase activates a MAPK kinase which, in turn, activates the MAPK through serial phosphorylation. As well reviewed,[39] ERK1/2 is activated by various stimuli including growth factors, serum, phorbol esters, GPCRs, inflammatory cytokines, and microtubule disorganization.[40,41] ERK5 is activated by these same factors and also by oxidative stress and UV irradiation.[42] JNK and p38 are stress-activated kinases that respond most robustly to inflammatory cytokines and cellular stresses such as heat shock, hyperosmolarity, ischemia–reperfusion, UV radiation, oxidizing agents, DNA damage, and endoplasmic reticulum (ER) stress,[43,44] and less intensely by growth factors and GPCRs.

Each MAPK family has been implicated in cardiac myocyte hypertrophy, but definitive evidence supporting a central role has varied. For ERK1/2, overexpression and correlative approaches have implicated a role in cardiac hypertrophy,[39] but Purcell et al. found that reduced in ERK activity is not sufficient to prevent hypertrophy in response to various forms of hypertrophic stimuli in vivo.[45] For JNK, studies have been even more conflicting and the composite data from in-vitro and in-vivo studies suggests that JNK signaling tends to be antihypertrophic by excluding NFAT from the nucleus and upregulating JunD.[39] For p38, targeted activation of p38 in vivo did not induce cardiac hypertrophy.[46] On the other hand, there is fairly compelling data supporting a role for ERK5 in promoting eccentric cardiac hypertrophy. In-vitro studies indicated that activation of ERK5 signaling induces elongation of cultured myocytes and increase in serial sarcomere assembly, while blockade of ERK5 signaling prevented cellular elongation.[47] The unique role for ERK5 in this particular type of cell hypertrophy is supported by in-vivo studies in which transgenic overexpression of the MEK5β splice variant,[47] but not MEK5α,[48] induces ventricular thinning and dilation without a loss of cells consistent with eccentric hypertrophy. Further extending these studies, recent studies in a canine model of mitral regurgitation have also reported increased activated ERK5 in caveolae as eccentric hypertrophy develops.[49] Thus, despite significant variation among the MAPK pathways, there is increasing support for a functionally significant role for ERK5 signaling in eccentric hypertrophy that may be targetable via specific inhibitors.[39]

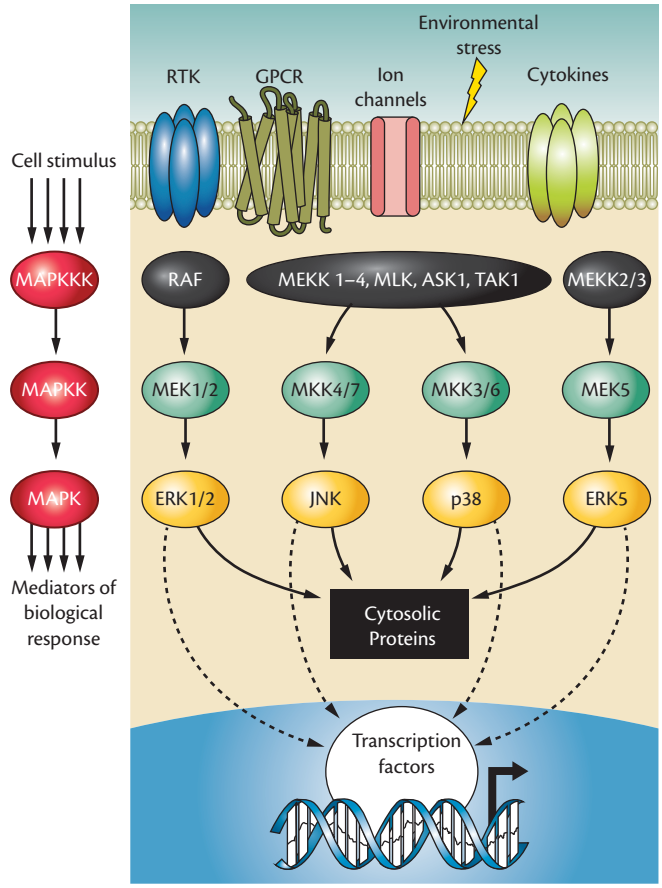

Fig. 2.4 Canonical mitogen-activated protein kinase (MAPK) signaling. MAPKs are prototypically activated by canonical three-tiered sequential phosphorylation events. The most well-known MAPKKK and MAPKK are listed for each MAPK; however, this is only a small representation of all identified upstream kinases. Furthermore, multiple steps may exist between the cell stimulus and activation of the MAPKKK and between activation of the MAPK and the biological response. Based on Rose BA, Force T, Wang Y. Mitogen-activated protein kinase signaling in the heart: angels versus demons in a heart-breaking tale. Physiol Rev. 2010; 90(4):1507–46.

Protein kinase C signaling in cardiac hypertrophy

Protein kinase C (PKC) is a family of serine–threonine protein kinases. In cardiac myocytes, PKC signaling is typically initiated by binding of specific plasma membrane GPCRs by endogenous ligands such as angiotensin II (AngII), phenylephrine (PE), and endothelin-1 (ET1) or exogenous agonists like phorbol myristate acetate (PMA). There are over a dozen different PKC isozymes that are grouped into different subtypes based on whether their signaling depends on diacylglycerol (DAG), calcium, or neither. Several PKC isoforms are expressed in heart, but there are significant interspecies differences that may affect the applicability of findings from one species to another.[50] In humans, the calcium-dependent isozymes α, βI, and βIIPKC, reside predominantly in the ventricle, δ