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A. E. Berezin, V. A. Vizir, O. V. Demidenko

CARDIOVASCULAR DISEASE

(«INTERNAL MEDICINE» MODULE 2)

PART 2

The executive task force for students of medical faculty of 5th cource

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Reviewers:

V. V. Syvolap - MD, PhD, professor, Head of Department of Propedeutics of Internal Diseases with the Course of Patients' Care, Zaporizhzhia State Medical University;

O. V. Kraydashenko - MD, PhD, professor, Head of Department of Clinical Pharmacology, Pharmacy and Pharmacotherapy with the Course of Cosmetology, Zaporizhzhia State Medical University.

Authors:

A. E. Berezin - MD, PhD, professor, Department of Internal Diseases 2;

V. A. Vizir - MD, PhD, professor, Department of Internal Diseases 2;

O. V. Demidenko -MD, PhD, Head of Department of Internal Diseases 2.

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Berezin A. E.

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The executive task force is provided for students of 5th courses of medical faculties for helping to study of some topics in the fields of cardiovascular diseases incorporated into the discipline «Internal Medicine». There is the information about the most important topics regarding diagnosis of cardiac diseases.

CONTENT

Index of acronyms

ACE	angiotensin-converting enzyme
ACEI	ACE inhibitors
ACEI	angiotensin-converting enzyme inhibitor
ACM	alcoholic cardiomyopathy
ACS	acute coronary syndrome
AHA	American Heart Association
AHF	acute heart failure
AHMD	alcoholic heart muscle disease
ANP	atrial natriuretic peptide
APA	aldosterone-producing adenomas
APAH	associated pulmonary arterial hypertension
APCs	atrial premature complexes
ARB	angiotensin receptor blockers
ARVC	arrhythmogenic right ventricular cardiomyopathy
ARVD	arrhythmogenic right ventricular dysplasia
ASD	atrial septal defect
AV	atrioventricular
AVNRT	Atrioventricular Nodal Reentrant Tachycardia
BAS	balloon atrial septostomy
BB	beta-adrenoblockers
BNP	B-type natriuretic peptide
BP	blood pressure
Bpm	beats per minute;
BSAC	British Society for Antimicrobial Chemotherapy
CA	calcium antagonists
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CCB	calcium channel blocker
CCSC	Canadian Cardiovascular Society Classification
CHD	coronary heart disease
CHF	chronic heart failure
CI	cardiac index
CK	creatine kinase
CMR	cardiac magnetic resonance imaging
CNS	central nervous system
CO	cardiac output
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CPR	cardiopulmonary resuscitation
CRP	C-reactive protein
CT	computed tomography
CTD	connective tissue disease
CTEPH	chronic thromboembolic pulmonary hypertension
CV	cardiovascular diseases

CVP	central venous pressure
CVVH	continuous veno-venous hemofiltration
DAD	delayed after-depolarization
DCM	dilated cardiomyopathy
DIC	disseminated intravascular coagulation
DM	diabetes mellitus
DOC	deoxycorticosterone
EA	electrical axis
EAD	early afterdepolarization;
ECG	electrocardiogram
EF	ejection fraction
EnaC	epithelial Na^+ channel
ERA	endothelin receptor antagonist
ESC	European cardiology Association
ESRD	renal failure;
GFR	glomerular filtration rate
GP	glycoprotein
GRA	glucocorticoid-remediable aldosteronism
HACEK	group organisms: Haemophilus species, Actinobacillus actinomyce-temcomitans, Cardiobacterium hominis, Eikenella species, Kingella kingae.
HCM	hypertrophic cardiomyopathy
HDL- C	high-density lipoprotein cholesterol
HF	heart failure
HIV	human immunodeficiency virus
i.v.	intravenous
IABC	intra-aortic balloon counter-pulsation
ICD	implantable cardioverter-defibrillator
IDC	implantable defibrillator-cardioverter
IE	infective endocarditis
IGF	insulin-like growth factor
INR	international normalized ratio
IPAH	idiopathic pulmonary arterial hypertension
ISH	isolated systolic hypertension
IVDU	Intravenous drug use
IVUS	intravascular ultrasound
JET	functional ectopic tachycardia
LA	left arm
LAFB	left anterior fascicular block
LBBB	left bundle branch block
LL	left leg
LMWH	low molecular weight heparin
LMWH	low molecular weight heparin
LQTS	long-QT syndrome
LV	left ventricle / ventricular

LVH	left ventricular hypertrophy
LVNC	left ventricular non-compaction
LVOT	left ventricular outflow tract
MAC	mitral annular calcification
MBC	minimum bactericidal concentration
MHC	myosin heavy chain
MI	myocardial infarction
MIC	minimal inhibitory concentration
MR	mitral regurgitation
MRI	magnetic resonance imaging
MVP	mitral valve prolapsed
NBTE	nonbacterial thrombotic endocarditis
NCCLS	USA National Commmittee for Clinical Laboratory Standards
NIPPV	non-invasive positive pressure ventilation
NO	nitric oxide
NOS	nitric oxide synthase
NSTEMI	non ST-elevation MI
NT-proBNP	N-terminal fragment of pro- brain natriuretic peptide
PA	pulmonary artery
PAC	pulmonary artery catheter
PAP	pulmonary arterial pressure
PCI	Percutaneous Coronary Intervention
PDEIs	phosphodiesterase inhibitors
PDGF	platelet-derived growth factor
PEA	pulmonary endarterectomy
PH	pulmonary hypertension
PHIRST	Pulmonary arterial Hypertension and ReSponse to Tadalafil
PJT	paroxysmal functional tachycardia
PK	pharmacokinetics
PK	pharmacokinetics
PNS	peripheral nervous system
PP	pulse pressure
PPCM	peripartum cardiomyopathy
PSVTs	paroxysmal supraventricular tachycardia’s
PVCs	premature ventricular complexes
PVD	peripheral vascular disease
PVE	prosthetic valve endocarditis
PVOD	pulmonary veno-occlusive disease
PVR	pulmonary vascular resistance
PVT	prosthetic valve thrombosis
PWP	pulmonary wedge pressure
RA	right arm
RAAS	rennin-angiotensin-aldosterone system
RAP	right atrial pressure
RBBB	right bundle branch block

RCM	restricted cardiomyopathy
RCT	randomized controlled trial
RHC	right heart catheterization
RV	right ventricle/ventricular
SAECG	signal-averaging electrocardiography
$SERCA^2$	sarcoplasmic reticulum Ca^{2+} adenosine triphosphatase pump
6MWT	6-minute walking test
SNP	sodium nitroprusside
SNS	sympathetic nervous system
SVC	superior vena cava
SVT	supraventricular tachycardia
t.i.d.	three times a day
TAPSE	tricuspid annular plane systolic excursion
TDI	tissue Doppler imaging
TEE	transesophageal echography
TEE	transesophageal echography
TF	tissue factor
TPG	transpulmonary pressure gradient (mean PAP – mean PWP)
TTE	transthoraxic echography
VA	ventriculoatrial
VF	ventricular fibrillation
VPC	ventricular premature complexes
VSR	ventricular septal rupture
VT	ventricular tachycardia
WHO	World Health Organization
WHO-FC	World Health Organization functional class
WPW	Wolff-Parkinson-White syndrome

PREFACE

The task force is addressed to students of 5th course of medical university for helping to study of some parts of internal medicine in field of cardiovascsular diseases. It includes the use of contemporary tools for identification of congenital and acquired heart diseases, coronary artery disease, arterial hypertension, heart failure, arrhythmias, pericardial diseases etc., including objectives, laboratory studies, genetic investigations, biopsy materials, X-ray, multidetector CT, angiography, MRI procedures. Etiology and pathophisiology are discussed also separately for each of cardiovascular disorders. Diagnostic algorithm and procedures choosing are considered obligatory with an elucidation of contemporary management and prevention of cardiovascular diseases. This book has been written in a concise and easy assimilable style to enable rapid understanding of the cardiovascular diseases. It has been structured in a format that incorporates information for quickly reminding and squeezes are applied also. Hopefully, in some way, all of the effort and expertise brought together here will help advance this field.

Authors.

CHAPTER 1

PRIMARY AND SECONDARYARTERIAL HYPERTENSION

Preface.

Hypertension is the most common disease-specific reason for a physician. It is currently among the leading causes of morbidity and mortality in the world and is expected to have an even greater impact on the health of the public as more of the world becomes developed. In addition to the morbidity and mortality directly attributable to hypertension, high blood pressure (BP) is a powerful risk factor (a condition or characteristic of an individual or a population) that in this case increases the likelihood that an individual or population will develop a wide variety of cardiovascular (CV) diseases. Hypertension even has been associated with an increased risk of certain cancers. Some authors have failed to appreciate thisrelationship when attributing certain cancers to particular antihypertensive treatments. All health care providers routinely encounter patients whose BP is elevated. In patients with definite hypertension, the paramount consideration is the choice of treatment, but in an increasing number of individuals, lowering BP may be beneficial even if definite hypertension cannot be diagnosed. In the next decade, it is expected that more and more patients will become candidates for antihypertensive therapy, especially as trials demonstrate the benefits of treatment and pharmacologic approaches become safer and more effective. Furthermore, many citizens, perhaps of the majority of those over 40 years of age, who do not yet meet the criteria for pharmacologic treatment for hypertension will benefit from lifestyle modification, a presumably safe and cost-effective public health approach to reducing BP. Many of the lifestyle habits that lower BP or slow the rate of rise of BP probably should be incorporated into everyone's lifestyle very early.

Definition and classification of hypertension

Historically more emphasis was placed on diastolic than on systolic blood pressure as a predictor of cardiovascular morbid and fatal events. This was reflected in the early guidelines of the Joint National Committee which did not consider systolic blood pressure and isolated systolic hypertension in the classification of hypertension.

It was reflected further in the design of early randomized clinical trials which almost invariably based patient recruitment criteria on diastolic blood pressure values. However, a large number of observational studies has demonstrated that cardiovascular morbidity and mortality bear a continuous relationship with both systolic and diastolic blood pressures. The relationship has been reported to be less steep for coronary events than for stroke which has thus been labelled as the most important 'hypertension related' complication. However, in several regions of Europe, though not in all of them, the attributable risk, that is the excess of death due to an elevated blood pressure, is greater for coronary events than for stroke because heart disease remains the most common cardiovascular disorder in these regions. Furthermore, both systolic and diastolic blood pressures show a graded independent relationship with heart failure, peripheral artery disease and end stage renal disease. Therefore, hypertension should be considered a major risk factor for an array of cardiovascular and related diseases as well as for diseases leading to a marked increase in cardiovascular risk. This, and the wide prevalence of high blood pressure in the population, explain why in a WHO report high blood pressure has been listed as the first cause of death worldwide.

Classification of hypertension

Blood pressure has a unimodal distribution in the population as well as a continuous relationship with cardiovascular risk down to systolic and diastolic levels of 115–110 mmHg and 75–70 mmHg, respectively. This fact makes the word hypertension scientifically questionable and its classification based on cutoff values arbitrary. However, changes of a widely known and accepted terminology may generate confusion while use of cutoff values simplifies diagnostic and treatment approaches in daily practice. Therefore the classification of hypertension used in the 2007 ESH/ESC Guidelines has been retained (Tabl.1.1) with the following provisos:

1. when a patient's systolic and diastolic blood pressures fall into different categories the higher category should apply for the quantification of total cardiovascular risk, decision about drug treatment and estimation of treatment efficacy;

2. isolated systolic hypertension should be graded (grades 1,2 and 3) according to the same systolic blood pressure values indicated for systolic-diastolic hypertension. However, as mentioned above, the association with a low diastolic blood pressure (e.g. 60–70 mmHg) should be regarded as an additional risk;
3. the threshold for hypertension (and the need for drug treatment) should be considered as flexible based on the level and profile of total cardiovascular risk.

Table 1.1

Definition and classification of hypertension

Category	Systolic	-	Diastolic
Optimal	<120	and	<80
Normal	120–129	and/or	80-84
High normal	130–139	and/or	85-90
Grade 1 hypertension	140–159	and/or	90-99
Grade 2 hypertension	160–179	and/or	100-109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

Epidemiology and risk

Physicians generally do not concern themselves with reducing BP when it is elevated because of the specific clinical problems they can attribute to that elevation. Instead, hypertension is treated because of the increased risk of mortality and CV disease that results from having an elevated BP. These risks have been well documented in numerous epidemiologic studies, beginning with the Framingham Heart Study and many others in the 1950s and 1960s and extending to the present. More recently, meta-analyses of pooled data have confirmed the robust, continuous relationship between BP level and cerebrovascular disease and coronary artery disease (CAD) in both western and eastern populations. In addition, BP is directly related to left ventricular hypertrophy (LVH) and heart failure (HF), peripheral vascular disease (PVD), carotid atherosclerosis, renal disease, and "subclinical disease." The Framingham Heart Study has documented the fact that CV risk factors tend to cluster in hypertensives. Hypertensives are more likely to have dyslipidemias, especially elevated serum triglycerides and low levels of high-density lipoprotein cholesterol (HDL-C), and

type 2 DM. The common denominator may be insulin resistance, perhaps as a result of the frequent association of hypertension and obesity. In the last several years, it has become increasingly clear that the risks attributed to hypertension are much more strongly related to the level of systolic BP than to diastolic BP, especially in those over age 50 or 60 years. Some have argued that one should not measure diastolic BP other than perhaps to calculate pulse pressure (PP). Pulse pressure, the difference between systolic and diastolic BP, is an even better predictor of risk than is systolic BP in most of the epidemiologic studies done to date. A wide PP, unless it is a result of aortic insufficiency or an arteriovenous malformation, is a simple clinical indicator of stiffer and less compliant large central arteries and significant arterial damage. Data from the Framingham Heart Study cohort had showed that at all levels of systolic BP (even as low as 110 to 130 mmHg), risk is less with higher diastolic BPs. More recent analyses by this group have suggested that these findings may be relevant only in those over age 60, and so it is not appropriate to ignore those with elevated diastolic BP level if their systolic readings are not above normal. With the exception of hypertensive encephalopathy, it has long been felt that few, if any, clinical symptoms can be attributed to increased BP levels. This may have to be reevaluated, however, as newer and very well tolerated drugs are developed and as improved methods of assessing subtle symptoms are perfected.

Concept of total cardiovascular risk

For a long time, hypertension guidelines focused on blood pressure values as the only or main variables determining the need and the type of treatment. New concept is based on the fact that only a small fraction of the hypertensive population has an elevation of blood pressure alone, with the great majority exhibiting additional cardiovascular risk factors, with a relationship between the severity of the blood pressure elevation and that of alterations in glucose and lipid metabolism. Furthermore, when concomitantly present, blood pressure and metabolic risk factors potentiate each other, leading to a total cardiovascular risk which is greater than the sum of its individual components. Finally, evidence is available that in high risk individuals thresholds and goals for antihypertensive treatment, as well as other treatment strategies, should be

different from those to be implemented in lower risk individuals. In order diabetes, and individuals with severely elevated single risk factors. In all these conditions the total cardiovascular risk is high, calling for the intense cardiovascular risk reducing measures that will be outlined in the following sections. However, a large number of hypertensive patients does not belong to one of the above categories and identification of those at high risk requires the use of models to estimate total cardiovascular risk so as to be able to adjust the intensity of the therapeutic approach accordingly (Figure 1.1).

Figure 1.1

Stratification of CV Risk in four categories

	Blood pressure (mmHg)				
Other risk factors, OD or Disease	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1–2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more risk factors, MS, OD or Diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Established CV or renal disease	Very high added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

Several computerized methods have been developed for estimating total cardiovascular risk, i.e. the absolute chance of having a cardiovascular event usually over 10 years. However, some of them are based on Framingham data which are only applicable to some European populations due to important differences in the incidence of coronary and stroke events. More recently, a European model has become available based on the large data-base provided by the SCORE project. SCORE charts are available for high and low risk countries in Europe. They estimate the risk of dying from cardiovascular (not just coronary) disease over 10 years and allow calibration of

the charts for individual countries provided that national mortality statistics and estimates of the prevalence of major cardiovascular risk factors are known.

The distinction between high and very high risk categories has been maintained in the present guidelines, thereby preserving a separate place for secondary prevention, i.e. prevention in patients with established cardiovascular disease. In these patients, compared with the high risk category, not only can total risk be much higher, but multidrug treatment may be necessary throughout the blood pressure range from normal to high. The dashed line drawn in Figure 1 illustrates how total cardiovascular risk evaluation influences the definition of hypertension when this is correctly considered as the blood pressure value above which treatment does more good than harm.

The most common clinical variables that should be used to stratify the risk are follow:

1. The metabolic syndrome has been mentioned because it represents a cluster of risk factors often associated with high blood pressure which markedly increases cardiovascular risk. No implication is made that it represents a pathogenetic entity.
2. Further emphasis has been given to identification of target organ damage, since hypertension-related subclinical alterations in several organs indicate progression in the cardiovascular disease continuum50 which markedly increases the risk beyond that caused by the simple presence of risk factors.
3. The list of renal markers of organ damage has been expanded, to include estimates of creatinine clearance by the Cockroft-Gault formula or of glomerular filtration rate by the MDRD formula, because of the evidence that these estimated values are a more precise index of the cardiovascular risk accompanying renal dysfunction.
4. Microalbuminuria has now been considered as an essential component in the assessment of organ damage because its detection is easy and relatively inexpensive.
5. Concentric left ventricular hypertrophy has been identified as the cardiac structural parameter that more markedly increases cardiovascular risk.
6. Whenever possible the recommendation is made to measure organ damage in different tissues (e.g. heart, blood vessels, kidney and brain) because multiorgan damage is associated with a worse prognosis.
7. Increased pulse wave velocity is added to the list of factors influencing prognosis as an early index of large artery stiffening, although with the caveat that it has a limited availability in the clinical practice.

8. A low ankle to brachial blood pressure ratio (<0.9) is listed as a relatively easy to obtain marker of atherosclerotic disease and increased total cardiovascular risk.
9. Not only is assessment of organ damage recommended pre-treatment (in order to stratify risk) but also during therapy because of the evidence that regression of left ventricular hypertrophy and reduction of proteinuria indicate treatment-induced cardiovascular protection.
10. There may be reasons to include an elevated heart rate as a risk factor because of a growing body of evidence that elevated heart rate values relate to the risk of cardiovascular morbidity and mortality as well as to all cause mortality. Also, there is evidence that an elevated heart rate increases the risk of new onset hypertension and is frequently associated with metabolic disturbances and the metabolic syndrome.
11. The major diagnostic elements for classifying subjects in the high or very high risk categories are summarized in Table 3. It is worth noticing that multiple risk factors, diabetes or organ damage invariably place a subject with hypertension, and even with high normal blood pressure, in the high risk category.

Pathophysiology

Hypertension is a disorder of BP regulation and results from a multitude of causes. Control of BP involves a complex interaction among the kidneys, the central nervous system (CNS) and peripheral nervous system (PNS), and the vascular endothelium thoughout the body as well as a variety of the other organs, such as the adrenal and pituitary glands. The heart is the organ that responds to many of the changes mediated by these systems. It also secretes hormones locally and systemically that interact with substances produced elsewhere and help regulate BP levels. In those genetically predisposed to develop hypertension, an imbalance occurs among the various systems that modulate the level of BP. The sympathetic nervous system (SNS), the rennin-angiotensin-aldosterone (RAA) system, vasopressin (VP), nitric oxide (NO), and a host of vasoactive peptides, including endothelin, adrenomedullin, and others produced by the heart and a host of different cells (endothelial and vascular smooth cells, for example), modulate the responses of these systems and help maintain BP over a range commensurate with optimum physical and mental activity. Additionally, these systems affect the ability of the kidney to handle sodium (Na^+) and volume, which Guyton and colleagues feel is the primary controller of BP. Sym-

pathetic Nervous System and Renal Sodium Handling Guyton and colleagues noted that while the SNS and the RAA system are important for short-term changes in BP, ultimately it is the kidney that is responsible for long-term blood volume and BP control. High-pressure baroreceptors in the carotid sinus and aortic arch respond to acute elevations in systemic BP by causing a reflex vagal bradycardia that is mediated though the parasympathetic system and inhibition of sympathetic output from the CNS. Low-pressure cardiopulmonary receptors in the atria and ventricles likewise respond to increases in atrial filling by increasing heart rate (HR) through inhibition of the cardiac SNS, increasing atrial natriuretic peptide (ANP) release, and inhibiting VP release. These reflexes are largely controlled centrally, particularly in the nucleus tractus solitarii of the dorsal medulla. This vasomotor center also receives input from the limbic system and hypothalamus in response to emotional or psychological stress. The consequences of SNS stimulation are peripheral vasoconstriction, an increase in HR, release of norepinephrine from the adrenals, and a resultant rise in systemic BP. The increase in SNS activity also plays a role in mediating local vascular hypertrophy and stiffness. Renal efferent sympathetics also are activated and cause internal vasoconstriction with a fall in renal blood flow and an increase in renal vascular resistance. The renal SNS also directly stimulates Na^+ reabsorption and renin release from the juxtaglomerular apparatus. Thus the SNS and CNS have effects on renal handling of $Na^{+.}$

Hyperactivity of the SNS has been described in patients with essential hypertension, particularly in the young and those with "high-normal" BP (130 to 139/80 to 89 mmHg). Elevated plasma norepinephrine levels with increased HR and cardiac indexes have been described in people with newly diagnosed hypertension. These individuals frequently show exaggerated BP responses to emotional (mental arthimetic) and physical stressors such as ice-water immersion. Additionally, a subset of these patients exhibit elevated plasma renin levels that may reflect beta-adrenergic stimulation of renin secretion.

A defect in baroreceptor sensitivity has been postulated to be responsible for abnormal responsiveness of the SNS and thus may contribute to the increase in BP and

HR variability noted in some hypertensive patients. SNS activity also is increased in certain high-risk groups with hypertension, including African-Americans, those with obesity, those with insulin resistance, and those who ingest or inhale certain agents, such as nicotine, alcohol, cyclosporine, and cocaine. A very small subset of patients may have hypertension caused by compression of the lateral medulla by cranial nerves and/or vessels. This results in increased SNS activity. Selective decompression of these nerves may ameliorate the hypertension in rare instances. Activation of the CNS/SNS also may result from renal afferent sympathetics from the kidney in hypertensive patients. In experimental models of hypertension, renal sympathectomy resulted in a reduction in BP. The influence of the SNS on Na^+ handling in the kidney also has been examined in detail. Several studies have linked SNS hyperactivity with greater than normal increases in BP in response to a given Na^+ load. Indeed, Dahl and Heine were the first to show that hypertension can be transferred from a hypertensive Dahl salt-sensitive rat to a nonhypertensive Dahl saltresistant rat by transplantation of the kidney. Patients with essential hypertension and associated renal failure have been cured of the underlying hypertension by renal transplantation from a normotensive donor. Most authorities believe that the mechanism by which the kidney causes hypertension is impairment in the excretion of Na^+. This impairment may be related to genetic changes in various Na^+ exchangers in the proximal and distal tubules that result in altered responses to stimulation by the SNS and the RAA system. Epidemiologic studies have linked the relative Na^+ content in the diet with the prevalence of hypertension in various populations, although the value of dietary Na^+ restriction in reducing BP remains controversial. Interventional studies with Na^+ restriction and/or loading have revealed that the BP responses in many hypertensive patients are "salt-sensitive": Their BP rises with a salt load. In addition, several studies have shown that salt loading of patients with essential hypertension results in a net total body Na^+ accumulation. Three genetic diseases associated with hypertension in childhood (Liddle's syndrome, the syndrome of apparent mineralocorticoid excess, and glucocorticoid-remediable aldosteronism) all are associated with increased reabsorption of

Na^+ by the kidney. A genetically mediated defect in the ability of the kidney to excrete Na^+ does not readily explain certain observations:

- Young hypertensive subjects appear to excrete Na^+ normally or supernormally.
- Individuals with high-normal BP may have a low blood volume.
- As many as 40 percent of people with hypertension do not show a change in BP with Na^+ loading ("salt resistance").
- With aging, salt sensitivity increases both in frequency and in degree such that by age 70, the majority of hypertensive patients are salt-sensitive.

In fact, it has been argued from meta-analyses that salt restriction is not important either in normotensives or in patients with hypertension under age 40. All these findings are consistent with the possibility that the defect in Na^+ excretion in hypertensive patients is acquired rather than genetically determined. It should be kept in mind, however, that abnormal Na^+ handling is a mechanism that contributes to elevating BP in many but probably not all patients with hypertension.

The Renin-Angiotensin-Aldosterone System is one of the most important physiologic mediators that regulate blood volume and BP. Plasma angiotensinogen, which is released primarily from the liver, is acted on by rennin from the kidney to generate angiotensin I, which is further degraded in the presence of angiotensinconverting enzyme to angiotensin II (AII). In addition to the systemic RAA system, there is now evidence that a local RAA system is present in blood vessels, the heart, the kidney, and elsewhere, where it may mediate local effects (such as tissue remodeling) independent of circulating renin or angiotensinogen levels. Most of the actions of AII are mediated by the AT_1 receptor and include stimulating vascular smooth muscle contraction and hypertrophy, increasing cardiac contractility, stimulating the SNS in the CNS and PNS, increasing NO production, causing aldosterone and VP release, and increasing thirst. Within the kidney, stimulation of the AT_1 receptor by AII also causes renal vasoconstriction (especially of the efferent arteriole and vasa rectae), a fall in renal blood flow, and an increase in renal vascular resistance. Angiotensin II also increases Na^+ reabsorption both by increasing aldosterone release and through

direct effects on the proximal tubule. Additionally, AII increases the sensitivity of the tubuloglomerular (TG) feedback response.

Angiotensin subtype 2 (AT_2) receptors also are stimulated by angiotensin II. These receptors produce virtually opposite actions in some experimental systems and are clearly active during fetal development. Their role in healthy adults and even in those with cardiac or vascular damage is still uncertain. The role of the RAA system in essential hypertension is complex. Whereas plasma renin activity

(PRA) is elevated in 20 percent of hypertensive patients, PRA is either normal (50 percent) or low (30 percent) in the majority. However, in many patients with normal plasma renin levels, PRA may be inappropriately high in relation to total body Na^+. This has been suggested by the observation that Na^+ depletion accentuates and Na^+ infusion blunts changes in PRA levels in patients with hypertension. Additional evidence to support this concept comes from the observation that BP in these patients frequently is reduced after the use of ACE-Is or ARBs. Sealey and colleagues have suggested that the reason for widely varying PRA levels may be nephron heterogeneity within individual kidneys, in which there are some ischemic nephrons that make excess renin and other hyperfiltering nephrons in which renin secretion is suppressed. They postulated that the increased renin release from the ischemic nephrons enters the circulation and then leads to AII generation, which causes inappropriate vasoconstriction and Na^+ reabsorption in the other hyperfiltering nephrons. This results in Na^+ retention and the development of hypertension. Unfortunately, this is only part of the explanation, since PRA is relatively low in African-Americans and the elderly, two populations with a high prevalence of hypertension and a high rate of complications from hypertension. Low PRA, however, does not necessarily mean that the RAA is not active, since tissue effects and local actions are not necessarily evident from PRA alone.

Vasopressin. While VP has been clearly shown *not* to play a role in the genesis of essential hypertension, it does play an important role in the maintenance of established hypertension, especially in African-Americans. In African-Americans, studies have shown that selective inhibition of V_1A receptors reduces systolic BP by an addi-

tional 8 to 12 mmHg in the presence of a high-salt diet (suppression of the RAA system) and clonidine (suppression of SNS). Interestingly, this is not observed in whites. In light of the interaction between arginine vasopressin (AVP), AII, and endothelin on cellular growth and vascular responsiveness, it appears that AVP may have a potentiating effect on one of these other hormones.

Endothelin is known to be the most potent vasoconstrictor in humans. Comparative studies with AII have demonstrated not only that the endothelin family of hormones has cellular actions similar to those of AII but that the two hormones work in concert to potentiate each other's vascular and cellular effects. Given this, however, the specific role of endothelin in the etiology of essential hypertension is minimal. It plays a far more important role in cyclosporine-induced hypertension and decreased renal function as well as in maintaining BP in people with HF. Endothelin is the major mechanism by which cyclosporine constricts the afferent arteriole of the kidney and reduces renal function. Calcium antagonists and endothelin receptor blockade prevent this reduction. Additionally, endothelin A receptors have been shown to play a major role in contributing to the maintenance of elevated renal perfusion pressure in patients with HF.

Nitric Oxide is the vasodilator produced by the endothelium in response to vasoconstrictor hormones, and so the contribution of NO to the maintenance of normal BP is vitally important. Defects in NO release or synthesis that are induced by atherosclerosis or that are genetically programmed are a major determinant in predisposing individuals to the development of atherosclerosis and hypertension. NO serves as a major counterbalancing factor that maintains BP within the range necessary to maintain organ perfusion but avoid injury. It counterbalances vasoconstrictive hormones, cytokines such as AII, platelet-derived growth factor (PDGF), tumor necrosis factor-alpha, and other hormones that stimulate its release. Transgenic animal models that do not have the ability to synthesize NO have very high BP and die of CV causes earlier than do animals that can produce NO. Additionally, NO plays a major role in the genesis of hypertension in people who are insulinresistant. The underlying mechanisms and the factors that may govern the interaction between insulin and NO have

been studied extensively in healthy people and insulin-resistant subjects. It appears that a genetic and/or acquired defect of NO synthesis could represent a central defect that triggers many of the metabolic, vascular, and sympathetic abnormalities characteristic of insulinresistant states, all of which may predispose to CV.

Ion Transport Abnormalities

A number of dietary factors affect the SNS, the CNS, and the RAA system in those genetically predisposed to develop hypertension. These dietary factors, such as high Na^+ intake and low potassium (K^+), Ca^{2+}, and/or magnesium (Mg^{2+}) intake, may produce, worsen, or attenuate changes in BP. Substantial evidence from animal models of hypertension as well as diabetic and nondiabetic hypertensive individuals supports an association between the hypertension and changes in intracellular pH as well as electrolyte composition. These observations have led to various hypotheses regarding the importance of one ion relative to others. Numerous investigators have documented increases in cytosolic free Na^+ concentrations in cells of hypertensive or diabetic patients compared with age- and sex-matched normotensive or nondiabetic controls. These increases result from altered activity of the Na^+/H^+ antiporter and the Na^+/Li^+ countertransporter. These increases in intracellular Na^+ are highly correlated with the presence of an elevated diastolic BP. The relationship between intracellular Mg^{2+} and BP is less clearly defined. Data from experimental models of hypertension as well as from patients with hypertension demonstrate an inverse relation between intracellular Mg^{2+} concentration and BP elevation. The primary mechanism responsible for this relative reduction in intracellular Mg^{2+} relates to Na^+-dependent Mg^{2+} efflux through the plasmalemma membrane. Increases in the intracellular Ca^{2+} concentration are seen commonly in obese and essential hypertensive subjects. Like Na^+, these changes reflect altered membrane ion transport activity. Early clinical studies demonstrated that oral Ca^{2+} ingestion reduces BP, but the results from clinical trials do not consistently show a reduction in BP after Ca^{2+} supplementation. Increased K^+ intake is well known to have effects on BP control through multiple mechanisms, including opening K^+ channels in the vasculature, altering sympathetic neuronal output, and increasing vasodilatory prostaglandins. This is exemplified by the fact that hypo-

kalemia in patients will blunt reductions in blood pressure by antihypertensive medication, perhaps because it results in the closure of K^+ channels. Potassium also plays a role in modulating vascular responsiveness in salt-sensitive individuals. In a recent clinical study, increasing dietary K^+ for 3 weeks in 16 predefined salt-sensitive subjects and salt-resistant subjects resulted in the conversion of all salt-sensitive subjects from nocturnal nondipping to dipping status. These results suggest that a positive relationship between dietary K^+ intake and BP modulation can exist even when daytime BP is unchanged by a high-K^+ diet. Taken together, these data suggest that both univalent and divalent cations affect vascular responses to stimuli such as those mediated by the RAA and the SNS. Changes in vascular responses are linked to altered function of membrane ion transporters (Na^+/H^+ antiporter, $Na^{+/}K^{+/}$ATPase, Mg^{2+}/Na^+ exchanger, Ca^{2+}/H^+ exchanger, Ca^{2+} ATPase, and others). Both the Na^+/K^+/ATPase and the Ca^{2+}/ATPase pumps are important in maintaining the Ca^{2+} homeostasis of the cell.

Extracellular Volume Homeostasis

Whereas an acute infusion of saline administered to animals with experimentally induced hypertension will initially raise blood volume and cardiac output, the increase in cardiac output is transient and is replaced by a rise in systemic vascular resistance (SVR). There are several potential mechanisms for this observation. First, the normal response to a salt load is inhibition of the SNS. However, it is known that in salt-sensitive patients, the SNS is not inhibited and even may be activated with a salt load. A possible explanation is that in the setting of renal dysfunction or intrarenal ischemia, salt loading triggers an intense tuboglomerular feedback signal that activates the renal afferent SNS. This renal response subsequently triggers a CNS response. Indeed, there is evidence that renal afferent nerves activate CNS sympathetic activity in both experimental hypertension and chronic renal disease. Second, parabiotic experiments have suggested there may be circulating factors in salt-loaded animals with hypertension that are responsible for some of the increase in SVR. One class of factors is circulating Na^+/K^+/ATPase inhibitors, which have been documented in some patients with essential hypertension. These substances, one of which

is ouabain, are digitalis-like and adrenally derived. It has suggested that these substances, which presumably are secreted in an attempt to facilitate Na^+ excretion, may have the adverse consequence of increasing intracellular Na^+ and thus facilitating Na^+-Ca^{2+} exchange in vascular smooth muscle cells. This would lead to a rise in intracellular Ca^{2+} and stimulate vascular smooth muscle contraction, vasoconstriction, and a rise in SVR. A third mechanism is the loss of a vasodepressor substance. There is good evidence that a lipidlike vasodepressor factor termed adrenomedullin is expressed in some of the interstitial cells in the renal medulla and the juxtamedullary region. Release of this factor into the circulation appears to depend on medullary blood flow and can be inhibited if activation of renal SNS or inhibition of NO reduces blood flow. Thus, one might expect to see lower circulating levels of this substance in the setting of tubulointerstitial (TI) injury and intrarenal ischemia. Fourth, the increase in pressure associated with a saline load could cause increased tension in the peripheral vasculature, leading to microvascular rarefaction (which has been observed in the forearms and nail beds of patients with essential hypertension) that could raise the SVR. An increased pressure load on the vessels also could result in compensatory vascular hypertrophy mediated by local growth factors and the local RAA system. Indeed, there is evidence that AII, PDGF, and basic fibroblast growth factor are involved in these processes.

Mechanisms of Na^+ Retention in Essential Hypertension

A rise in systemic BP normally is associated with brisk natriuresis. This is thought to be due to a transient rise in pressure in the peritubular capillaries in the juxtamedullary region, with a subsequent increase in interstitial pressure and a backflow of Na+ through the paracellular space of the proximal tubule. Numerous studies have confirmed that most patients with essential hypertension have a defect in the pressure natriuresis curve, in which higher systemic pressures are required to excrete a Na^+ load. A second mechanism for decreased Na^+ excretion is an enhancement of TG feedback. Tubuloglomerular feedback is a reflex vasoconstriction that occurs with chloride delivery to the macula densa, and the vasoconstrictive response will reduce glomerular filtration and Na^+ excretion. TG feedback can be enhanced in the

setting of increased local vasoconstrictors such as AII and adenosine or by a reduction in local vasodilators such as NO. TG feedback appears to be enhanced in models of experimental hypertension. Finally, alterations in intrarenal vasoactive mediators may be involved in the impairment of Na^+ excretion in patients with hypertension. In both experimental and human hypertension, there may be low levels of renal vasodilators, such as prostaglandins, dopamine, and NO as well as elevated levels of renal vasoconstrictors such as AII and adenosine and increased activity of the renal SNS. In addition to their effects of enhancing TG feedback, alterations in the levels of these agents could contribute to net Na^+ reabsorption because of their direct effects on tubular Na^+ transport. Some studies have shown that TI injury can be induced in rats with either catecholamine (phenylephrine) or AII infusion and that subsequently these animals will develop hypertension when placed on a high-salt diet. Evaluation of these biopsies demonstrated focal areas of peritubular capillary rarefaction. This also has been observed in kidney biopsies of patients with essential hypertension. The loss of peritubular capillaries could help explain the impairment of pressure natriuresis. The ischemia related to the vasoconstriction and capillary loss could lead to alterations in the various vasoactive mediators. Indeed, there is some evidence that NO levels fall and adenosine levels rise with TI injury and ischemia, and this could contribute to the enhanced TG feedback that has been observed. While this pathway links a hyperactive SNS or RAA system with TI injury and salt-dependent hypertension, it is likely that TI injury induced in other ways could result in salt-sensitive hypertension. Indeed, it is of interest that TI disease is associated with reflux nephropathy, chronic pyelonephritis, DM, cyclosporine, radiation, lead and analgesic nephropathy, hypercalcemia/nephrocalcinosis, and gout, all of which are strongly associated with hypertension. In addition, it is noteworthy that many high-risk groups associated with salt-dependent essential hypertension, such as aged persons, obese persons, and African-Americans, have a high prevalence of TI disease.

Insulin Resistance is a metabolic disorder that is manifested by a reduction in peripheral skeletal muscle utilization of glucose. To fully understand the contribution of insulin resistance to the genesis of hypertension, one has to evaluate the effects of

insulin resistance and hyperinsulinemia on factors that contribute to BP elevation. High levels of insulin cause sodium retention and other vascular effects, such as cellular proliferation and matrix expansion. In the presence of hyperinsulinemia, neurohumoral factors such as AII, endothelin, and VP also potentiate proliferation of endothelial and vascular smooth muscle cells. Lastly, the effect of insulin on various growth factors contributes to the development of vascular injury through its potentiation of the atherosclerotic process. These factors in a person genetically predisposed to develop nephropathy can potentiate injury to the vasculature and end organs. It should be noted, however, that not all subjects with insulin resistance have all the associated components of insulin resistance syndrome or syndrome X, i.e., lipid abnormalities, hyperuricemia, type 2 DM, glucose intolerance, hypertension, microalbuminuria, left ventricular hypertrophy, salt sensitivity, and obesity, among others. Studies in the normotensive offspring of hypertensive nondiabetic parents demonstrate the presence of insulin resistance. This is also true for nondiabetic first-degree relatives of patients with type 2 DM. Thus, a genetic predisposition seems to be needed to develop this syndrome.

Genetic Factors. Commonly accepted candidate genes associated with the genesis of hypertension are summarized below. Insulin resistance is clearly associated with hypertension. A possible genetic link between the presence of insulin resistance and the development of hypertension has been proposed. Recent studies also have identified insulin resistance in the normotensive offspring of parents with essential hypertension. Thus, the development of hypertension does not necessarily correlate with the presence of either hyperinsulinemia or insulin resistance in certain racial groups.

Candidate genes associated with the genesis of hypertension

Monogenic forms

- Glucocorticoid-remediable aldosteronism
- Liddle's syndrome

Polygenic forms that affect

- Angiotensinogen gene
- Na^+-Li^+ countertransport

- Epithelial amiloride-sensitive sodium channel
- Nitric oxide generation
- Alpha-adducin
- G_3 beta subunit (intracellular signal transduction)
- Insertion/deletion of ACE gene

The delineation of a gene profile that will predict who will develop hypertension is near. A number of federally funded studies to gather sib pairs and families to identify candidate genes that predispose individuals to the development of hypertension are under way. Data from these studies may lead to the identification of such genes within the next 5 to 10 years. Thus, until these genetic profiles are delineated, it will be necessary to rely on the data garnered from epidemiologic studies to identify subjects at risk for the development of hypertension and CV events. These are several clear examples of genetic influences in hypertension.

Glucocorticoid-remediable aldosteronism. This is an inherited autosomal dominant disorder that mimics an aldosterone-producing adenoma. An important clinical clue to diagnosing this disease is the age at onset of hypertension. Patients with glucocorticoid-remediable aldosteronism (GRA) typically are diagnosed with high BP as children, whereas patients with other mineralocorticoid excess states, such as aldosterone-producing adenomas (APA) and idiopathic adrenal hyperplasia, usually are diagnosed in the third through sixth decades of life. A strong family history of hypertension is the rule, often associated with early death of affected family members from cerebrovascular accidents, as is seen characteristically in some GRA families. In GRA, the RAA system is suppressed and aldosterone secretion is regulated solely by ACTH. As a result, plasma aldosterone levels usually decline during the course of an upright posture study, similar to what is seen in patients with APA. The administration of exogenous ACTH to patients with GRA is associated with aldosterone hyperresponsiveness compared with normal subjects. Moreover, in contrast to normal subjects in whom continuous ACTH administration is associated with a rise and a subsequent fall in aldosterone to basal levels over days, patients with GRA exhibit an exuberant aldosterone response that is sustained as long as ACTH is infused. GRA is caused by a genetic mutation that results in a hybrid or chimeric gene product fusing

nucleotide sequences of the 11-hydroxylase and aldosterone synthase genes. Characterization of this chimeric gene indicates that it arose from unequal crossing between 11-hydroxylase and aldosterone synthase genes. These two genes are located in close proximity on human chromosome 8, are 95 percent homologous in nucleotide sequence, and have an identical intron-exon structure. The structure of the duplicated gene contains the 5. regulatory sequences that confer the ACTH responsiveness of 11-hydroxylase fused to more distal coding sequences of the aldosterone synthase gene. Therefore, this hybrid gene is expected to be regulated by ACTH and have aldosterone synthase activity. This hybrid gene allows ectopic expression of aldosterone synthase activity in the ACTH-regulated zona fasciculata, which normally produces cortisol. This abnormal gene duplication can be detected readily by southern blotting, allowing for direct genetic screening for this disorder with a small blood sample.

Glucocorticoid resistance. The structure, growth, and secretory activity of the adrenal cortical zona fasciculata are regulated largely by ACTH. Only cortisol can inhibit ACTH release. An increase in ACTH release raises the levels of cortisol, which then inhibits the release of ACTH. This continuous inhibitory feedback effect of cortisol on ACTH release is interrupted in patients with glucocorticoid resistance. In this disorder, although cortisol levels are exceedingly high, ACTH release is not inhibited, leading to uninhibited ACTH secretion, which in turn stimulates the adrenal cortex to produce 11-deoxycorticosterone (DOC). If sufficient DOC is secreted, salt and water retention ensue, precipitating hypertension and hypokalemia. Animal studies indicate that the mechanism for this may in part be related to changes in hippocampal steroid receptor building. Animal studies also indicate that an expressional downregulation of endothelial cell nitric oxide synthase (NOS III) may contribute to the hypertension caused by glucocorticoids. Ingestion of dexamethasone by telemetrically instrumented rats increased BP progressively over 7 days. Plasma oxidation products of NO decreased to 40 percent, and the expression of endothelial NOS III was found to be downregulated in the aorta and several other tissues in glucocorticoid-treated rats. Dexamethasone treatment significantly attenuated the relaxation to the

endotheliumdependent vasodilator acetylcholine but not to the endothelium-independent vasodilator S-nitroso-*N*-acetyl-D,L-penicillamine. Additionally, incubation of human umbilical vein endothelial cells or bovine aortic endothelial cells with several glucocorticoids reduced NOS III mRNA and protein expression to 60 to 70 percent of control, an effect that was prevented by the glucocorticoid receptor antagonist mifepristone.

Liddle's syndrome is an autosomal dominant disorder that mimics the signs and symptoms of mineralocorticoid excess. The fault appears to lie with continuously avid Na^+ channels in the distal nephron, resulting in excessive salt absorption and K^+ wasting (despite negligible aldosterone production) and severe hypertension. A prominent feature is premature death from stroke or HF. The clinical manifestations can be corrected by triamterene and amiloride but not by spironolactone. Triamterene and amiloride directly block the Na+ channel, whereas spironolactone inhibits Na^+ absorption by binding the aldosterone receptor. The cellular defect associated with this syndrome is located on the apical portion of the tubule where the epithelial Na^+ channel (EnaC) located on the apical membrane plays a critical role in Na^+ absorption. Mutations in this channel cause diseases of Na+ homeostasis, including a genetic form of hypertension (Liddle's syndrome inhibits cAMP-mediated stimulation of EnaC). Thus, the apical Na^+ channels and transepithelial Na+ current are inhibited. Experimental data indicate that cAMP-mediated translocation of EnaC to the cell surface is defective in patients with Liddle's syndrome.

Diagnosis of hypertension

Estimation of the pressure generated by the heart during its normal contractile cycle has been measured for more than 100 years. The value of such readings in predicting prognosis was recognized in the early 1930s by insurance companies, which probably have the best data correlating causal BP measurements and the risk of future disability and death. Since the second half of the 1800s, palpation of the pulse and appreciation of the contour and pressure within a peripheral artery were skills learned only through extensive experience. Such subjective observations were supplanted by objective (albeit indirect) measurements after the introduction of the Riva-Rocci

sphygmomanometer in the late nineteenth century. This instrument was refined by Janeway and Korotkoff, who characterized the sounds heard when using a stethoscope placed over the compressed artery in 1906. Even today, the terminology introduced by Korotkoff is still used: Systolic BP is recognized when clear and repetitive tapping sounds are heard; diastolic BP is recorded when the sounds disappear. Exceptions to these general rules are still recognized among patients who have audible sounds even down to zero mmHg and in obstetric patients: In both situations, the "muffling" of the sounds (Korotkoff phase IV) is recorded either in addition to the phase V measurement or as the diastolic BP, respectively.

Blood pressure measurement

Blood pressure is characterized by large spontaneous variations both during the day and between days, months and seasons. Therefore the diagnosis of hypertension should be based on multiple blood pressure measurements, taken on separate occasions over a period of time. If blood pressure is only slightly elevated, repeated measurements should be obtained over a period of several months to define the patients 'usual' blood pressure as accurately as possible. On the other hand, if the patient has a more marked blood pressure elevation, evidence of hypertensionrelated organ damage or a high or very high cardiovascular risk profile, repeated measurements should be obtained over shorter periods of time (weeks or days). In general, the diagnosis of hypertension should be based on at least 2 blood pressure measurements per visit and at least 2 to 3 visits, although in particularly severe cases the diagnosis can be based on measurements taken at a single visit. Blood pressures can be measured by the doctor or the nurse in the office or in the clinic (office or clinic blood pressure), by the patient or a relative at home, or automatically over 24 h. Based on specific recommendations of the European Society of Hypertension, these procedures can be summarized as follows:

- Office or clinic blood pressure
    - Blood pressure can be measured by a mercury sphygmomanometer the various parts of which (rubber tubes, valves, quantity of mercury, etc.) should be kept in proper working order. Other non-invasive devices (auscultatory or oscillometric

semiautomatic devices) can also be used and will indeed become increasingly important because of the progressive banning of the medical use of mercury.

- Ambulatory blood pressure
    - Several devices (mostly oscillometric) are available for automatic blood pressure measurements in patients allowed to conduct a near normal life. They provide information on 24-hour average blood pressure as well as on mean values over more restricted periods such as the day, night or morning. This information should not be regarded as a substitute for information derived from conventional blood pressure measurements.
- Home blood pressure
    - Self-measurement of blood pressure at home cannot provide the extensive information on daily life blood pressure values provided by ambulatory blood pressure monitoring

When measuring 24-hour blood pressure care should be taken to:

- Use only devices validated by international standardized protocols.
- Use cuffs of appropriate size and compare the initial values with those from a sphygmomanometer to check that the differences are not greater than 5 mmHg.
- Set the automatic readings at no more than 30 min intervals to obtain an adequate number of values and have most hours represented if some readings are rejected because of artefact.
- Automatic deflation of the equipment should be at a rate of no more than 2 mmHg/s.
- Instruct the patients to engage in normal activities but to refrain from strenuous exercise, and to keep the arm extended and still at the time of cuff inflations.
- Ask the patient to provide information in a diary on unusual events and on duration and quality of night sleep.
- Obtain another ambulatory blood pressure if the first examination has less than 70% of the expected number of valid values because of frequent artefacts. Ensure that the proportion of valid values is similar for the day and night periods.
- Remember that ambulatory blood pressure is usually several mmHg lower than office blood pressure. A different population studies indicate that office values of 140/90 mmHg correspond to average 24-h values of either 125–130 mmHg systolic and 80 mmHg diastolic, the corresponding average daytime and nighttime values being 130–135/85 and 120/70 mmHg. These values may be regarded as approximate threshold values for diagnosing hypertension by ambulatory blood pressure.
- Clinical judgement should be mainly based on average 24-hour, day and/or night values.

Nomenclature.

A. Essential Hypertension – no identifiable etiology.

Elevated blood pressure remains elevated because of an increase in peripheral arterial resistance that may be related to either of the following:

1. Inappropriate renal retention of salt and water
2. Increased endogenous pressure activity

B. Secondary Hypertension – can occur in the following conditions as well as others:

1. Polycystic Kidneys
2. Renovascular disease
3. Aortic coarctation
4. Cushing's syndrome

Isolated office or white coat hypertension

In some patients office blood pressure is persistently elevated while daytime or 24-hour blood pressure, or home blood pressure, are within their normal range. This condition is widely known as 'white coat hypertension', although the more descriptive and less mechanistic term 'isolated office (or clinic) hypertension' is preferable because the office ambulatory blood pressure difference does not correlate with the office blood pressure elevation induced by the alerting response to a doctor or a nurse, that is the true 'white coat effect'. Regardless of the terminology, evidence is now available that isolated office hypertension may be present in about 15% of the general population and that it may account for a noticeable fraction (one third or more) of individuals in whom hypertension is diagnosed.

Isolated ambulatory or masked hypertension

The reverse phenomenon of 'white coat hypertension' has also been described: individuals with normal office blood pressure (<140/90 mmHg) may have elevated ambulatory or home blood pressure values, a condition termed 'isolated ambulatory hypertension' or 'masked hypertension'. The prevalence in the population is about the same as that of isolated office hypertension and it has been calculated that about 1 in 7 or 8 subjects with a normal office blood pressure may fall into this category. Although limited information exists on the persistence of this condition over time, such individuals have been shown to have greater than normal prevalence of organ damage, with an increased prevalence of metabolic risk factors compared with subjects with a truly normal blood pressure.

Blood pressure during exercise and laboratory stress

Both physical and mental stressors have been applied in the laboratory to assess the blood pressure response to challenging stimuli and its potential clinical utility. Physical stress involves active physical activity (dynamic or static exercise) or passive physical stress, such as the cold pressor test. Mental stress is evoked via a problem of mathematical, technical or decisional nature.

In conclusion, the results on the independent relationships of the blood pressure response to physical and mental stressors, future hypertension and target organ damage are not consistent and, if significant, the additional explained variance is small. As to the prediction of cardiovascular events, the 21-year follow-up study mentioned above suggests that an exercise test may provide some additional prognostic information at least in subjects with mild blood pressure elevation, because in the absence of other risk factors or organ damage a decision on the need for therapeutic intervention may be difficult.

Central blood pressure

Due to the variable superimposition of incoming and reflected pressure waves along the arterial tree, aortic systolic and pulse pressure (i.e. the pressure exerted at the level of the heart, brain and kidney) may be different from the conventionally measured brachial pressure. Furthermore, the claim has long been made that peripheral and central systolic and pulse pressures may be differently affected by antihypertensive drugs. The need for invasive measurement of central blood pressure has confined this issue to research. However, recently a method has been described to non-invasively estimate aortic blood pressure by calculating the ‘augmentation index’ from the pulse wave pressure contour recorded from a peripheral artery. Use of this method has confirmed that the effects of antihypertensive drugs on central systolic and pulse pressure do not invariably reflect those seen at the brachial artery level.

Family and clinical history

A comprehensive family history should be obtained with particular attention to hypertension, diabetes, dyslipidaemia, premature coronary heart disease, stroke, peripheral artery or renal disease.

The clinical history should include:

a) duration and previous levels of high blood pressure;
b) symptoms suggestive of secondary causes of hypertension and intake of drugs or substances that can raise blood pressure, such as liquorice, nasal drops, cocaine, amphetamines, oral contraceptives, steroids, non-steroidal anti-inflammatory drugs, erythropoietin, and cyclosporin;
c) lifestyle factors, such as dietary intake of fat (animal fat in particular), salt and alcohol, quantification of smoking and physical activity, weight gain since early adult life;
d) past history or current symptoms of coronary disease, heart failure, cerebrovascular or peripheral vascular disease, renal disease, diabetes mellitus, gout, dyslipidaemia, asthma or any other significant illnesses, and drugs used to treat those conditions;
e) previous antihypertensive therapy, its results and adverse effects;
f) personal, family and environmental factors that may influence blood pressure, cardiovascular risk, as well as the course and outcome of therapy.

Also, physicians should enquire of the patient and/or partner about snoring which may be a sign of sleep apnoea syndrome and increased cardiovascular risk.

Physical examination. In addition to blood pressure heart rate should be carefully measured (pulse counting over at least 30 s or longer if arrhythmias are reported) because the repeated finding of values above normal may be an indication of greater risk, increased sympathetic or decreased parasympathetic activity, or of heart failure. Physical examination should search for evidence of additional risk factors, for signs suggesting secondary hypertension, and for evidence of organ damage. Waist circumference should be measured with the patient standing and body weight and height should be obtained to calculate body mass index by a standard formula.

Laboratory investigations are directed at providing evidence for additional risk factors, searching for secondary hypertension and looking for the absence or presence of organ damage. Investigations should progress from the most simple to the more complicated. The younger the patient, the higher the blood pressure and the faster the development of hypertension, the more detailed the diagnostic work-up should be. However, the minimum laboratory investigations needed remain a matter of debate.

Routine laboratory investigations should include: blood chemistry for fasting glucose, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides (fasting), urate, creatinine, potassium, haemoglobin and haematocrit; urinalysis by a dipstick

test that permits the detection of microalbuminuria; urine microscopic examination and an electrocardiogram. Serum creatinine is an imprecise measure of renal function.

Genetic analysis

There is often a family history of high blood pressure in hypertensive patients, suggesting that inheritance contributes to the pathogenesis of this disorder. Essential hypertension is a highly heterogeneous disorder, which points to a multi-factorial aetiology and polygenic abnormalities. Variants in some genes might render an individual sensitive to a given factor in the environment. A number of mutations in genes encoding for major blood pressure controlling systems has been recognized in humans, but their exact role in the pathogenesis of essential hypertension is still unclear.

Searching for subclinical organ damage

Due to the importance of subclinical organ damage as an intermediate stage in the continuum of vascular disease and as a determinant of overall cardiovascular risk, signs of organ involvement should be sought carefully. It should be pointed out that a large body of evidence is now available on the crucial role of subclinical organ damage in determining the cardiovascular risk of individuals with and without high blood pressure.

1. Microalbuminuria has been shown repeatedly to be associated with an increased incidence of cardiovascular disease not only in diabetes but also in non-diabetic subjects. In addition, an increased risk has been documented for urinary protein levels lower than those defined as microalbuminuria.
2. There has been further confirmation of the adverse prognostic role of left ventricular hypertrophy, as well as of carotid intima-media thickness together with evidence that their prevalence in ordinary hypertensive individuals is much more common than observed when only routine investigations are performed. Without ultrasound investigations for left ventricular hypertrophy and vascular thickening or plaques, up to 50% of hypertensive subjects may be mistakenly classified as at low or moderate added risk, whereas the presence of cardiac or vascular damage classifies them within a higher risk group.

3. Retrospective analyses of prospective trials have shown that treatment-induced reductions in proteinuria and left ventricular hypertrophy are accompanied by a reduced incidence of cardiovascular events, suggesting that measuring organ damage is advisable not only to quantify total cardiovascular risk initially but also to monitor treatment-induced protection.

Therapeutic management of hypertension

Recommendations about therapy for hypertension are here preceded by some considerations on the strength of available evidence on the benefits associated with antihypertensive treatment as well as on the comparative benefits of the various classes of drugs.

The decision to start antihypertensive treatment should be based on two criteria: the level of systolic and diastolic blood pressure (as classified in Table 1.1) and the level of total cardiovascular risk. This is illustrated in Figure 1.2

Figure 1.2

Initiation of antihypertensive treatment.

	Blood pressure (mmHg)				
Other risk factors OD or disease	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP≥180 or DBP≥110
No other risk factors	No BP intervention	No BP intervention	Lifestyle changes for several months then drug treatment if BP uncontrolled	Lifestyle changes for several weeks then drug treatment if BP uncontrolled	Lifestyle changes + Immediate drug treatment
1–2 risk factors	Lifestyle changes	Lifestyle changes	Lifestyle changes for several weeks then drug treatment if BP uncontrolled	Lifestyle changes for several weeks then drug treatment if BP uncontrolled	Lifestyle changes + Immediate drug treatment
≥3 risk factors, MS or OD	Lifestyle changes	Lifestyle changes and consider drug treatment	Lifestyle changes + Drug treatment	Lifestyle changes + Drug treatment	Lifestyle changes + Immediate drug treatment
Diabetes	Lifestyle changes	Lifestyle changes + Drug treatment			
Established CV or renal disease	Lifestyle changes + Immediate drug treatment	Lifestyle changes + Immediate drug treatment	Lifestyle changes + Immediate drug treatment	Lifestyle changes + Immediate drug treatment	Lifestyle changes + Immediate drug treatment

Goals of treatment

The primary goal of treatment of the hypertensive patient is to achieve the maximum reduction in the long-term total risk of cardiovascular morbidity and mortality. This requires treatment of all the reversible risk factors identified, including smoking, dyslipidaemia, abdominal obesity or diabetes, and the appropriate management of associated clinical conditions, as well as treatment of the raised blood pressure per se.

Blood pressure target in the general hypertensive population

In hypertensive patients, the primary goal of treatment is to achieve maximum reduction in the longterm total risk of cardiovascular disease.

- This requires treatment of the raised BP per se as well as of all associated reversible risk factors.
- BP should be reduced to at least below 140/90 mmHg (systolic/diastolic), and to lower values, if tolerated, in all hypertensive patients.
- Target BP should be at least <130/80 mmHg in diabetics and in high or very high risk patients, such as those with associated clinical conditions (stroke, myocardial infarction, renal dysfunction, proteinuria).
- Despite use of combination treatment, reducing systolic BP to <140 mmHg may be difficult and more so if the target is a reduction to <130 mmHg. Additional difficulties should be expected in elderly and diabetic patients, and, in general, in patients with cardiovascular damage.
- In order to more easily achieve goal BP, antihypertensive treatment should be initiated before significant cardiovascular damage develops.

Position statement: Lifestyle changes

- Lifestyle measures should be instituted, whenever appropriate, in all patients, including those who require drug treatment. The purpose is to lower BP, to control other risk factors and to reduce the number of doses of antihypertensive drugs to be subsequently administered.
- Lifestyle measures are also advisable in subjects with high normal BP and additional risk factors to reduce the risk of developing hypertension.

- The lifestyle measures that are widely recognized to lower BP or cardiovascular risk, and that should be considered are:
  - smoking cessation
  - weight reduction (and weight stabilization)
  - reduction of excessive alcohol intake
  - physical exercise
  - reduction of salt intake
  - increase in fruit and vegetable intake and decrease in saturated and total fat intake
- Lifestyle recommendations should not be given as lip service but instituted with adequate behavioural and expert support, and reinforced periodically.
- Because long-term compliance with lifestyle measures is low and the BP response highly variable, patients under non-pharmacological treatment should be followed-up closely to start drug treatment when needed and in a timely fashion.

Choice of antihypertensive drugs

- The main benefits of antihypertensive therapy are due to lowering of BP per se.
- Five major classes of antihypertensive agents – thiazide diuretics, calcium antagonists, ACE inhibitors, angiotensin receptor antagonists and b-blockers – are suitable for the initiation and maintenance of antihypertensive treatment, alone or in combination. Beta-blockers, especially in combination with a thiazide diuretic, should not be used in patients with the metabolic syndrome or at high risk of incident diabetes.
- Because in many patients more than one drug is needed, emphasis on identification of the first class of drugs to be used is often futile. Nevertheless, there are many conditions for which there is evidence in favour of some drugs versus others either as initial treatment or as part of a combination.
- The choice of a specific drug or a drug combination, and the avoidance of others, should take into account the following:
  1. The previous favourable or unfavourable experience of the individual patient with a given class of compounds.

2. The effect of drugs on cardiovascular risk factors in relation to the cardiovascular risk profile of the individual patient.
3. The presence of subclinical organ damage, clinical cardiovascular disease, renal disease or diabetes which may be more favourably treated by some drugs than others.
4. The presence of other disorders that may limit the use of particular classes of antihypertensive drugs.
5. The possibilities of interactions with drugs used for other conditions.
6. The cost of drugs, either to the individual patient or to the health provider, but cost considerations should never predominate over efficacy, tolerability, and protection of the individual patient.

- Continuing attention should be given to side effects of drugs, because they are the most important cause of non-compliance. Drugs are not equal in terms of adverse effects, particularly in individual patients.
- The BP lowering effect should last 24 hours. This can be checked by office or home BP measurements at trough or by ambulatory BP monitoring.
- Drugs which exert their antihypertensive effect over 24 hours with a once-a-day administration should be preferred because a simple treatment schedule favours compliance.

Antihypertensive treatment: Preferred drugs

Identification of the first class of drugs to be used in the management of hypertension has always been a debated issue. However, there is now conclusive evidence from trials that combination treatment is needed to control blood pressure in the majority of patients.

Thus, if two or more drugs are taken for the lifetime of the patients it is of marginal relevance which is the one used alone for the first few weeks of therapy. However, drug classes (and even compounds within a given class) differ in type and frequency of adverse effects they may induce, and different individuals may be differently prone to develop a given adverse effect. Furthermore, drugs may have different

effects on risk factors, organ damage and cause-specific events and show specific protective influences in special groups of patients. This makes selection of a given agent alone or in association with other drugs mandatory or advisable according to the circumstances.

The criteria of choosing of antihypertensive drugs are listed below.

	Subclinical organ damage
LVH	ACEI, CA, ARB
Asympt. Atherosclerosis	CA, ACEI
Microalbuminuria	ACEI, ARB
Renal dysfunction	ACEI, ARB
	Clinical event
Previous stroke	any BP lowering agent
Previous MI	BB, ACEI, ARB
Angina pectoris	BB, CA
Heart failure	diuretics, BB, ACEI, ARB, antialdosterone agents
Atrial fibrillation	
• Recurrent	ARB, ACEI
• Permanent	BB, non-dihydropiridine CA
ESRD/proteinuria	ACEI, ARB, loop diuretics
Peripheral artery disease	CA
	Condition
ISH (elderly)	diuretics, CA
Metabolic syndrome	ACEI, ARB, CA
Diabetes mellitus	ACEI, ARB
Pregnancy	CA, methyldopa, BB
Blacks	diuretics, CA

Abbreviations: LVH - left ventricular hypertrophy; ISH – isolated systolic hypertension; ESRD - renal failure; ACEI -ACE inhibitors; ARB - angiotensin receptor antagonists; CA - calcium antagonists; BB - beta-adrenoblockers.

As a general scenario the choice or the avoidance of drugs should take into account the following:

1) the previous favourable or unfavourable experience of the individual patient with a given class of compounds both in relation to blood pressure lowering and side effects;
2) the effect of drugs on cardiovascular risk factors in relation to the cardiovascular risk profile of the individual patient;

3) the presence of subclinical organ damage, clinical cardiovascular disease, renal disease or diabetes which may be more favourably treated by some drugs than others;
4) the presence of other disorders that may limit the use of particular classes of antihypertensive drugs;
5) the possibility of interactions with drugs used for other conditions present in the patient;
6) the cost of drugs, either to the individual patient or to the health provider.

Treatment can start with a single drug, which should initially be administered at low dose. If blood pressure is not controlled, either a full dose of the initial agent can be given or patients can be switched to an agent of a different class (which should also be administered, first at low and then at full dose). Switching to an agent from a different class is mandatory in case the first agent had no blood pressure lowering or induced important side effects. This 'sequential monotherapy' approach may allow to find the drug to which any individual patient best responds both in terms of efficacy and tolerability. However, although the so called 'responder rate' (systolic and diastolic blood pressure reduction ≥20 and 10 mmHg, respectively) to any agent in monotherapy is approximately 50%,588 the ability of any agent used alone to achieve target blood pressure values (<140/90 mmHg) does not exceed 20–30% of the overall hypertensive population except in subjects with grade 1 hypertension. Furthermore the procedure is laborious and frustrating for both doctors and patients, leading to low compliance and unduly delaying urgent control of blood pressure in high risk hypertensives. Hopes are placed on pharmacogenomics, which in the future may succeed in identifying the drugs having the best chance of being effective and beneficial in individual patients.

Monotherapy versus combination therapy

- Regardless of the drug employed, monotherapy allows to achieve BP target in only a limited number of hypertensive patients.

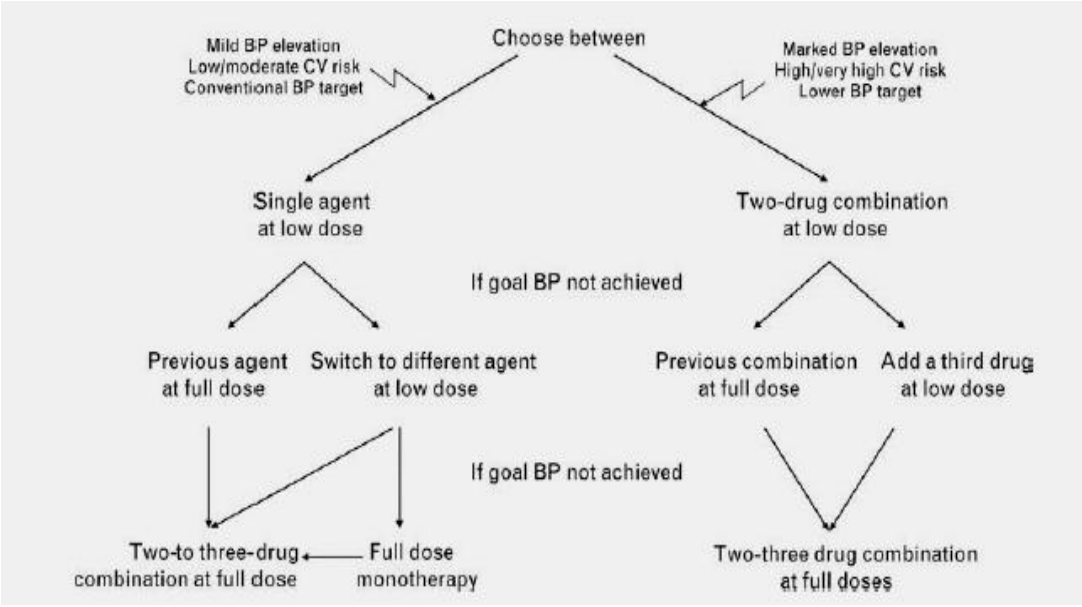
- Use of more than one agent is necessary to achieve target BP in the majority of patients. A vast array of effective and well tolerated combinations is available (Figure 1.3).
- Initial treatment can make use of monotherapy or combination of two drugs at low doses with a subsequent increase in drug doses or number, if needed
- Monotherapy could be the initial treatment for a mild BP elevation with a low or moderate total cardiovascular risk. A combination of two drugs at low doses should be preferred as first step treatment when initial BP is in the grade 2 or 3 range or total cardiovascular risk is high or very high.
- Fixed combinations of two drugs can simplify treatment schedule and favour compliance.
- In several patients BP control is not achieved by two drugs, and a combination of three of more drugs is required.
- In uncomplicated hypertensives and in the elderly, antihypertensive therapy should normally be initiated gradually. In higher risk hypertensives, goal blood pressure should be achieved more promptly, which favours initial combination therapy and quicker adjustment of doses.

Antihypertensive drugs of different classes can be combined if

1) they have different and complementary mechanisms of action,
2) there is evidence that the antihypertensive effect of the combination is greater than that of either combination component,
3) the combination may have a favourable tolerance profile, the complementary mechanisms of action of the components minimizing their individual side effects.

Figure 1.3

Monotherapy versus combination therapy strategies

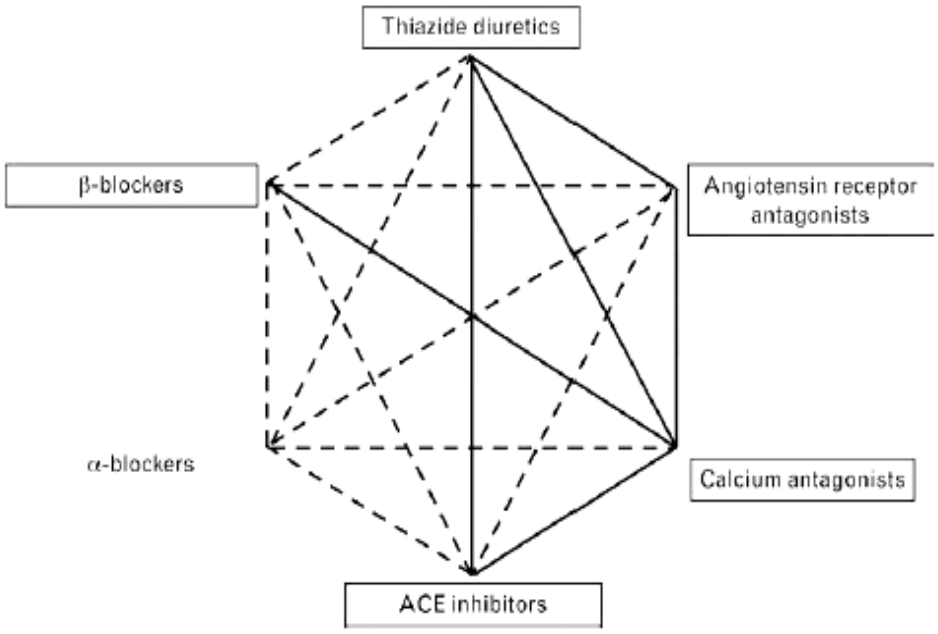


The following two-drug combinations have been found to be effective and well tolerated. They are indicated below and in Figure 1.4:

- Thiazide diuretic and ACE inhibitor
- Thiazide diuretic and angiotensin receptor antagonist
- Calcium antagonist and ACE inhibitor
- Calcium antagonist and angiotensin receptor antagonist
- Calcium antagonist and thiazide diuretic
- beta-blocker and calcium antagonist (dihydropiridine)

Possible combinations between some classes of antihypertensive drugs. The preferred combinations in the general hypertensive population are represented as thick lines. The frames indicate classes of agents proven to be beneficial in controlled intervention trials.

Figure 1.4.



Finally, combinations between two drugs in a single tablet, usually at low doses, (but sometimes both at lower and at higher doses), are now widely available, particularly those of an angiotensin receptor antagonist with a thiazide diuretic, or of an ACE inhibitor with a thiazide diuretic or with a calcium antagonist, of a b-blocker with a diuretic, and of a thiazide with a potassium sparing diuretic. Although the fixed dose of the combination components limits the flexibility of upward and

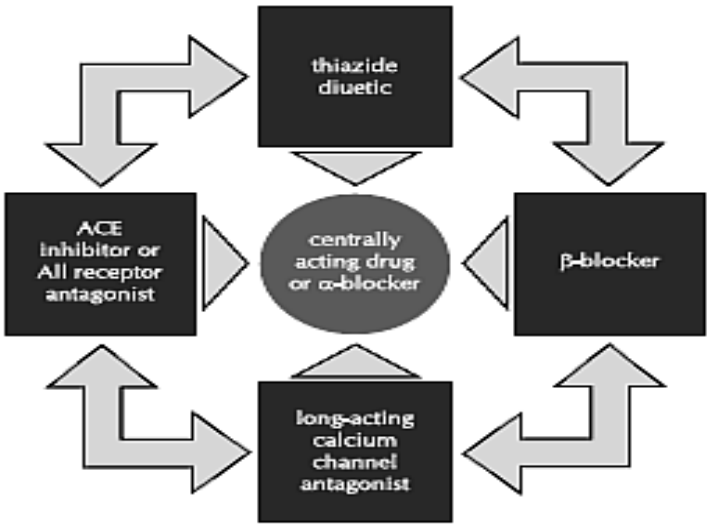
downward treatment strategies, fixed combinations reduce the number of tablets to be taken by the patient, and this has some advantage for compliance with treatment.

Antihypertensive treatment in the elderly

- Randomized trials in patients with systolic-diastolic or isolated systolic hypertension aged > 60 years have shown that a marked reduction in cardiovascular morbidity and mortality can be achieved with antihypertensive treatment.
- Initial doses and subsequent dose titration should be more gradual because of a greater chance of undesirable effects, especially in very old and frail subjects.
- Drug treatment can be initiated with thiazide diuretics, calcium antagonists, angiotensin receptor antagonists, ACE inhibitors, and b-blockers, in line with general guidelines. Trials specifically addressing treatment of isolated systolic hypertension have shown the benefit of thiazides and calcium antagonists but subanalysis of other trials also shows efficacy of angiotensin receptor antagonists.
- BP goal is the same as in younger patients, i.e. <140/90 mmHg or below, if tolerated. Many elderly patients need two or more drugs to control blood pressure and reductions to <140 mmHg systolic may be particularly difficult to obtain.
- Drug treatment should be tailored to the risk factors, target organ damage and associated cardiovascular and non-cardiovascular conditions that are frequent in the elderly. Because of the increased risk of postural hypotension, BP should always be measured also in the erect posture.
- In subjects aged 80 years and over, evidence for benefits of antihypertensive treatment is as yet inconclusive. However, there is no reason for interrupting a successful and well tolerated therapy when a patient reaches 80 years of age.
- The Birmingham system for choosing add-on therapy is illustrated below (Figure 1.5)
- Stabilisation, maintenance and follow up after initiation of antihypertensive drug therapy in elderly subjects is illustrated in Figure 1.6.

Figure 5

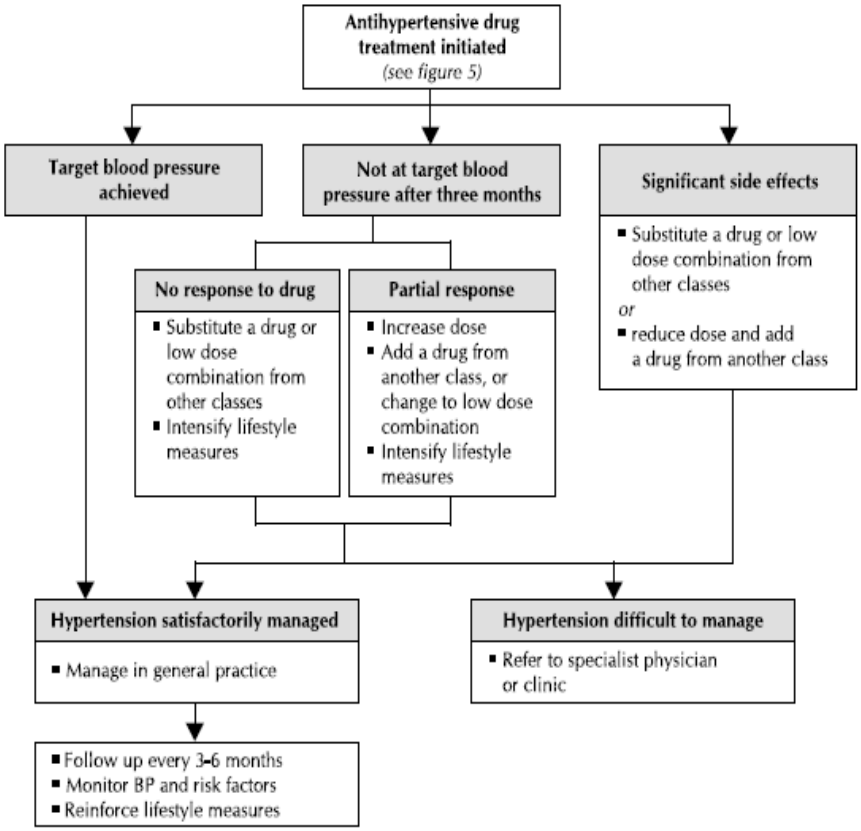
The Birmingham system for choosing add-on therapy in elderly subjects



Note: Start therapy at any square and use add-on therapy on either side as shown by the arrows. Drugs in adjacent squares have additive antihypertensive effects, complementary actions, and are usually well-tolerated. Multiple combinations may be required.

Figure 1.6

Stabilisation, maintenance and follow up after initiation of antihypertensive drug therapy in elderly subjects (WHO-ISH guideline)



Antihypertensive treatment in diabetics

- Where applicable, intense non-pharmacological measures should be encouraged in all diabetic patients, with particular attention to weight loss and reduction of salt intake in type 2 diabetes mellitus.
- Goal BP should be <130/80 mmHg and antihypertensive drug treatment may be started already when BP is in the high normal range.
- To lower BP, all effective and well tolerated drugs can be used. A combination of two or more drugs is frequently needed.
- Available evidence indicates that lowering BP also exerts a protective effect on appearance and progression of renal damage. Some additional protection can be obtained by the use of a blocker of the renin-angiotensin system (either an angiotensin receptor antagonist or an ACE inhibitor).
- A blocker of the renin-angiotensin system should be a regular component of combination treatment and the one preferred when monotherapy is sufficient.
- Microalbuminuria should prompt the use of antihypertensive drug treatment also when initial BP is in the high normal range. Blockers of the renin-angiotensin system have a pronounced antiproteinuric effect and their use should be preferred.
- Treatment strategies should consider an intervention against all cardiovascular risk factors, including a statin.
- Because of the greater chance of postural hypotension, BP should also be measured in the erect posture.

Antihypertensive therapy in patients with renal dysfunction

- Renal dysfunction and failure are associated with a very high risk of cardiovascular events.
- Protection against progression of renal dysfunction has two main requirements:
    - a) strict blood pressure control (<130/80 mmHg and even lower if proteinuria is 1 g/day);
    - b) lowering proteinuria to values as near to normal as possible.
- To achieve the blood pressure goal, combination therapy of several antihypertensive agents (including loop diuretics) is usually required.
- To reduce proteinuria, an angiotensin receptor blocker, an ACE inhibitor or a combination of both are required.
- There is controversial evidence as to whether blockade of the rennin -angiotensin system has a specific beneficial role in preventing or retarding nephrosclerosis in non-diabetic non-proteinuric hypertensives, except perhaps in Afro-American individuals. However, inclusion of one of these agents in the combination therapy required by these patients appears well founded.

- An integrated therapeutic intervention (antihypertensive, statin and antiplatelet therapy) has to be frequently considered in patients with renal damage because, under these circumstances, cardiovascular risk is extremely high.

Antihypertensive treatment in patients with cerebrovascular disease

- In patients with a history of stroke or transient ischaemic attacks, antihypertensive treatment markedly reduces the incidence of stroke recurrence and also lowers the associated high risk of cardiac events.
- Antihypertensive treatment is beneficial in hypertensive patients as well as in subjects with BP in the high normal range. BP goal should be <130/80 mmHg.
- Because evidence from trials suggests that the benefit largely depends on BP lowering per se, all available drugs and rational combinations can be used.
- There is at present no evidence that BP lowering has a beneficial effect in acute stroke but more research is under way. Until more evidence is obtained antihypertensive treatment should start when post-stroke clinical conditions are stable, usually several days after the event. Additional research in this area is necessary because cognitive dysfunction is present in about 15% and dementia in 5% of subjects aged ≥ 65 years.
- In observational studies, cognitive decline and incidence of dementia have a positive relationship with BP values. There is some evidence that both can be somewhat delayed by antihypertensive treatment.

Antihypertensive treatment in patients with coronary heart disease and heart failure

- In patients surviving a myocardial infarction, early administration of b-blockers, ACE inhibitors or angiotensin receptor antagonists reduces the incidence of recurrent myocardial infarction and death. These beneficial effects can be ascribed to the specific protective properties of these drugs but possibly also to the associated small BP reduction.
- Antihypertensive treatment is also beneficial in hypertensive patients with chronic coronary heart disease. The benefit can be obtained with different drugs and drug combinations (including calcium antagonists) and appears to be related to the de-

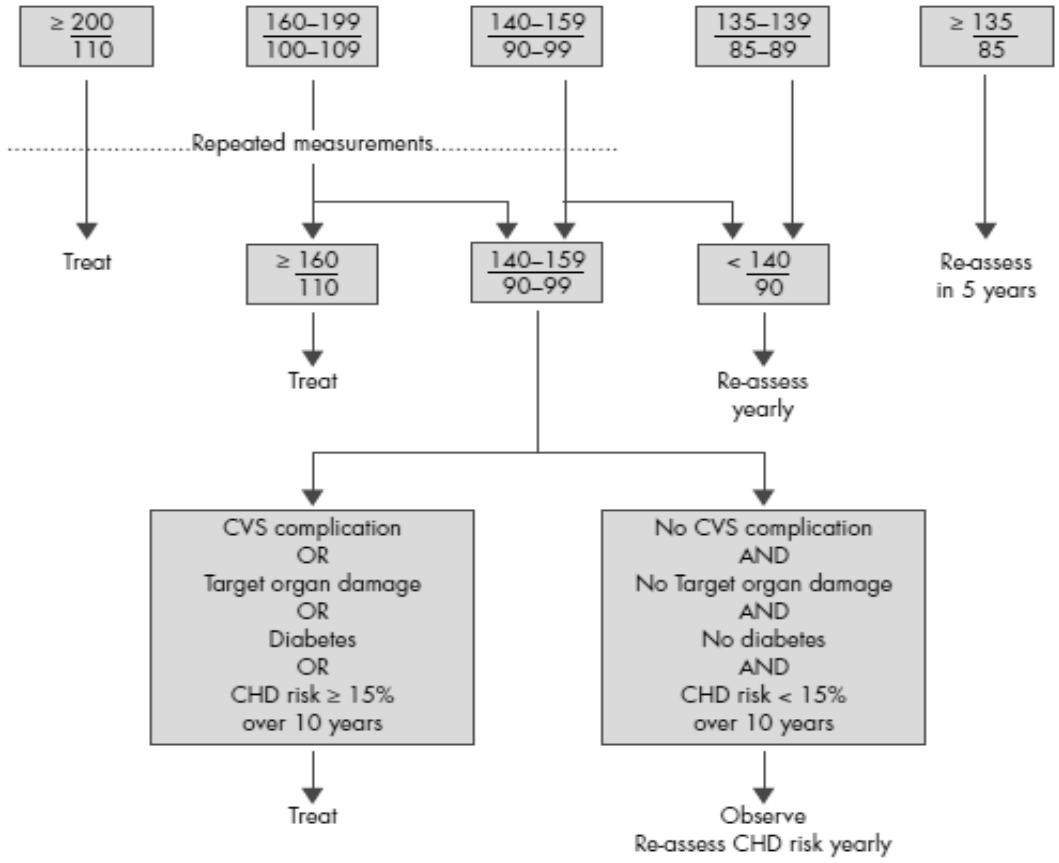
gree of BP reduction. A beneficial effect has been demonstrated also when initial BP is <140/90 mmHg and for achieved BP around 130/80 mmHg or less.

- A history of hypertension is common while a raised BP is relatively rare in patients with congestive heart failure. In these patients, treatment can make use of thiazide and loop diuretics, as well as of b-blockers, ACE inhibitors, angiotensin receptor antagonists and antialdosterone drugs on top of diuretics. Calcium antagonists should be avoided unless needed to control BP or anginal symptoms.
- Diastolic heart failure is common in patients with a history of hypertension and has an adverse prognosis. There is at present no evidence on the superiority of specific antihypertensive drugs.

Summary of recommendations for targeting of antihypertensive treatment in patients with arterial hypertension associated with cardiovascular conditions and diseases are presented in Figure 1.7.

Figure 1.7

Summary of recommendations in the British Hypertension Society guidelines for targeting of antihypertensive treatment (2007)



Resistant hypertension

Hypertension is usually defined as resistant or refractory to treatment when a therapeutic plan that has included attention to lifestyle measures and the prescription of at least three drugs (including a diuretic) in adequate doses has failed to lower systolic and diastolic blood pressure to goal. According to this definition prevalence of resistant hypertension is high: for instance in the ALLHAT cohort 8% of the patients were prescribed 4 or more drugs, and it has been calculated that a minimum of 15% would have been classified as having resistant hypertension. In such situations, referral to a specialist or a hypertension centre should be considered, because resistant hypertension is recognized to be often associated with subclinical organ damage and a high added cardiovascular risk.

Causes of resistant hypertension

- Poor adherence to therapeutic plan
- Failure to modify lifestyle including:
    - weight gain
    - heavy alcohol intake (NB: binge drinking)
- Continued intake of drugs that raise blood pressure (liquorice, cocaine, glucocorticoids, non-steroid anti-inflammatory drugs, etc.)
- Obstructive sleep apnoea
- Unsuspected secondary cause
- Irreversible or scarcely reversible organ damage
- Volume overload due to:
    - inadequate diuretic therapy
    - progressive renal insufficiency
    - high sodium intake
    - hyperaldosteronism

Hypertensive emergencies are observed when severe forms of high blood pressure are associated with acute damage to target organs. Marked rises in blood pressure associated with acute worsening of organ damage, such as those sometimes occurring in the elderly with isolated systolic hypertension, are improperly defined

emergencies, and should be treated promptly but in the same way as chronic blood pressure elevations are.

The most important emergencies are listed below.

Hypertensive Emergencies

- Hypertensive encephalopathy
- Hypertensive left ventricular failure
- Hypertension with myocardial infarction
- Hypertension with unstable angina
- Hypertension and dissection of the aorta
- Severe hypertension associated with subarachnoid haemorrhage or cerebrovascular accident
- Crisis associated with phaeochromocytoma
- Use of recreational drugs such as amphetamines, LSD, cocaine or ecstasy
- Hypertension perioperatively
- Severe pre-eclampsia or eclampsia

Such emergencies are rare but can be life threatening. In these conditions, the management of hypertension must be rapid. Care should be taken, however, that extremely rapid falls in blood pressure may not be associated with complications such as underperfusion of the brain and cerebral infarction or damage to the myocardium and kidneys.

Malignant hypertension

Whilst there is a clear overlap between resistant and malignant hypertension, in most developed societies malignant phase hypertension is observed infrequently and mostly in economically deprived strata. Malignant hypertension embraces a syndrome of severe elevation of arterial blood pressure (diastolic blood pressure usually but not always >140 mmHg) with vascular damage that can be particularly manifest as retinal haemorrhages, exudates and/or papilloedema. Some physicians use the term accelerated hypertension when such a syndrome appears but papilloedema on retinal examination is absent. Malignant hypertension may be seen in a variety of conditions. Severe or poorly treated essential hypertension is usually the commonest harbinger of

malignant phase hypertension, although in various studies the presence of a secondary cause of hypertension has probably been underestimated.

The prevalence of this condition amongst hypertensive patients has obviously diminished as a result of earlier treatment of hypertension and more efficient therapeutic programmes, as well as a decrease of most predisposing causes. What causes malignant hypertension to be a condition with such a sinister prognosis is the breakdown of autoregulation as a result of the arterial wall being continuously exposed to extremely high levels of blood pressure. Pathological studies of the vascular wall demonstrate that there is myointimal proliferation and fibrinoid necrosis. The severity of the proliferative response parallels the severity and length of exposure to the high blood pressure.

The fibrinoid necrosis represents spasm and forced dilatation of small arterioles. The leaking of fluid into the extracellular space is associated with small haemorrhages and of course target organ damage. The most dangerous condition that is associated with malignant phase hypertension is hypertensive encephalopathy. It is associated with reversible alterations in neurological function and can include headache, disturbed mental status and visual impairment. Also associated with this condition is a deterioration in renal function, which has been described as being prognostically important, with more severe forms of renal failure being associated with reduced life expectancy despite prompt and effective management of the hypertension. In some patients there is irreversible renal damage necessitating renal replacement therapy including dialysis on a permanent basis. Malignant phase hypertension is also associated with haemolysis, red blood cell fragmentation and evidence of disseminated intravascular coagulation. When malignant hypertension is untreated, its prognosis is extremely poor, with 50% of individuals dying within 12 months. However, following the institution of effective management programmes the incidence of such initial problems has declined. Survival is better and reflects not only improved blood pressure control, but also good identification of secondary causes and more widely available services such as renal dialysis and transplantation. Malignant phase hypertension must be regarded as a hypertension emergency. Oral medication can be used if blood

pressure is responsive, with the goal to bring diastolic blood pressure down to 100–110 mmHg over 24 hours.

Screening and treatment of secondary forms of hypertension

A specific cause of blood pressure elevation can be identified in a small proportion of adult patients with hypertension. Simple screening for secondary forms of hypertension can be obtained from clinical history, physical examination and routine laboratory investigations. Furthermore, a secondary form of hypertension is suggested by a severe blood pressure elevation, sudden onset or worsening of hypertension and blood pressure responding poorly to drug therapy. In these cases, specific diagnostic procedures may become necessary, as outlined below.

Renal parenchymal disease is the most common cause of secondary hypertension. The finding of bilateral upper abdominal masses at physical examination is consistent with polycystic kidney disease and should lead to an abdominal ultrasound examination. Renal ultrasound has now almost completely replaced intravenous urography in the anatomical exploration of the kidney. While the latter requires the injection of potentially nephrotoxic contrast medium, ultrasound is non-invasive and provides all the necessary anatomic data about kidney size and shape, cortical thickness, urinary tract obstruction and renal masses. Assessing the presence of protein, erythrocytes and leucocytes in the urine, as well as measuring serum creatinine concentration, are the appropriate functional screening tests for renal parenchymal disease. These tests should be performed in all patients with hypertension.

Renal parenchymal disease may be excluded if urine analysis and serum creatinine concentration are normal on repeated determinations. The presence of erythrocytes and leucocytes should be confirmed by microscopic examination of the urine. If the screening tests for renal parenchymal hypertension are positive, a detailed work-up for kidney disease should ensue.

Renovascular hypertension is the second most common cause of secondary hypertension, its prevalence being approximately 2% of adult patients with blood pressure elevation when assessed in specialized centres. This is caused by one or more stenoses of the extra-renal arteries which in the elderly population have fre-

quently an atherosclerotic nature. Fibromuscular dysplasia accounts for up to 25% of total cases and is the most common variety in young adults. Arterial hypertension of abrupt onset or worsening as well as high blood pressures increasingly difficult to treat suggest the presence of this condition. Signs of renal artery stenosis include abdominal bruit with lateralization, hypokalaemia and progressive decline in renal function. However, these signs are not present in many patients with renovascular hypertension. Determination of the longitudinal diameter of the kidney using ultrasound can be used as a screening procedure. However, a difference of more than 1.5 cm in length between the two kidneys, which is usually considered as being diagnostic for renal artery stenosis is only found in 60–70% of the patients with renovascular hypertension. Colour Doppler ultrasonography is often able to detect stenosis of the renal artery, particularly when localized close to the origin of the vessel. In addition, it allows determination of the resistance index that can be predictive of outcome from angioplasty and stenting. There is evidence that investigations of the renal vasculature by breath-hold three-dimensional, gadoliniumenhanced magnetic resonance angiography is the diagnostic procedure of choice for renovascular hypertension. Another imaging procedure with similar sensitivity is spiral computed tomography, which, however, requires the application of contrast media and the use of relatively high X-ray doses. Once there is a strong suspicion of renal artery stenosis, intra-arterial digital subtraction angiography should be performed for confirmation. This invasive procedure is still the gold standard for the detection of renal artery stenosis. The determination of the renal vein rennin ratio requires multiple catheterization and its invasiveness and complexity is not compensated by an acceptable level of sensitivity or specificity. It cannot thus be recommended as a screening procedure.

Treatment of patients with renovascular hypertension is a controversial issue due to the limited number of large scale long-term outcome trials comparing different therapeutic approaches, and to the difficulty of predicting the blood pressure response to renal revascularization procedures in individual patients. However, available data justify the following recommendations:

1) refractory hypertension (i.e. elevated blood pressure values despite administration of at least three drugs, including a diuretic at adequate doses) as well as a progressive decline in renal function represent an indication for revascularization;

2) although different opinions exist, surgical revascularization is now performed less frequently and is being progressively replaced by angioplasty;

3) angioplasty alone is the treatment of choice in fibromuscular dysplasia in which it is followed by a high rate of therapeutic success, i.e. persistent blood pressure normalization or reduction with values more responsive to drug treatment. Success rate is less common in atherosclerotic disease, which has a greater incidence of restenosis, but restenosis can be reduced by stenting which is thus now almost regularly added to angioplasty in renovascular stenoses of atherosclerotic nature.

4) Medical treatment has been compared with angioplasty in a number of trials, the meta-analysis of which has shown a modest but significant advantage of angioplasty. The result of this procedure, however, heavily depends on the physician's skill and experience, and medical treatment remains of paramount importance for patients with atherosclerotic renovascular disease.

It should be regarded as the preferable option when renal function is preserved, blood pressure control can be achieved, renal artery stenosis is not tight or there is a long (e.g. >10 years) history of hypertension. Because of the high risk of progression of atherosclerotic lesions, their treatment consists of intense lifestyle modifications, low dose aspirin, statin and multiple antihypertensive drug administration. Use should be made of a thiazide diuretic at appropriate doses and a calcium antagonist with the possible addition of a renin-angiotensin blocker, except in the presence of bilateral renal artery stenosis. This treatment can lower blood pressure in the majority of patients with renovascular disease. The main risk is acute deterioration of renal function and increase in serum creatinine due to a marked reduction in perfusion pressure beyond the stenotic site. This is more common when a blocker of the renin-angiotensin system is used, but the serum creatinine change normally reverts when treatment is withdrawn.

Phaeochromocytoma is a very rare secondary hypertensive state (0.2–0.4% of all cases of elevated blood pressure) with an estimated annual incidence of 2–8 per million population. It can be inherited or acquired. Hypertension occurs in about 70% of all cases of phaeochromocytoma, being stable or paroxysmal (presenting with symptoms such as headache, sweating, palpitations and pallor) in approximately equal proportions. The diagnosis is based on establishing an increase in plasma or urinary catecholamines or their metabolites. It can be supported by pharmacological tests which should precede the carrying out of functional imaging procedures designed to localize the tumour. The test that achieves the highest sensitivity (97–98%) is the measurement of plasma free metanephrines, together with urinary fractionated metanephrines. However, because measurement of plasma free metanephrines is not available for routine diagnosis, measurement of urinary fractionated metanephrines and urinary cathecolamines remains the diagnostic test of choice. Very high values require no further testing. On the other hand, when plasma or urine values are only modestly elevated, despite there being a strong clinical suspicion of phaeochromocytoma, then stimulation or suppression tests with glucagon or clonidine, respectively, can be carried out, although in case of borderline results of biochemical tests (and given the limited specificity of the responses to pharmacological tests) many clinicians prefer to proceed directly to imaging methods. The glucagon test must be performed after the patient has been effectively treated with an alpha-adrenoreceptor antagonist to prevent marked blood pressure increases after injection of the hormone. The clonidine suppression test is regarded as negative when there is a marked reduction of plasma catecholamines. After the diagnosis of phaeochromocytoma has been made, localization of the tumour is mandatory. Ninety-five per cent are located in or close to the adrenal glands and, since they are often large tumours, they can sometimes be detected by ultrasound. However, the most sensitive procedures (98–100%) are CT and, particularly, magnetic resonance imaging (MRI), which, however, has a low specificity (50%). Complementary to a CT scan or MRI, isotopic scanning using meta-iodobenzylguanidine may be useful in localizing extra-adrenal phaeochromocytomas and metastases from the 10% of phaeochromocytomas that are malignant, or to

functionally confirm phaeochromocytomas localized by CT or MRI. There are several familial disorders that are associated with an increased incidence of phaeochromocytoma, and these include multiple endocrine neoplasia type 2 (MEN2), von Hippel-Lindau disease (VHL), and neurofibromatosis type 1. Familial paragangliomas also cluster with pheochromocytoma. It is therefore recommended to offer genetic tests to patients and their family members, especially if phaeochromocytoma is associated with hereditary syndromes. To date, germline mutations in five genes have been described leading to familial disorders associated with phaechromocytomas. Definite treatment requires excision of the tumour. In advance of this the patient must be adequately prepared. This requires the introduction of an a adrenoreceptor blocker and, after adequate treatment with this blocker, b-blockers can be introduced. Surgical excision, these days often carried out laparoscopically, can then follow, but after adequate fluid replacement had been effected. This is necessary because protracted exposure to phaeochromocytoma causes pressure natriuresis and venoconstriction with a marked volume depletion.

Primary aldosteronism has become a prominent area of controversy in hypertension management in recent years. This is because the prevalence varies in different studies of unselected primary hypertensives from 1% to 11%. As a screening test the determination of serum potassium levels is regarded as important but only a small number of patients will have hypokalaemia at an early stage in their disease. Thirty per cent of cases of primary aldosteronism are caused by adrenal adenomas which are commoner in women and rarer in children. Seventy per cent of cases are caused by adrenal hyperplasia and there are rare cases of adrenal carcinoma and the autosomal dominant condition of glucocorticoid remediable aldosteronism. The blood pressure profile is one of a moderate or marked elevation resistant to treatment. Glucocorticoid remediable hypertension appears early in life and usually in childhood. There are associations of primary aldosteronism with phaeochromocytoma, hyperparathyroidism and acromegaly. It has been suggested that only patients with unprovoked hypokalaemia or truly resistant hypertension should be evaluated for primary aldosteronism. The condition should be suspected in resistant hypertension and in unprovoked hypo-

kalaemia. It can be confirmed by the fludrocortisones suppression test (failure of 4 day administration of the hormone to reduce plasma aldosterone below its threshold value), and measurement of aldosterone and renin under standardized conditions. In recent years there has been a move to measure the aldosterone-to-renin ratio. However, aldosterone can be high or the renin low in elderly people or black patients. Also, a high aldosterone-to-renin ratio is seen in chronic renal disease, where a high potassium stimulates aldosterone release, and in the case of rare genetic mutations leading to increased aldosterone levels. The usefulness of these measurements is therefore controversial. Imaging of the adrenal glands is now usually carried out using CT, magnetic resonance imaging or isotopic techniques using radio labelled cholesterol. However, adenomas on CT or magnetic resonance imaging can turn out to be due to hyperplasia. False positive results are likely to be relatively frequent, because nodular hyperplasia of the zona glomerulosa is reported even in the presence of functioning adenomas, and observed adenomas may actually be non-functioning. This means that, if imaging is used, it may have to be supplemented with adrenal venous sampling. There are reports suggesting that unless this is carried out, on the basis of CT alone, 25% of patients would have had unnecessary adrenalectomy. The surgical technique for removal of a suspected adenoma is laparoscopic adrenalectomy. Series report no deaths and minimal morbidity with a mean post-operative stay of 2.6 days. Prior to surgery or in the case of adrenal hyperplasia, treatment with an aldosterone antagonist such as spironolactone is advised. However, this is associated with side effects such as gynaecomastia which may reduce its usefulness. In this case eplerenone may be considered, although at recommended doses its effect is less than that of spironolactone.

Cushing's syndrome affects <0.1% of the total population. Hypertension is a very common finding and is reported in about 80% of such patients, with a 50% prevalence when the disease occurs in children and adolescents. Usually, the syndrome is suggested by the typical body habitus of the patient. The determination of 24-hour urinary cortisol excretion is the most practical and reliable diagnostic test and a value exceeding 110 mmol (40 mg) is highly suggestive of Cushing's syndrome. The diag-

nosis is confirmed by the 2-day, low-dose dexamethasone suppression test (0.5 mg every 6 h for eight doses) or the overnight dexamethasone suppression test (1 mg at 23.00 h). In the 2-day test, a urinary cortisol excretion higher than 27 mmol (10 mg) per day on day 2 indicates Cushing's syndrome. The same is true if plasma cortisol concentration is greater than 140 mmol/l (5 mg/dl) at 8.00 h in the overnight test. A normal result excludes the possibility of Cushing's syndrome. Recently the determination of mid/late-night serum or salivary cortisol has been suggested as a simpler approach to the diagnosis. Further tests and imaging procedures have to be used to differentiate the various forms of the syndrome.

Obstructive sleep apnoea (OSA) is characterized by recurrent episodes of cessation of respiratory airflow caused by upper airway inspiratory collapse during sleep, with a consequent decrease in oxygen saturation. It is important to consider sleep apnoea in the characterization of obese patients, especially those with hypertension resistant to conventional drug therapy. Furthermore, hypertensive patients, who are classified as 'non-dippers' on ambulatory pressure measurements, should be investigated for obstructive sleep apnoea. Signs and symptoms include daytime somnolence, impaired concentration, unrefreshing and restless sleep, choking episodes during sleep, witnessed apnoeas, nocturia, irritability and personality changes, decreased libido and increased motor vehicle accidents. Where suspected, one should use one of the validated questionnaires: the Epworth Sleepiness Scale or the Berlin Questionnaire.

Polysomnography remains the 'gold standard' diagnostic tool for assessing sleep-disordered breathing. The apnoea-hypopnoea index (i.e. the number of apnoeic and hypopnoeic events per hour) is used as an index of the presence and severity of the syndrome. An apnoeahypopnoea index of 5 to 15 indicates mild apnoea; of 15 to 30, moderate apnoea; and of greater than 30, severe apnoea. Untreated obstructive sleep apnoea may have direct and deleterious effects on cardiovascular function and structure through several mechanisms, including sympathetic activation, oxidative stress, inflammation and endothelial dysfunction. The syndrome may contribute to the elevated pressure in a large proportion of hypertensive patients, the pressor effect

being possibly generated by an impairment of reflex cardiovascular regulation and endothelial dysfunction. Weight loss in obese subjects ameliorates the syndrome, which is also improved by using positive pressure breathing equipment.

Coarctation of the aorta is a rare form of hypertension in children and young adults. The diagnosis is usually evident from physical examination. A midsystolic murmur, which may become continuous with time, is heard over the anterior part of the chest and also over the back. The femoral pulse is absent or delayed relative to the radial pulse. Hypertension is found in the upper extremities concomitantly with low or unmeasurable blood pressure in the legs. After repair or stenting, especially in adults, hypertension may persist due to haemodynamic and vascular effects, and many patients need to continue antihypertensive therapy.

Drug-induced hypertension. Substances or drugs that can raise blood pressure include: liquorice, oral contraceptives, steroids, non steroidal anti-inflammatory drugs, cocaine and amphetamines, erythropoietin, cyclosporins, tacrolimus. The patient should be asked about their medication at the time their clinical history is taken, and the use of drugs that can raise blood pressure should be monitored carefully.

In conclusion, a realization of these objectives will depend largely on the efforts of doctors in general practice. Surveys revealing incomplete detection, treatment, and control of hypertension indicate a serious failure to implement the knowledge we have. Ideally, all practices or primary care groups should develop a protocol for hypertension management that covers screening policy; initial evaluation and investigation; estimation of cardiovascular risk; non-pharmacological measures; use of antihypertensive drugs, aspirin, and statins; treatment targets; follow up strategy; and methods for identifying and recalling patients who drop out of follow up.

CHAPTER 2

ACUTE AND CHRONIC HEART FAILURE. DIAGNOSIS AND MANAGEMENT APPROACHES

Foreword

Heart failure is the end stage of cardiac disease after the myocardium has used all its reserve and compensatory mechanisms. Once overt signs appear, half of patients die within 5 years despite medical management. Heart failure is most often a consequence of hypertension, CHD, valve deformity, diabetes, or cardiomyopathy. The various etiologies tend to coexist. CHD, frequently accompanied by hypertension, is responsible in more than 50 percent of cases and has been increasing in prevalence among new cases of heart failure. Left ventricular hypertrophy, hypertension, and valvular diseases are diminishing determinants. The risk of cardiac failure is increased two- to sixfold with CHD, angina conferring half the risk compared with MI. The dominant cause continues to be hypertension, which precedes failure in 75 percent of patients.

Based on the Framingham Study, heart failure is equally frequent in men and women, and the annual occurrence approaches 10 per 1000 population after 65 years of age. Survival following the diagnosis of heart failure is worse in men than in women, but even in women fewer than 15 percent survive much longer than 8 to 12 years. The prognosis is not much better than for most forms of cancer. The 1-year fatality rate for heart failure is high, with one in five patients dying. Sudden death is a common mode of exitus, occurring at six to nine times the general population rate. With an increasing geriatric population, heart failure is a formidable problem. There is little indication that the declines in death rates from heart disease in general and from CHD in particular in the United States have been accompanied by an improvement in the incidence of heart failure. This cannot be readily explained. Some postulate that improved survival of patients with angina, MI, and hypertensive heart disease may result in an increased prevalence of chronic heart disease and ultimately heart failure. Data from the Framingham Study indicate very little improvement to date in the ominous outlook following the onset of CHF. The median survival of 652

incident cases of CHF was only 1.7 years in men and 3.2 years in women, and the overall survival rates at 5 years were only 25 percent for men and 38 percent for women. The mortality increased with age in both sexes. If one adjusts for age, no significant changes in the prognosis of CHF are evident over the past four decades despite improvements in treatment. Advances in treatment of hypertension, myocardial ischemia, and valvular heart disease have not resulted in dramatic improvements in survival once heart failure ensues. Despite the availability of potent glycosides, diuretics, and antihypertensive agents, heart failure continues at a high incidence. Because of the high attributable risk of hypertension and CHD, their prevention and effective treatment would appear to be required to make a significant impact on the incidence of congestive heart failure.

The Task Force has classified and ranked heart failure as at least two different conditions: acute or acute decompensated HF and chronic HF.

Part I. Acute Heart Failure

Definition

Acute heart failure (AHF) is defined as the rapid onset of symptoms and signs secondary to abnormal cardiac function. It may occur with or without previous cardiac disease. The cardiac dysfunction can be related to systolic or diastolic dysfunction, to abnormalities in cardiac rhythm, or to preload and afterload mismatch. It is often life threatening and requires urgent treatment. AHF can present itself as acute de novo (new onset of acute heart failure in a patient without previously known cardiac dysfunction) or acute decompensation of CHF.

The patient with AHF may present with one of several distinct clinical conditions:

- Acute decompensated heart failure (de novo or as decompensation of CHF) with signs and symptoms of AHF, which are mild and do not fulfil criteria for cardiogenic shock, pulmonary oedema, or hypertensive crisis.
- Hypertensive AHF: Signs and symptoms of heart failure are accompanied by high blood pressure and relatively preserved left ventricular function with a chest radiograph compatible with acute pulmonary oedema.

- Pulmonary oedema (verified by chest X-ray) accompanied by severe respiratory distress, with crackles over the lung and orthopnoea, with O2 saturation usually, 90% on room air prior to treatment.
- Cardiogenic shock: Cardiogenic shock is defined as evidence of tissue hypoperfusion induced by heart failure after correction of preload. There is no clear definition for haemodynamic parameters, which explains the differences in prevalence and outcome reported in studies, but cardiogenic shock is usually characterized by reduced blood pressure (systolic BP < 90 mmHg or a drop of mean arterial pressure .30 mmHg) and/or low urine output (0.5 ml/kg/h), with a pulse rate <60 bpm with or without evidence of organ congestion. There is a continuum from low cardiac output syndrome to cardiogenic shock.
- High output failure is characterized by high cardiac output, usually with high heart rate (caused by arrhythmias, thyrotoxicosis, anaemia, Paget's disease, iatrogenic or by other mechanisms), with warm peripheries, pulmonary congestion, and sometimes with low BP as in septic shock.
- Right heart failure is characterized by low output syndrome with increased jugular venous pressure, increased liver size and hypotension.

Various other classifications of the AHF syndrome are utilized in coronary care and intensive care units. The Killip classification is based on clinical signs and chest X-ray findings, and the Forrester classification is based on clinical signs and haemodynamic characteristics. These classifications have been validated in AHF after AMI and thus are best applied to de novo AHF. The third 'clinical severity' classification has been validated in a cardiomyopathy service and is based on clinical findings. It is most applicable to chronic decompensated heart failure.

Killip classification.

The Killip classification was designed to provide a clinical estimate of the severity of myocardial derangement in the treatment of AMI:

- Stage I - No heart failure. No clinical signs of cardiac decompensation;

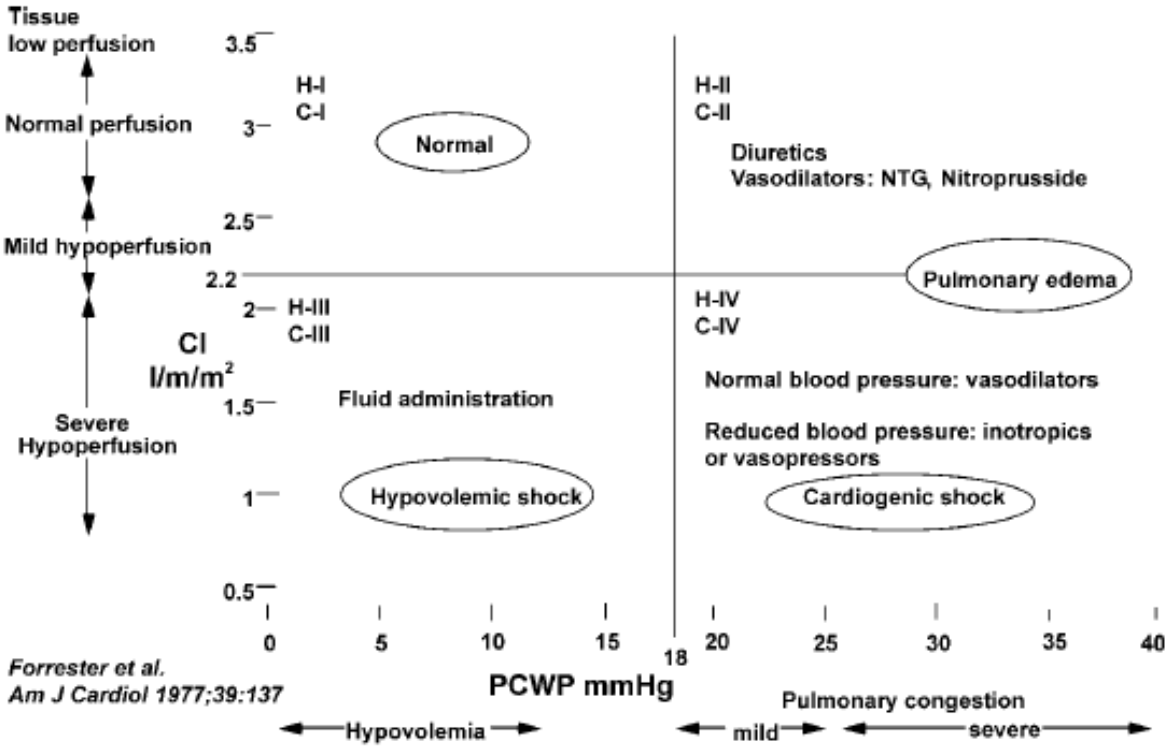
- Stage II - Heart failure. Diagnostic criteria include rales, S3 gallop and pulmonary venous hypertension. Pulmonary congestion with wet rales in the lower half of the lung fields;
- Stage III - Severe heart failure. Frank pulmonary oedema with rales throughout the lung fields;
- Stage IV - Cardiogenic shock. Signs include hypotension (SBP ≤ 90 mmHg), and evidence of peripheral vasoconstriction such as oliguria, cyanosis, and diaphoresis.

Forrester classification.

The Forrester AHF classification was also developed in AMI patients, and describes four groups according to clinical and haemodynamic status (Figure 2.1).

Figure 2.1.

Clinical classification of the mode of heart failure (Forrester classification). H I–IV refers to haemodynamic severity, with reference figures for cardiac index and pulmonary capillary pressures shown on the vertical and horizontal axes, respectively. C I–IV refers to clinical severity.



Patients are classified clinically on the basis of peripheral hypoperfusion (filliform pulse, cold clammy skin, peripheral cyanosis, hypotension, tachycardia, confu-

sion, oliguria) and pulmonary congestion (rales, abnormal chest X-ray), and haemodynamically on the basis of a depressed cardiac index (≤2.2 L/min/m2) and elevated pulmonary capillary pressure (18 mmHg). The original paper defined the treatment strategy according to the clinical and haemodynamic status. Mortality was 2.2% in group I, 10.1% in group II, 22.4% in group III, and 55.5% in group IV.

Clinical severity classification.

The clinical severity classification is based on observation of the peripheral circulation (perfusion) and on auscultation of the lungs (congestion). The patients can be classified as Class I (Group A) (warm and dry), Class II (Group B) (warm and wet), Class III (Group L) (cold and dry), and Class IV (Group C) (cold and wet). This classification has been validated prognostically in a cardiomyopathy service and is therefore applicable to patients with CHF, whether hospitalized or outpatients.

The clinical syndrome of AHF

AHF is a clinical syndrome, with reduced cardiac output, tissue hypoperfusion, increase in the pulmonary capillary wedge pressure, and tissue congestion. The underlying mechanism may be cardiac or extra-cardiac, and may be transient and reversible with resolution of the acute syndrome or may induce permanent damage leading to chronic heart failure. The cardiac dysfunction can be related to systolic or diastolic myocardial dysfunction (mainly induced by ischaemia or infection), acute valvular dysfunction, pericardial tamponade, abnormalities of cardiac rhythm, or preload/afterload mismatch. Multiple extra-cardiac pathologies may result in AHF by changing the cardiac loading conditions for example (I) increased afterload due to systemic or pulmonary hypertension or massive pulmonary emboli, (II) increased preload due to increased volume intake or reduced excretion due to renal failure or endocrinopathy, or (III) high output state due to infection, thyrotoxicosis, anaemia, and Paget's disease. Heart failure can be complicated by co-existing end-organ disease. Severe heart failure can also induce multi-organ failure, which may be lethal.

Appropriate long-term medical therapy and, if possible, anatomical correction of the underlying pathology may prevent further AHF syndrome 'attacks' and improve the poor long-term prognosis associated with this syndrome. The clinical AHF syn-

drome may be classified as predominantly left or right forward failure, left or right backward failure, or a combination of these.

Forward (left and right) AHF may be mild-to-moderate with only effort fatigue, up to severe with manifestations of reduced tissue perfusion at rest with weakness, confusion, drowsiness, paleness with peripheral cyanosis, cold clammy skin, low blood pressure, filliform pulse, and oliguria, culminating in the full blown presentation of cardiogenic shock.

This syndrome may be induced by a large variety of pathologies. An adequate history may indicate the main diagnosis for example acute coronary syndrome with the relevant risk factors, past history, and suggestive symptoms; acute myocarditis with a recent history suggestive of acute viral infection; acute valvular dysfunction with a history of chronic valve disease or valve surgery, infection with the possibility of bacterial endocarditis, or chest trauma; pulmonary embolism with a relevant history and suggestive symptoms; or pericardial tamponade.

Physical examination of the cardiovascular system may be indicative of the main diagnosis, for example by distended neck veins and paradoxical pulse (pericardial tamponade), muffled heart sounds related to myocardial systolic dysfunction, or the disappearance of artificial valve sounds or an appropriate murmur indicating a valvular problem.

In forward AHF immediate management should include supportive treatment to improve cardiac output and tissue oxygenation. This can be achieved with vasodilating agents, fluid replacement to achieve an optimal preload, short-term inotropic support and (sometimes) intra aortic balloon counterpulsation.

Left-heart backward failure.

Left-heart backward failure may be related to left ventricular dysfunction with varying degrees of severity from mild-to-moderate with only exertional dyspnoea, to pulmonary oedema presenting with shortness of breath (dry cough, sometimes with frothy sputum), pallor or even cyanosis, cold clammy skin, and normal or elevated blood pressure. Fine rales are usually audible over the lung fields.

Chest X-ray shows pulmonary congestion/oedema.

Pathology of the left heart may be responsible for this syndrome, including: myocardial dysfunction related to chronic existing conditions; acute insult such as myocardial ischaemia or infarction; aortic and mitral valve dysfunction; cardiac rhythm disturbances; or tumours of the left heart. Extra-cardiac pathologies may include severe hypertension, high output states (anaemia, thyrotoxicosis), and neurogenic states (brain tumours or trauma).

Physical examination of the cardiovascular system, including the apex beat, the quality of the heart sounds, the presence of murmurs, and auscultation of the lungs for fine rales and expiratory wheezing (‘cardiac asthma’) may be indicative of the main diagnosis. In left heart backward failure patients should be treated mainly with vasodilation and the addition of diuretics, bronchodilators, and narcotics, as required. Respiratory support may be necessary. This can either be with continuous positive airway pressure (CPAP) or non-invasive positive pressure ventilation, or in some circumstances invasive ventilation may be required following endotracheal intubation.

Right-heart backward failure.

The syndrome of acute right heart failure is related to pulmonary and right heart dysfunction, including exacerbations of chronic lung disease with pulmonary hypertension, or acute massive lung disease (e.g. massive pneumonia or pulmonary embolism), acute right ventricular infarction, tricuspid valve malfunction (traumatic or infectious), and acute or subacute pericardial disease. Advanced left heart disease progressing to right sided failure should also be considered, and similarly long standing congenital heart disease with evolving right ventricular failure should be taken into account. Non-cardiopulmonary pathologies include nephritic/nephrotic syndrome and end-stage liver disease. Various vasoactive peptidesecreting tumours should also be considered.

The typical presentation is with fatigue, pitting ankle oedema, tenderness in the upper abdomen (due to liver congestion), shortness of breath (with pleural effusion), and distension of the abdomen (with ascites). The fullblown syndrome includes anasarca with liver dysfunction and oliguria.

History and physical examination should confirm the syndrome of acute right heart failure, indicate the suspected diagnosis and guide further investigation, which is likely to include ECG, blood gases, D-dimer, chest X-ray, cardiac Doppler-echocardiography, pulmonary angiography, or chest CT scan.

In right heart backward failure fluid overload is managed with diuretics, including spironolactone and sometimes with a short course of low dose (‘diuretic dose’) of dopamine. Concomitant treatment may include antibiotics for pulmonary infection and bacterial endocarditis; Ca^{2+} channel blockers, nitric oxide, or prostaglandins for primary pulmonary hypertension; and anticoagulants, thrombolytics, or thrombectomy for acute pulmonary embolism.

Pathophysiology of AHF

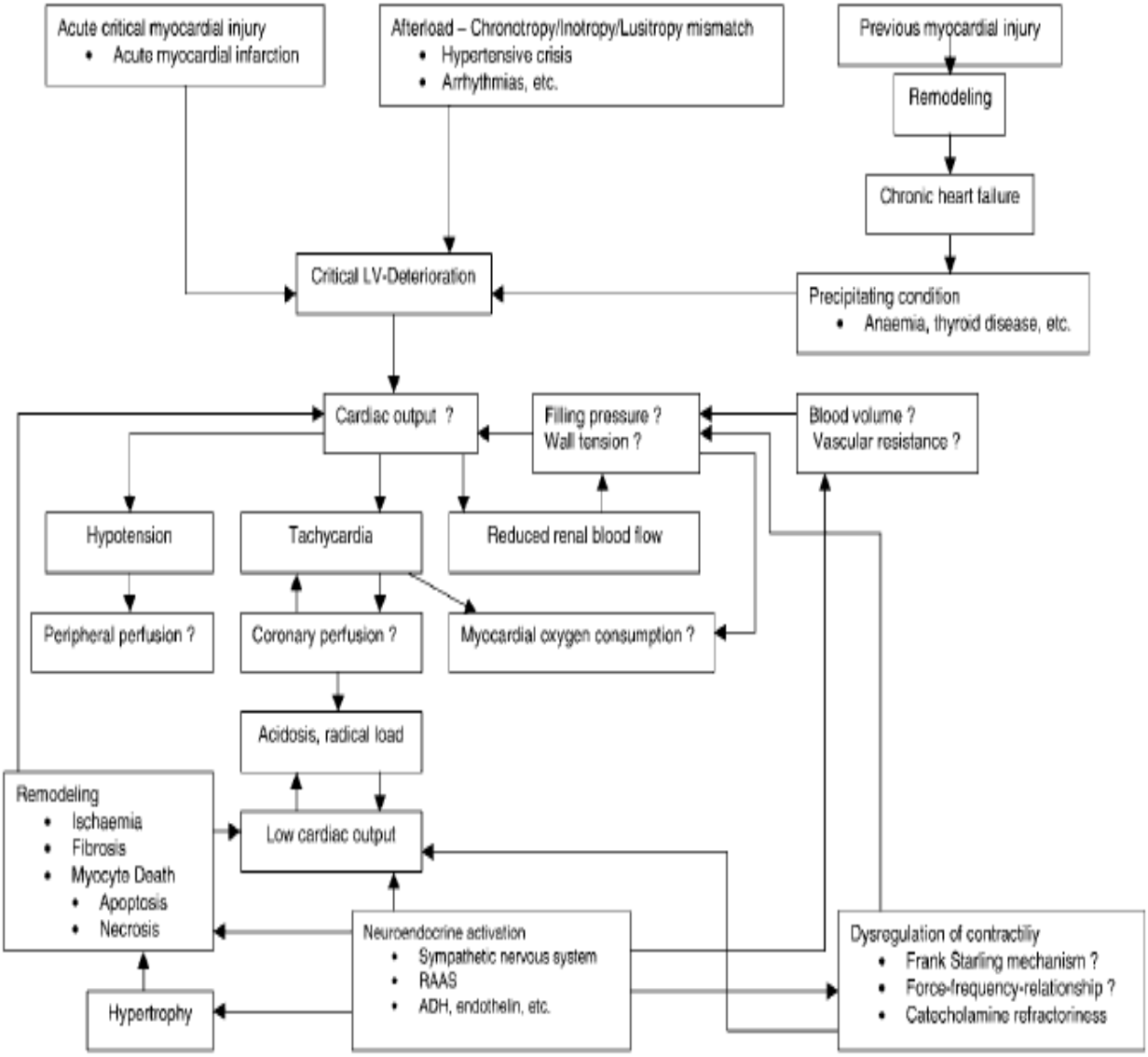
The vicious cycle in the acute failing heart

The final common denominator in the syndrome of AHF is a critical inability of the myocardium to maintain a cardiac output sufficient to meet the demands of the peripheral circulation. Irrespective of the underlying cause of AHF a vicious cycle is activated that, if not appropriately treated, leads to chronic heart failure and death. This is shown in Figure 2.2, and is described in detail elsewhere.

In order for patients with AHF to respond to treatment the myocardial dysfunction must be reversible. This is particularly important in AHF due to ischaemia, stunning or hibernation, where a dysfunctional myocardium can return to normal when appropriately treated.

Figure 2.2.

Pathophysiology of the syndrome of AHF. Following acute critical events, LV deterioration occurs rapidly and requires urgent medical treatment.



Myocardial stunning

Myocardial stunning is the myocardial dysfunction that occurs following prolonged ischaemia, which may persist in the short-term even when normal blood flow is restored. This phenomenon has been described experimentally as well as clinically. Mechanisms of dysfunction are excessive oxidative stress, changes in Ca^{2+} homeostasis, and Ca^{2+} desensitization of contractile proteins, as well as myocardial depressant factors. The intensity and duration of stunning is dependent on the severity and duration of the preceding ischaemic insult.

Hibernation

Hibernation is defined as an impairment of myocardial function due to severely reduced coronary blood flow although myocardial cells are still intact. By improving

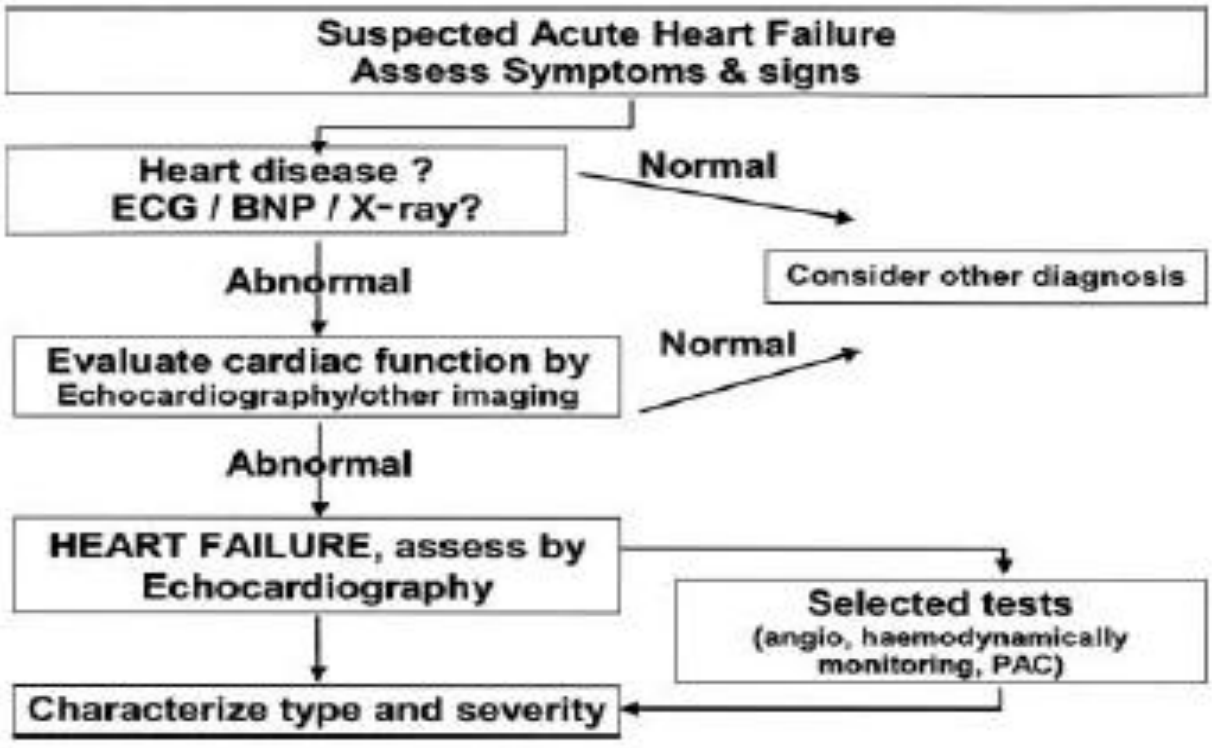
blood flow and oxygenation, hibernating myocardium can restore its normal function. Hibernation can be regarded as an adaptive mechanism to reduce oxygen consumption to prevent ischaemia and necrosis following reduced blood flow to the myocardium. Hibernating myocardium and stunning can co-exist. Hibernation improves in time with reinstitution of blood flow and oxygenation, whilst stunned myocardium retains inotropic reserve and can respond to inotropic stimulation. Since these mechanisms depend on the duration of myocardial damage, a rapid restoration of oxygenation and blood flow is mandatory to reverse these pathophysiological alterations.

Diagnosis of AHF

The diagnosis of AHF is based on the symptoms and clinical findings, supported by appropriate investigations such as ECG, chest X-ray, biomarkers, and Doppler-echocardiography (Figure 2.3).

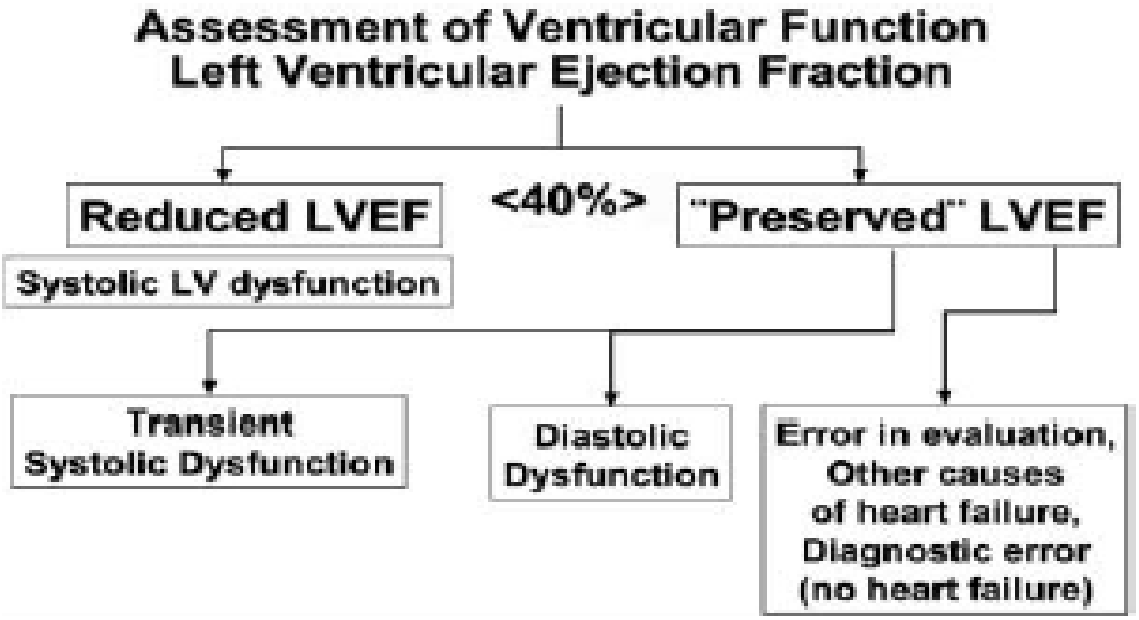
Figure 2.3.

Diagnosis of AHF.



The patient should be classified according to previously described criteria for systolic and/or diastolic dysfunction (Figure 2.4), and by the characteristics of forward or backward left or right heart failure.

Figure 2.4.



Clinical evaluation

Systematic clinical assessment of the peripheral circulation, venous filling, and peripheral temperature are important. Right ventricular filling in decompensated heart failure may usually be evaluated from the central jugular venous pressure. When the internal jugular veins are impractical for evaluation (e.g. due to venous valves) the external jugular veins can be used. Caution is necessary in the interpretation of high measured central venous pressure (CVP) in AHF, as this may be a reflection of decreased venous compliance together with decreased RV compliance even in the presence of inadequate RV filling. Left sided filling pressure is assessed by chest auscultation, with the presence of wet rales in the lung fields usually indicating raised pressure. The confirmation, classification of severity, and clinical follow up of pulmonary congestion and pleural effusions should be done using the chest X-ray. In acute conditions the clinical evaluation of left sided filling pressure may be misleading due to the rapidly evolving clinical situation. Cardiac palpation and auscultation for ventricular and atrial gallop rhythms (S3, S4) should be performed. The quality of the heart sounds, and presence of atrial and ventricular gallops and valvular murmurs are important for diagnosis and clinical assessment. Assessment of the extent of arteriosclerosis by detecting missing pulses and the presence of carotid and abdominal bruits is often important, particularly in elderly subjects.

Electrocardiogram

A normal electrocardiogram (ECG) is uncommon in AHF. The ECG is able to identify the rhythm, and may help determine the aetiology of AHF and assess the loading conditions of the heart. It is essential in the assessment of acute coronary syndromes. The ECG may also indicate acute right or left ventricular or atrial strain, perimyocarditis and pre-existing conditions such as left and right ventricular hypertrophy or dilated cardiomyopathy. Cardiac arrhythmia should be assessed in the 12-lead ECG as well as in continuous ECG monitoring.

Chest X-ray and imaging techniques

Chest X-ray and other imaging should be performed early for all patients with AHF to evaluate pre-existing chest or cardiac conditions (cardiac size and shape) and to assess pulmonary congestion. It is used both for confirmation of the diagnosis, and for follow-up of improvement or unsatisfactory response to therapy. Chest X-ray allows the differential diagnosis of left heart failure from inflammatory or infectious lung diseases. Chest CT scan with or without contrast angiography and scintigraphy may be used to clarify the pulmonary pathology and diagnose major pulmonary embolism. CT scan, transesophageal echocardiography, or MRI should be used in cases of suspicion of aortic dissection.

Laboratory tests

A number of laboratory tests should be performed in AHF patients. Arterial blood gas analysis (Astrup' micro method) enables assessment of oxygenation (pO_2), respiratory adequacy (pCO_2), acid–base balance (pH), and base deficit, and should be assessed in all patients with severe heart failure. Non-invasive measurement with pulse oximetry and end-tidal CO_2 can often replace Astrup (Level of evidence C) but not in very low output, vasocontricted shock states. Measurement of venous O_2 saturation (i.e. in the jugular vein) may be useful for an estimation of the total body oxygen supply–demand balance.

Plasma B-type natriuretic peptide (BNP) is released from the cardiac ventricles in response to increased wall stretch and volume overload and has been used to exclude and/or identify congestive heart failure in patients admitted for dyspnoea to the

emergency department. Decision cut points of 300 pg/mL for NT-proBNP and 100 pg/mL for BNP have been proposed, but the older population has been poorly studied. During' 'flash' pulmonary oedema, BNP levels may remain normal at the time of admission. Otherwise, BNP has a good negative predictive value to exclude heart failure. The data are not consistent on reference values and on the effect of treatment. Various clinical conditions may affect the BNP concentration, including renal failure and septicaemia. If elevated concentrations are present, further diagnostic tests are required. If AHF is confirmed, increased levels of plasma BNP and NT-pro BNP carry important prognostic information. The exact role of BNP remains to be fully clarified.

Echocardiography

Echocardiography is an essential tool for the evaluation of the functional and structural changes underlying or associated with AHF, as well as in the assessment of acute coronary syndromes.

Echocardiography with Doppler imaging should be used to evaluate and monitor regional and global left and right ventricular function, valvular structure and function, possible pericardial pathology, mechanical complications of acute myocardial infarction, and, on rare occasions, space occupying lesions. Cardiac output can be estimated by appropriate Doppler aortic or pulmonary time velocity contour measurements. An appropriate echo-Doppler study can also estimate pulmonary artery pressures (from the tricuspid regurgitation jet) and has been also used for the monitoring of left ventricular preload. Echocardiography has not been validated with right heart catheterisation in patients with AHF.

Other investigations

In cases of coronary artery related complications such as unstable angina or myocardial infarction, angiography is important and angiography-based revascularization therapy has been shown to improve prognosis.

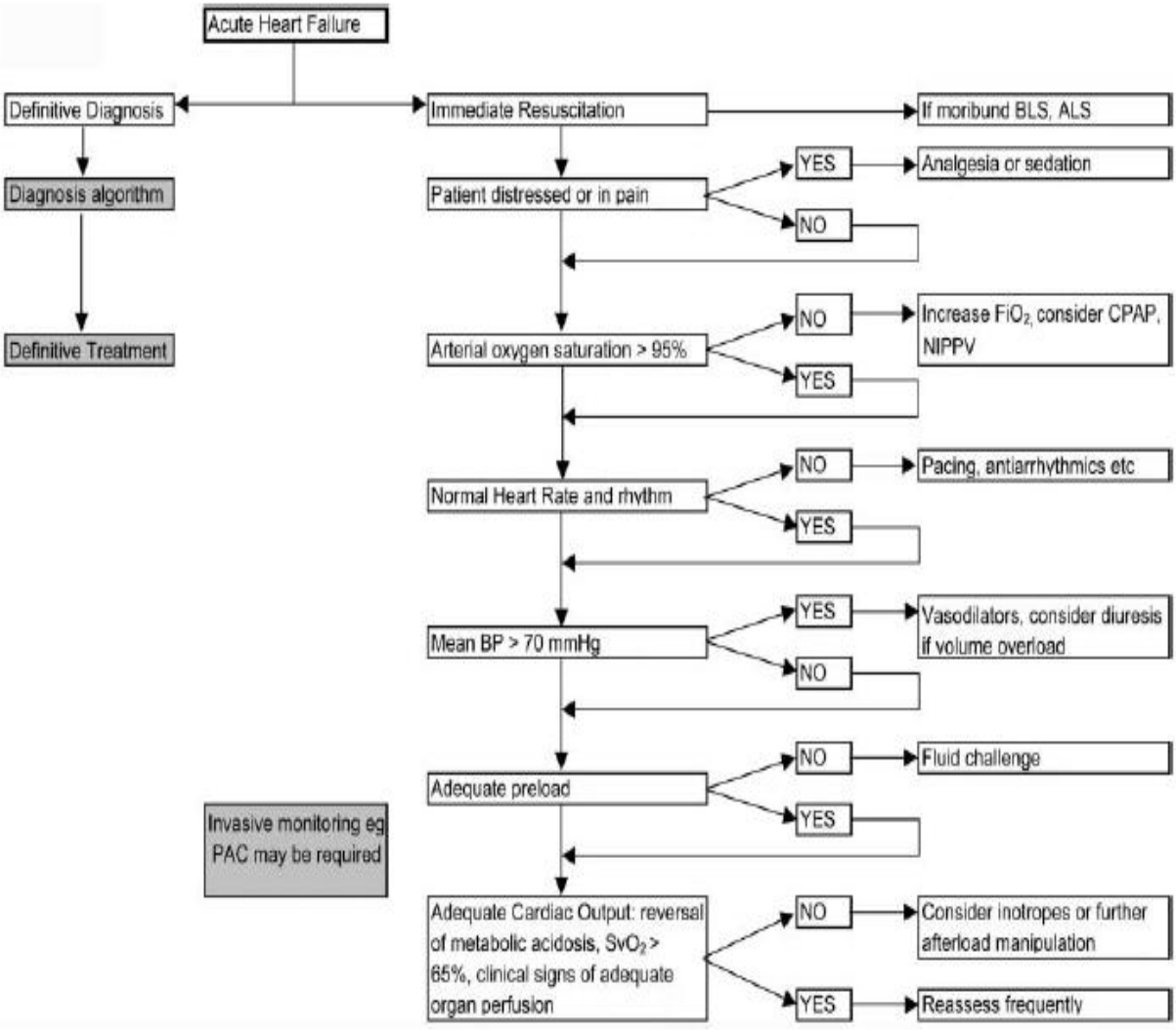
Coronary arteriography is also often indicated in prolonged AHF, unexplained by other investigations, as recommended in the guidelines for diagnosis of CHF. Insertion of a pulmonary artery catheter (PAC) may assist the diagnosis of and follow up AHF.

Goals of the treatment of AHF

The immediate goals are to improve symptoms and to stabilize the haemodynamic condition (Figure 2.5).

Figure 2.5.

Immediate goals in treatment of the patients with acute heart failure.



Note: in coronary patients mean blood pressure (mBP) should be higher to ensure coronary perfusion, mBP .70, or systolic .90 mmHg

An improvement in the haemodynamic parameters (primarily an increase in cardiac output and stroke volume and a reduction in the pulmonary capillary wedge pressure and right atrial pressure) have traditionally been regarded as beneficial effects of the treatment of AHF. An improvement in haemodynamic parameters only may be misleading, and a concomitant improvement in symptoms (dyspnoea and/or fatigue) is generally required. These short-term benefits must also be accompanied by

favourable effects on longerterm outcomes. This is likely to be achieved by avoidance, or limitation, of myocardial damage. Dyspnoea is the dominant symptom in AHF but is subjective. Objective assessment can be made by standardized tools, such as the Borg Rating of perceived exertion, indexes of dyspnoea, and various visual analogue scales. Changes from the initial assessment may be used as measures of improvement or deterioration. Another objective of treatment is the reduction in the clinical signs of heart failure, although these may often be difficult to quantify. A reduction in body weight and/or an increase in diuresis are beneficial effects of therapy in congestive and oliguric patients with AHF. Similarly, an improvement in oxygen saturation and in laboratory tests such as renal and/or hepatic function and/or serum electrolytes are meaningful goals of treatment. Plasma BNP concentration can reflect haemodynamic improvement and decreased levels are beneficial. However, short-term haemodynamic benefits may be dissociated from a favourable effect on prognosis. Thus, a beneficial (or at least a neutral) effect on patient outcome is required in addition to an improvement in symptoms and/or clinical signs. Beneficial effects of therapy on outcome include a reduction in the duration of intravenous vasoactive therapy, the length of stay (both in the intensive care unit and in the hospital), and a reduction in the readmission rate with an increase in the time to readmission. A reduction in both in-hospital and long-term mortality is the major goal of treatment although the effect of short-term treatment may be dissociated from the long-term effects. Lastly, a favourable safety and tolerability profile is also necessary for any treatment used in patients with AHF. Any agent used in this condition should be associated with a low withdrawal rate with a relatively low incidence of untoward side effects.

Instrumentation and monitoring of patients in AHF

Monitoring of the patient with AHF should be initiated as soon as possible after his/her arrival at the emergency unit, concurrently with ongoing diagnostic measures addressed at determining the primary aetiology. The types and level of monitoring required for any individual patient vary widely depending on the severity of the cardiac decompensation and the response to initial therapy. Local logistic issues may al-

so be relevant. There are no prospective randomized controlled outcome-based studies on the use of different monitoring modalities in AHF. The guidelines discussed here are therefore based on expert opinion.

Non-invasive monitoring

In all critically ill patients, monitoring the routine basic observations of temperature, respiratory rate, heart rate, the ECG, and blood pressure are mandatory. Some laboratory tests should be done repeatedly, i.e. electrolytes, creatinine and glucose or markers for infection or other metabolic disorders. Hypo- or hyperkalaemia must be controlled. These can all be monitored easily and accurately with modern automated equipment. If the patient becomes more unwell, the frequency of these observations will need to be increased. ECG monitoring (arrhythmias and ST segment) is necessary during the acute decompensation phase, particularly if ischaemia or arrhythmia is responsible for the acute event.

Blood pressure monitoring is critical during the institution of therapy and should be checked regularly (e.g. every 5 min), until the dosage of vasodilators, diuretics, or inotropes has been stabilized. The reliability of noninvasive, automatic plethysmographic measurement of blood pressure is good in the absence of intense vasoconstriction and very high heart rate.

The pulse oximeter is a simple non-invasive device that estimates the arterial saturation of haemoglobin with oxygen (SaO_2). The estimate of the SaO_2 is usually within 2% of a measured value from a co-oximeter, unless the patient is in cardiogenic shock. The pulse oximeter should be used continuously on any unstable patient who is being treated with a fraction of inspired oxygen (FiO_2) that is greater than air. It should also be used at regular intervals (every hour) in any patient receiving oxygen therapy for an acute decompensation.

Cardiac output and preload can be monitored noninvasively with the use of Doppler techniques. There is little to no evidence to help choose which of these monitors to use and it makes no difference as long as the limitations of an individual device are understood and the data are used appropriately.

Invasive monitoring

Arterial line. The indications for the insertion of an indwelling arterial catheter are the need for either continuous beat-to-beat analysis of arterial blood pressure due to haemodynamic instability especially with IABC or the requirement for multiple arterial blood analyses. The complication rate for the insertion of a 20-gauge 2-inch radial artery catheter is low.

Central venous pressure (CVP) *lines* provide access to the central venous circulation and are therefore useful for the delivery of fluids and drugs and can also be used to monitor the CVP and venous oxygen saturation (SvO_2) in the superior vena cava (SVC) or right atrium, which provides an estimate of oxygen transport. Caution has to be advised, however, to avoid the overinterpretation of right atrial pressure measurements, as these rarely correlate with left a trial pressures (and therefore LV filling pressures) in patients with AHF. CVP measurements are also affected by the presence of significant tricuspid regurgitation and positive endexpiratory pressure (PEEP) ventilation.

Pulmonary artery catheter. The pulmonary artery catheter (PAC) is a balloon flotation catheter that measures pressures in SVC, right atrium, right ventricle, and pulmonary artery as well as cardiac output. Modern catheters can measure the cardiac output semi-continuously as well as the mixed venous oxygen saturation and right ventricular end-diastolic volume and ejection fraction. The acquisition of these data can allow for a comprehensive evaluation of the cardiovascular haemodynamics. Although the insertion of a pulmonary artery catheter for the diagnosis of AHF is usually unnecessary, PAC can be used to distinguish between a cardiogenic and a non-cardiogenic mechanism in complex patients with concurrent cardiac and pulmonary disease. PAC is also frequently used to estimate PCWP, CO, and other haemodynamic variables and therefore guide therapy in the presence of severe diffuse pulmonary pathology or ongoing haemodynamic compromise not resolved by initial therapy. However, it should be remembered that PCWP is not an accurate reflection of LVEDP in patients with mitral stenosis (MS) or aortic regurgitation (AR), pulmonary and occlusion disease, ventricular interdependence, high airway pressure, and stiff LV (due to, e.g., LVH, diabetes, fibrosis, inotropes, obesity, ischaemia). Severe tri-

cuspid regurgitation, frequently found in patients with AHF, can overestimate or underestimate CO measured by thermodilution. Several retrospective studies assessing the use of the PAC in AMI demonstrated increased mortality with the PAC. These observations were partially explained by case-mix differences between the groups of the study. Similar observational findings have subsequently been reported in other groups of patients. A recent prospective randomized study enrolled a mixed group of critically ill patients to either a PAC group or to treatment without the use of data from a PAC. This study did not follow a protocol therapy in either group and failed to demonstrate a difference in outcome. Management with PAC led to increased fluid resuscitation within the first 24 h. The PAC did not cause harm to patients, rather it was the use of the information derived from the catheter (sometimes in an inappropriate fashion) that was detrimental. The use of a PAC is recommended in haemodynamically unstable patients who are not responding in a predictable fashion to traditional treatments, and in patients with a combination of congestion and hypoperfusion. In these cases, it is inserted in order to ensure optimal fluid loading of the ventricles and to guide vasoactive therapies and inotropic agents. Because the complications are increasing with the duration of its utilization, it is critical to insert the catheter when specific data are needed (usually regarding the fluid status of the patient) and to remove it as soon as it is not of further help (i.e. when diuretic and vasodilating therapy have been optimized).

In cardiogenic shock and prolonged severe low-output syndrome, it is recommended to measure the mixed venous oxygen saturation from the pulmonary artery as an estimation of oxygen extraction (SpO_2–SvO_2). The aim should be to maintain SvO_2. 65% in patients with AHF. Yet, severe MR may be misleading by increasing O_2 saturation measured from PAC.

II. Treatment of AHF

General medical issues in the treatment of AHF Infections: Patients with advanced AHF are prone to infectious complications, commonly respiratory or urinary tract infections, septicaemia, or nosocomial infection with Gram positive bacteria. In elderly patients with heart failure, infection such as pneumonia may be a cause for

worsening heart failure and dyspnoea. An increase in C-reactive protein (CRP) and a decrease in general condition may be the only signs of infection - fever may be absent. Meticulous infection control and measures to maintain skin integrity are mandatory. Routine cultures are recommended. Prompt antibiotic therapy should be given when indicated.

Diabetes: AHF is associated with impaired metabolic control. Hyperglycemia occurs commonly. Routine hypoglycemic drugs should be stopped and glycaemic control should be obtained by using short acting insulin titrated according to repeated blood glucose measurements. Normoglycemia improves survival in diabetic patients who are critically ill.

Catabolic state: Negative caloric and nitrogen balance is a problem in ongoing AHF. This is related to reduced caloric intake due to reduced intestinal absorption. Care should be undertaken to maintain calorie and nitrogen balance. Serum albumin concentration, as well as nitrogen balance, may help to monitor metabolic status.

Renal failure: A close interrelationship exists between AHF and renal failure. Both may cause, aggravate, and influence, the outcome of the other. Close monitoring of renal function is mandatory. Preservation of renal function is a major consideration in the selection of the appropriate therapeutic strategy for these patients.

Oxygen and ventilatory assistance

Rationale for using oxygen in AHF

The main priority in treating patients with AHF is the achievement of adequate levels of oxygenation at the cellular level in order to prevent end-organ dysfunction and the onset of multiple organ failure. The maintenance of SaO_2 within the normal range (95–98%) is thus important in order to maximize oxygen delivery to the tissues and tissue oxygenation.

This is best achieved first by ensuring that there is a patent airway and then by administration of an increased FiO_2. Maintenance of a patent airway is imperative. This can be achieved by using simple maneuvers or equipment. Endotracheal intubation is indicated if these measures fail to improve tissue oxygenation.

Despite this intuitive approach to giving oxygen, there is little to no evidence available that giving increasing doses of oxygen results in an improved outcome. The evidence available is controversial. Studies have demonstrated that hyperoxia can be associated with reduced coronary blood flow, reduced cardiac output, increased blood pressure, and increased systemic vascular resistance.

Ventilatory support without endotracheal intubation (non-invasive ventilation)

Two techniques are used for ventilatory support: CPAP or non-invasive positive pressure ventilation (NIPPV). NIPPV is a method of providing mechanical ventilation to patients without the need for endotracheal intubation. There is a strong consensus that one of these two techniques should be used before endotracheal intubation and mechanical ventilation. Utilization of noninvasive techniques dramatically reduce the need for endotracheal intubation and mechanical ventilation.

Medical treatment

Morphine and its analogues in AHF. Morphine is indicated in the early stage of the treatment of patient admitted with severe AHF especially if they present with restlessness and dyspnoea. Morphine induces venodilatation and mild arterial dilatation and has the ability to reduce heart rate. In most studies, intravenous boluses of morphine 3 mg were administered as soon as the intravenous line was inserted in AHF patients. It acts to relieve breathlessness and other symptoms in patients with CHF and AHF. This dosing can be repeated if required.

Anticoagulation is well established in acute coronary syndrome with or without heart failure. The same is true in atrial fibrillation. There is less evidence for the initiation of unfractionated heparin or low molecular heparin (LMWH) in AHF. A large placebo controlled trial of enoxaparine 40 mg subcutaneoulsy in acutely ill and hospitalised patients including a major group of heart failure patients showed no clinical improvement but less venous thrombosis. There are no large comparative studies comparing LMWH with unfractionated heparin (given as 5000 IU twice or three times daily). Careful monitoring of the coagulation system is mandatory in AHF as there is often concomitant liver dysfunction. LMWH is contraindicated if the creati-

nine clearance is 30 mL/min or should be used with extreme care with monitoring of the anti-Factor Xa level.

Vasodilators in the treatment of AHF. Vasodilators are indicated in most patients with AHF as first line therapy, if hypoperfusion is associated with an adequate blood pressure and signs of congestion with low diuresis, to open the peripheral circulation and to lower preload.

Nitrates relieve pulmonary congestion without compromising stroke volume or increasing myocardial oxygen demand in acute left heart failure, particularly in patients with acute coronary syndrome. At low doses they only induce venodilation, but as the dose is gradually increased they cause the arteries, including the coronary arteries, to dilate. With appropriate doses nitrates exert balanced vasodilation of the venous and arterial side of the circulation, thereby reducing left ventricular preload and afterload, without impairing tissue perfusion. Their effect on cardiac output depends on pre-treatment preload and afterload and the ability of the heart to respond to baroreceptorinduced increases in sympathetic tone. Initially nitrates may be given orally but intravenous nitrates are also well tolerated in AMI. Two randomized trials in AHF have established the efficacy of intravenous nitrates in combination with furosemide and have demonstrated that dose titration to the highest haemodynamically tolerable dose of nitrates with low dose furosemide is superior to high dose diuretic treatment alone.

In one of these randomized studies, furosemide and isosorbide dinitrate as bolus injections was tested and reported that intravenous high dose nitrate was more effective than furosemide treatment in controlling severe pulmonary oedema. In practical use, nitrates have a U-shaped curve effect. If given in sub-optimal doses vasodilators may have a limited effect in preventing acute heart failure recurrences. However, administration of high doses may also reduce their effectiveness. One disadvantage of nitrates is the rapid development of tolerance especially when given intravenously in high doses, limiting their effectiveness to 16–24 h only. Nitrates should be given at doses aimed at achieving optimal vasodilation, leading to an increase in cardiac index (CI)

and decrease in pulmonary wedge pressure. Inappropriate vasodilation may induce a steep reduction in blood pressure, which may result in haemodynamic instability.

Nitroglycerin can be administered orally or by inhalation [glycerylnitrate (GTN) spray 400 mg (2 puffs) every 5–10 min)] or buccally (isosorbide dinitrate 1 or 3 mg), while monitoring blood pressure. The intravenous administration and dosing of nitrates (GTN 20 mg/min increasing dose up to 200 mg/min, or isosorbide dinitrate 1–10 mg/h) should be done with extreme caution, under careful blood pressure monitoring, titrating the dose administered against blood pressure decrease. One should be particularly cautious when administering nitrates to a patient with aortic stenosis, although this therapy may help in these complex situations. The dose of nitrates should be reduced if systolic blood pressure decreases below 90–100 mmHg and discontinued permanently if blood pressure drops further. From a practical point of view a reduction of 10 mmHg in mean arterial pressure should be achieved.

Sodium nitroprusside (SNP) (0.3 mg/kg/min uptitrating carefully to 1 mg/kg/min up to 5 mg/kg/min) is recommended in patients with severe heart failure, and in patients with predominantly increased afterload such as hypertensive heart failure or mitral regurgitation. SNP should be titrated cautiously and usually requires invasive arterial monitoring and close supervision. Prolonged administration may be associated with toxicity from its metabolites, thiocyanide and cyanide, and should be avoided especially in patients with severe renal or hepatic failure. Controlled trials with SNP in AHF are lacking and its administration in AMI has yielded equivocal results SNP should be tapered down to avoid rebound effects. In AHF caused by acute coronary syndromes, nitrates are favoured over SNP as SNP may cause ‘coronary steal syndrome’.

Nesiritide. Recently, nesiritide, a new class of vasodilator, has been developed for the treatment of AHF. Nesiritide is a recombinant human brain peptide or BNP which is identical to the endogenous hormone produced by the ventricle in response to increased wall stress, hypertrophy, and volume overload. Nesiritide has venous, arterial, and coronary vasodilatory properties that reduce preload and afterload, and increase cardiac output without direct inotropic effects. Systemic infusion of nesiritide

in patients with congestive heart failure has beneficial haemodynamic actions, results in an enhanced sodium excretion and suppression of the renin–angiotensin–aldosterone and sympathetic nervous system. The drug has been shown to be efficacious in improving subjective dyspnoea score as well as inducing significant vasodilation. Nesiritide was compared with intravenous nitroglycerin and resulted in improvement in haemodynamics more effectively and with fewer adverse effects. Clinical experience with nesiritide is still limited. Nesiritide may cause hypotension and some patients are non-responders. Use of nesiritide has not translated into improvement in clinical outcome.

Calcium antagonists are not recommended in the treatment of AHF. Diltiatzem, and verapamil, and dihydropyridines should be considered contraindicated.

ACE inhibitors in AHF. ACE-inhibitors are not indicated in the early stabilization of patients with AHF. However, as these patients are at high risk, ACE inhibitors have a role in early management of AHF patients and AMI. Short-term treatment is accompanied by a decrease in AII and aldosterone and an increase in angiotensin I and plasma renin activity. ACE inhibitors decrease renal vascular resistance, increase renal blood flow, and promote Na. and water excretion. The glomerular filtration rate (GFR) remains unchanged or falls slightly, and thus, filtration fraction is decreased. This is due to the relatively greater effect in dilating the glomerular efferent rather than afferent arterioles, leading to a reduction in glomerular capillary hydrostatic pressure and GFR. Natriuresis is due to the improvement in renal haemodynamics and a decreased release of aldosterone and bradykinin, which exert direct tubular effects, and inhibiton of the direct renal effects of angiotensin II.

Intravenous ACE-inhibition should be avoided. The initial dose of the ACE-inhibitor should be low and increased progressively after early stabilization within 48 h with monitoring of blood pressure and renal function. The duration of therapy, when initiated, should be at least 6 weeks.

ACE inhibitors should be used with caution in patients with marginal cardiac output as they may significantly reduce glomerular filtration.The risk of intolerance

to the ACE-inhibitors is increased by the concomitant administration of non-steroid anti-inflammatory agents and in the presence of bilateral renal artery stenosis.

Diuretics. Administration of diuretics is indicated in patients with AHF decompensated heart failure in the presence of symptoms secondary to fluid retention. Diuretics increase the urine volume by enhancing the excretion of water, sodium chloride, and other ions, leading to a decrease in plasma and extracellular fluid volume, total body water and sodium, and a reduction in right and left ventricular filling pressures and a decrease in peripheral congestion and pulmonary oedema. Intravenous administration of loop diuretics also exerts a vasodilating effect, manifested by an early (5–30 min) decrease in right atrial and pulmonary wedge pressure as well as pulmonary resistances. With high bolus doses (≥1 mg/kg) there is a risk of reflex vasoconstriction. As opposed to chronic use of diuretics, in severe decompensated heart failure, the use of diuretics normalizes loading conditions and may reduce neurohormonal activation in the short term. Especially in acute coronary syndromes diuretics should be used in low doses and preference given to vasodilator therapy.

Intravenous administration of loop diuretics (furosemide, bumetanide, torasemide), with a strong and brisk diuretic effect the preferred choice in patients with AHF. Therapy can safely be initiated before hospital admission and the dose should be titrated according to the diuretic response and relief of congestive symptoms. Administration of a loading dose followed by continued infusion of furosemide or torasemide have been shown to be more effective than bolus alone. Thiazides and spironolactone can be used in association with loop diuretics, the combination in low doses being more effective and with less secondary effects than the use of higher doses of a single drug. Combination of loop diuretics with dobutamine, dopamine or nitrates is also a therapeutic approach that is more effective and produces fewer secondary effects than increasing the dose of the diuretic.

New diuretic agents. Some new compounds with diuretic and other effects are under investigation, including vasopressin V_2 receptor antagonists, brain natriuretic peptides, and adenosine receptor antagonists. Vasopressin V_2 receptor antagonists inhibit the action of vasopressin on the collecting duct, thereby increasing free water

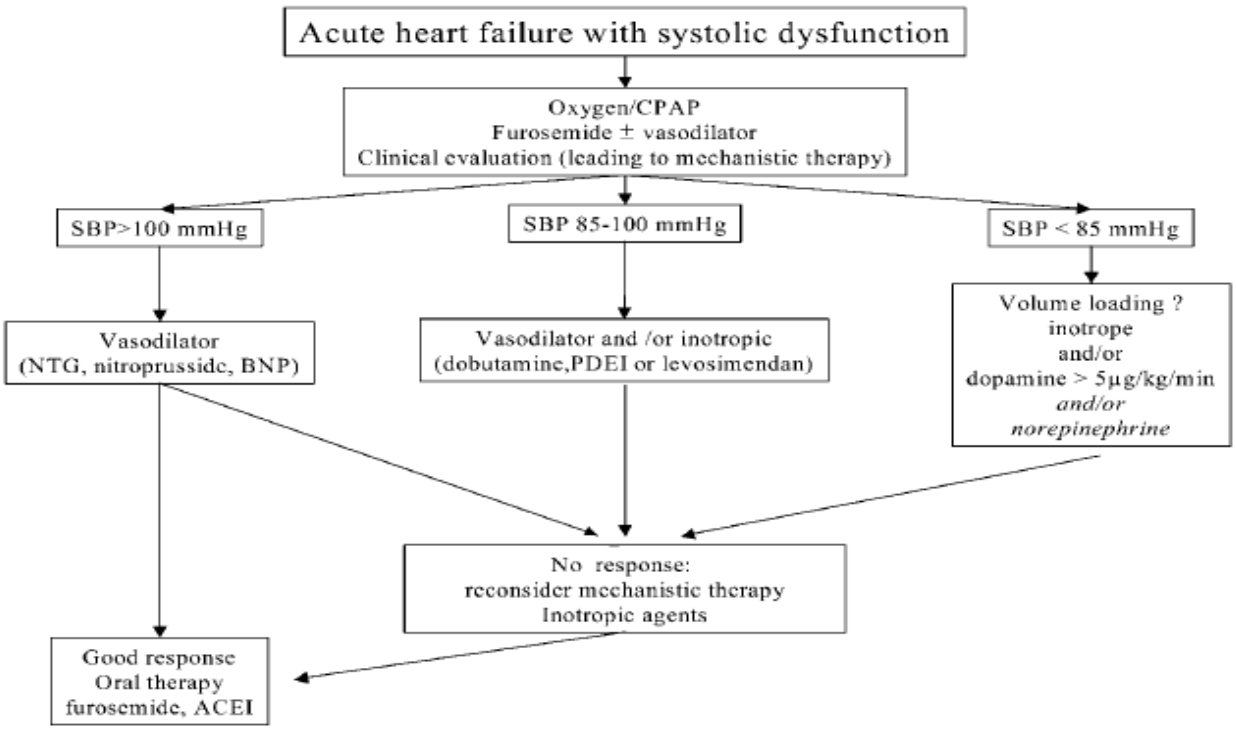
clearance. The diuretic effect is independent of the levels of sodium and these agents could be helpful in the presence of hyponatraemia. Adenosine receptor antagonists exert a diuretic effect reducing proximal tubular Na^+ and water reabsortion without inducing kaliuresis.

β-Blocking agents. Intravenous administration should be considered in patients with ischaemic chest pain resistant to opiates, recurrent ischaemia, hypertension, tachycardia, or arrhythmia. In patients with overt AHF and more than basal pulmonary rales, β-blockers should be used cautiously. Among such patients where ongoing ischaemia and tachycardia are present, intravenous metoprolol can be considered. In patients with CHF b-blockers should be initiated when the patient has stabilized after the acute episode (usually after 4 days).

Inotropic agents are indicated in the presence of peripheral hypoperfusion (hypotension, decreased renal function) with or without congestion or pulmonary oedema refractory to volume replacement diuretics and vasodilators at optimal doses (Figure 2.6).

Figure 2.6

Rationale for inotropic drugs in AHF.



Their use is potentially harmful as they increase oxygen demand and calcium loading and they should be used with caution. In patients with decompensated CHF the symptoms, clinical course, and prognosis of the disease may become critically dependent on the haemodynamics. Thus, improvements in the haemodynamic parameters may become a goal of treatment and inotropic agents may be useful and life saving in this setting. The beneficial effects of an improvement in the haemodynamic parameters is, however, partially counteracted by the risks of arrhythmias and, in some cases, myocardial ischaemia and by the possible long-term progression of myocardial dysfunction caused by an excessive increase in energy expenditure.

The risk–benefit ratio may not, however, be the same for all the inotropic agents. Those acting through the stimulation of the b1-adrenergic receptors which increase cytoplasmic myocardial cell Ca^{2+} concentration may be associated with the greatest risk. Lastly, only a few controlled trials with inotropic agents in patients with AHF have been performed, and very few have assessed their effects on the symptoms and signs of heart failure and their long-term effects on prognosis.

Dopamine. Dopamine is an endogenous catecholamine, and a precursor of norepinpephrine. Its effects are dose-dependent and they involve three different receptor populations: dopaminergic, b-adrenergic, and a-adrenergic receptors. At low doses (<2 mg/kg/min i.v.) it acts only on peripheral dopaminergic receptors and lowers peripheral resistance both directly and indirectly. Vasodilation occurs predominantly in the renal, splanchnic, coronary, and cerebral vascular beds. At this dosage, its action may cause an improvement in the renal blood flow, glomerular filtration rate, diuresis and sodium excretion rate, with an increased response to the diuretic agents, in patients with renal hypoperfusion and failure.

At higher doses (>2 mg/kg/min i.v.) dopamine stimulates the b-adrenergic receptors both directly and indirectly with a consequent increase in myocardial contractility and cardiac output. At doses >5 mg/kg/min dopamine acts on a-adrenergic receptors with an increase in the peripheral vascular resistance which, though potentially useful in the hypotensive patients, may be deleterious in the patients with heart failure as it may augment the left ventricular afterload, pulmonary artery pressure,

and resistance. The effects of dopamine in patients with AHF have been studied only in small study groups and no controlled trials regarding its long-term effects on renal function and survival have been performed. In addition, concerns regarding its potential untoward effects on pituitary function, T-cell responsiveness, gastrointestinal perfusion, chemoreceptor sensitivity, and ventilation have been raised.

Dobutamine is a positive inotropic agent acting mainly through stimulation of β1-receptors and β2-receptors in a 3:1 ratio. Its clinical action is the result of direct dose-dependent positive inotropic and chronotropic effects and secondary adaptation to increased cardiac output, such as a decrease in sympathetic tone in heart failure patients, leading to a decrease in vascular resistance. The resultant benefit may therefore differ from patient to patient. At low doses, dobutamine induces mild arterial vasodilatation, which augments stroke volume by reductions in afterload. At higher doses dobutamine causes vasoconstriction. Heart rate is generally increased in a dose-dependent manner to a lesser extent than with other cathecholamines. However, in patients with atrial fibrillation, heart rate may be increased to undesirable rates, due to facilitation of atrio-ventricular conduction. Systemic arterial pressure usually increases slightly, but may remain stable, or decrease. Similarly pulmonary arterial pressure and capillary wedge pressure usually decrease, but may remain stable or even increase in some patients with heart failure. The improved diuresis observed during dobutamine infusion in patients with CHF is the result of improved haemodynamics with an increased renal blood flow in response to improved cardiac output.

Dopamine may be used as an inotrope (0.2 mg/kg/min i.v.) in AHF with hypotension. Infusion of low doses of dopamine (<2–3 mg/kg/min i.v.) may be used to improve renal blood flow and dieresis in decompensated heart failure with hypotension and low urine output. However if no response is seen, the therapy should be terminated. Dobutamine is used to increase the cardiac output. It is usually initiated with a 2–3 mg/kg/min infusion rate without a loading dose. The infusion rate may then be progressively modified according to symptoms, diuretic response or haemodynamic monitoring. Its haemodynamic actions are proportional to its dosage, which can be increased to 20 mg/kg/min. The elimination of the drug is rapid after cessation of in-

fusion, making it a very convenient inotropic agent. In patients receiving b-blocker therapy with metoprolol, dobutamine doses have to be increased as high as 15–20 mg/kg/min to restore its inotropic effect. The effect of dobutamine differs in patients receiving carvedilol: It can lead to an increase in pulmonary vascular resistance during the infusion of increasing doses of dobutamine (5–20 mg/kg/min).

Prolonged infusion of dobutamine (>24–48 h) is associated with tolerance and partial loss of haemodynamic effects. Weaning from dobutamine may be difficult because of recurrence of hypotension, congestion, or renal insufficiency. This can sometimes be solved by very progressive tapering of dobutamine (i.e. decrease in dosage by steps of 2 mg/kg/min every other day) and optimization of oral vasodilator therapy such as with hydralazine and/or an ACE-inhibitor. It is sometimes necessary to tolerate some renal insufficiency or hypotension during this phase. Infusion of dobutamine is accompanied by an increased incidence of arrhythmia originating from both ventricles and atria. This effect is dose-related and may be more prominent than with PDEI and should prompt strict potassium compensation during intravenous diuretic use. Tachycardia may also be a limiting parameter, and dobutamine infusion may trigger chest pain in patients with coronary artery disease. In patients with hibernating myocardium, dobutamine appears to increase contractility in the short term at the expense of myocyte necorosis and loss in myocardial recovery.

Phosphodiesterase inhibitors. The Type III Phosphodiesterase inhibitors (PDEIs) block the breakdown of cyclic-AMP (cAMP) into AMP. Milrinone and enoximone are the two PDEIs used in clinical practice. When administered to patients with advanced heart failure, these agents are associated with a significant inotropic, lusitropic, and peripheral vasodilating effects, with an increase in cardiac output and stroke volume and a concomitant decline in pulmonary artery pressure, pulmonary wedge pressure, and systemic and pulmonary vascular resistance. Their haemodynamic profile is intermediate between that of a pure vasodilator, like nitroprusside, and that of a predominant inotropic agent, like dobutamine. As their site of action is distal to the b-adrenergic receptors, PDE-Is maintain their effects even during concomitant b-blocker therapy.

Type III PDEI are indicated when there is evidence of peripheral hypoperfusion with or without congestion refractory to diuretics and vasodilators at optimal doses, and preserved systemic blood pressure.

These agents may be preferred to dobutamine in patients on concomitant b-blocker therapy and/or with an inadequate response to dobutamine.

In practical use milrinone is administered as a 25 mg/kg bolus over 10–20 min followed by a continuous infusion at 0.375–0.75 mg/kg/min. Similarly, enoximone is administered as a bolus of 0.25–0.75 mg/kg followed by a continuous infusion at 1.25–7.5 mg/kg/min. Hypotension caused by excessive peripheral venodilation is an untoward effect observed mainly in the patients with low filling pressures. It may be avoided by starting the infusion without any bolus. Distinctly from amrinone, the incidence of thrombocytopenia is relatively rare with milrinone (0.4%) and enoximone.

Milrinone or enoximone are used for the treatment of AHF on the basis of their favourable haemodynamic effects. The data regarding the effects of PDEI administration on the outcome of the patients with AHF are insufficient, but raise concerns about safety, particularly in patients with ischaemic heart failure.

Levosimendan has two main mechanisms of action: Ca^{2+} sensitization of the contractile proteins responsible for a positive inotropic action, and smooth muscle K. channel opening responsible for peripheral vasodilation. Some data suggest levosimendan may also have PDEI effect. Levosimendan has a potent acetylated metabolite that is also a Ca^{2+}-concentration dependent Ca^{2+} sensitizer. Its half-life is $\leq$80 h, which probably explains the prolonged haemodynamic effects of a 24 h levosimendan infusion. Levosimendan is indicated in patients with symptomatic low cardiac output heart failure secondary to cardiac systolic dysfunction without severe hypotension.

Levosimendan is generally administered as a continuous intravenous infusion at a dose of 0.05–0.1 mg/kg/ min preceded by a loading dose of 12–24 mg/kg, administered over 10 min. Its haemodynamic effects are dose-dependent and the infusion rate may be uptitrated to a maximal rate of 0.2 mg/kg/min. Most of the clinical data

have been obtained with intravenous infusions lasting from 6 h to 24 h but the haemodynamic effects persist for 48 h after the end of the infusion.

Levosimendan infusion in patients with acutely decompensated HF caused by LV systolic dysfunction has been associated with a dose-dependent increase in the cardiac output and stroke volume; a decline in the pulmonary wedge pressure, systemic vascular resistance, and pulmonary vascular resistance; and a slight increase in the heart rate and decrease in the blood pressure.

An improvement in symptoms of dyspnoea and fatigue and a favourable outcome has been shown in randomized trials comparing levosimendan with dobutamine. Differently from dobutamine, the haemodynamic response to levosimendan is maintained, or even of greater magnitude, in patients on concomitant b-blocker therapy. Tachycardia and hypotension are described with highdose levosimendan infusion and it is not currently recommended in patients with systolic blood pressure <85 mmHg. Levosimendan has not been associated with an increased frequency of malignant arrhythmias in comparative trials with either placebo1 or dobutamine. A reduction in the haematocrit, haemoglobin, and plasma potassium, likely secondary to vasodilation described and seem to be dose dependent.

Vasopressor therapy in cardiogenic shock. When the combination of inotropic agent and fluid challenge fails to restore adequate arterial and organ perfusion despite an improvement in cardiac output, therapy with vasopressors may be required. Vasopressors may also be used, in emergencies, to sustain life and maintain perfusion in the face of life-threatening hypotension. Since cardiogenic shock is associated with high vascular resistances, any vasopressor should be used with caution and only transiently, because it may increase the afterload of a failing heart and further decrease end-organ blood flow.

Epinephrine is a catecholamine with high affinity for β_1-, β_2-, and α-receptors. Epinephrine is used generally as an infusion at doses of 0.05–0.5 mg/kg/min when dobutamine refractoriness is present and the blood pressure remains low. The use of epinephrine requires direct arterial pressure monitoring, and monitoring of haemodynamic response by PAC is recommended.

Norepinephrine is a catecholamine with high affinity for a-receptors and is generally used to increase systemic vascular resistance. Norepinephrine-induced increases in heart rate are less than with epinephrine. The dosing is similar to epinephrine. The choice between epinephrines depends on clinical situation. Norepinephrine (0.2–1 mg/kg/min) is favoured in situations with low blood pressure related to reduced systemic vascular resistances such as septic shock. Norepinephrine is often combined with dobutamine to improve haemodynamics. Norepinehrine may reduce end-organ perfusion. Other new modes of treatments in septic shock are out of the scope of this report.

Cardiac glycosides inhibit myocardial Na/K-ATPase, thereby increasing Ca^{2+}/Na. exchange mechanisms, producing a positive inotropic effect. In heart failure, the positive inotropic effect following b-adrenergic stimulation is attenuated and the positive force-frequency relationship is impaired. In contrast to b-adrenoceptor agonists, the positive inotropic effect of cardiac glycosides is unchanged in failing hearts and the force–frequency relationship is partially restored. In patients with severe heart failure following episodes of acute decompensation, cardiac glycosides have shown to be efficacious in reducing the re-occurrence of acute decompensation. Predictors for these beneficial effects are a third heart sound, extensive LV dilatation, and distended jugular veins during the AHF episode. However, in patients following myocardial infarction with heart failure, a substudy of the AIRE Investigation has shown adverse effects on the outcome after AMI accompanied by heart failure. Furthermore, following AMI, an increase of creatine kinase was more pronounced in patients receiving cardiac glycosides. In addition, for patients with myocardial infarction and AHF, digitalis was a predictor for life-threatening pro-arrhythmic events. Therefore, inotropic support with cardiac glycosides cannot be recommended in AHF, in particular following myocardial infarction. Indication for cardiac glycosides in AHF may be tachycardia-induced heart failure, e.g. in atrial fibrillation with insufficient rate control by other agents such as b-blockers. Rigorous control of heart rate in tachyarrhythmia during the course of AHF can control heart failure symptoms. Contraindications to the use of cardiac glycosides include bradycardia, second and

third degree AV-block, sick sinus syndrome, carotid sinus syndrome, Wolff–Parkinson–White syndrome, hypertrophic obstructive cardiomyopathy, hypokalaemia, and hypercalcaemia.

Underlying diseases and co-morbidities in AHF. There are several acute morbidities which can cause de novo AHF or trigger decompensation in CHF. Coronary heart disease and acute coronary syndromes are the most frequent causes for AHF. Non-cardiac comorbidities may also significantly complicate the therapy of AHF.

Coronary artery disease. AHF induced or complicated by coronary artery disease may present with forward failure (including cardiogenic shock), left-heart failure (including pulmonary oedema), or right-heart failure. The diagnosis is indicated by appropriate history (with background risk factors and suggestive chest pain), and a typical ECG with evidence of AMI or dynamic ST/T changes suggestive of myocardial ischaemia.

In acute coronary syndromes (unstable angina or myocardial infarction) complicated by AHF, coronary angiography is indicated. For further diagnostic purposes, an echocardiogram is helpful for the assessment of regional and global ventricular function, associated valve dysfunction (mainly mitral regurgitation) and ruling out other disease states (e.g. perimyocarditis, cardiomyopathy, and pulmonary embolism). All patients with AMI and signs and symptoms of heart failure should undergo an echocardiographic study. Special tests to provide evidence of reversible myocardial ischaemia are sometimes necessary.

In cardiogenic shock caused by acute coronary syndromes, coronary angiography and revascularization should be performed as soon as possible. Temporary stabilization of the patient can be achieved by adequate fluid replacement, intra-aortic balloon counter-pulsation, pharmacological inotropic support, nitrates, and artificial ventilation. Repeated blood samples for monitoring of electrolytes, glucose, renal function, and arterial blood gases should be taken, particularly in diabetic patients.

Metabolic support with high-dose glucose, insulin, and potassium cannot be recommended (except in diabetic patients) until the results from larger scale studies in AMI become available.

When the haemodynamic state continues to be unstable for several hours, the introduction of an indwelling PAC may be considered. Repeated measurements of mixed venous blood oxygen saturation from the PAC can be helpful.

When all these measures fail to achieve stabilization of the haemodynamic status, mechanical support with a left ventricular assist device should be considered, particularly if heart transplantation is contemplated. In left-heart failure/pulmonary oedema, the acute management is similar to other causes of pulmonary oedema. Inotropic agents may be deleterious. Intraaortic balloon counter-pulsation should be considered.

The long-term management strategy should include adequate coronary revascularization and where there is evidence of reduced LV function long-term treatment with RAAS-inhibition and b-blockade should follow. Acute right-heart failure is usually related to acute right ventricular ischaemia in acute coronary syndromes, particularly right ventricular infarction with a characeristic ECG and echocardiogram. Early revascularization of the right coronary artery and its ventricular branches is recommended. Supportive treatment should focus on fluid-loading and inotropic support.

Valvular disease

AHF can be caused by valvular conditions unrelated to acute coronary syndromes such as acute mitral or aortic valve incompetence (i.e. from endocarditis or trauma), aortic or mitral stenosis, thrombosis of a prosthetic valve, or aortic dissection. In patients with endocarditis, treatment is initially conservative with antibiotics and other medical means of treatment of AHF. Cardiac dyfunction may be aggravated by myocarditis. However, acute valve incompetence is the most common cause of AHF in patients with infective endocarditis. Heart failure should be promptly treated. Rapid diagnosis and therapeutic decisions require expert consultation. Surgical consultations are warranted. Surgical intervention should be performed early in severe acute aortic or mitral regurgitation. If there is a prolonged period of acute mitral regurgitation and the cardiac index has decreased to <1.5 L/min/ m^2 and the ejection fraction is <35%, urgent surgical intervention usually will not improve the prognosis.

Stabilization of the patient with intra-aortic balloon counterpulsation can be of great value. Urgent surgery is indicated in patients with endocarditis and severe acute aortic regurgitation.

Management of AHF due to prosthetic valve thrombosis

AHF from prosthetic valve thrombosis (PVT) is associated with a high mortality. All patients with heart failure symptoms and suspected prosthetic valve thrombosis should undergo chest fluoroscopy and an echocardiographic study (transthoracic and/or transesophageal if visualization of the prosthetic valve area is inadequate).

The management remains controversial. Thrombolysis is used for right-sided prosthetic valves, and for highrisk surgical candidates. Surgery is preferred for left sided prosthetic valve thrombosis. Surgical mortality is high for emergency operations in critically ill patients with haemodynamic instability (NYHA Class III/IV, pulmonary oedema, hypotension). However, thrombolysis takes several hours to be effective and this delay may lead to further deterioration of the patient, dramatically increasing the risk of re-operation if thrombolytic treatment fails.

For patients who are in NYHA I/II or with non-obstructive thrombus, surgical mortality is lower. Thrombolytic therapy is not effective when fibrous tissue ingrowth (pannus) is implicated in the obstruction with minor secondary thrombosis. In patients with very large and/or mobile thrombi, thrombolytic therapy is associated with a much higher risk for major embolism and stroke. In all these patients surgical intervention should be considered as an alternative. Before deciding therapy, pannus formation or structural defects of the prosthetic valve should be ruled out by transesophageal echocardiography. Echocardiography should be performed in all patients after thrombolytic therapy. Surgical intervention should be considered in all cases if thrombolysis fails to resolve the obstruction although repeated infusions of thrombolytic therapy is an alternative. The thrombolytics used are: rtPA 10 mg intravenous bolus followed by 90 mg infused over 90 min; streptokinase 250–500 000 IU over 20 min followed by 1–1.5 million IU infused over 10 h. After thrombolysis, unfractionated heparin should be administered by intravenous infusion in all patients (acti-

vated partial thromboplastin time 1.5–2.0 times control). Urokinase is also an alternative in a dose of 4400 IU/kg/h for 12 h without heparin or 2000 IU/kg/h with heparin for 24 h.

Aortic dissection. Acute aortic dissection (particularly Type 1) may present with symptoms of heart failure with or without pain. Following a period of pain, heart failure may become the main symptom. The AHF is usually related to a hypertensive crisis, acute aortic valve incompetence, or myocardial ischaemia. Immediate diagnosis and surgical consultation are warranted. Transoesophageal echocardiography is the best technique to assess the morphology and function of the valve. Speed in surgical intervention is usually vital.

AHF and hypertension. AHF is one of the well-known complications of hypertensive emergencies. The latter are defined as situations that require immediate blood pressure reduction (not necessarily to the normal values) to prevent or limit organ damage including encephalopathy, aortic dissection, or acute pulmonary oedema. The pathophysiology of hypertensive crisis is multifactorial and well described elsewhere. The epidemiology of hypertension-induced pulmonary oedema shows that it usually appears in older patients (particularly in women >65 years of age) with a long-lasting history of hypertension, LV hypertrophy (present in more than half of patients), and inadequate treatment of their hypertension. The clinical signs of AHF associated with a hypertensive crisis are almost exclusively the signs of pulmonary congestion. The latter can be mild or very severe with an acute pulmonary oedema throughout both lungs. It is called ‘flash pulmonary oedema’ because of its rapid onset. Rapid treatment with specific interventions is required. Systolic function is often preserved in patients hospitalized with pulmonary oedema and hypertension (more than half of patients have an LVEF $\geq$ 45%). In contrast, diastolic abnormalities with decreased LV compliance are often present.

The goals of the treatment of acute pulmonary oedema with hypertension are reduction in LV preload and afterload, reduction of cardiac ischaemia, and maintenance of adequate ventilation with clearing of the oedema. Treatment should be started immediately and in the following order: O_2 therapy, CPAP or non-invasive ventilation,

and if necessary, invasive mechanical ventilation, for usually a very short period, and administration of intravenous antihypertensive agent(s).

Antihypertensive therapy should aim for an initial rapid (within a couple of minutes) reduction of SBP or DBP of 30 mmHg, followed by a more progressive decrease of BP to the values measured before the hypertensive crisis: this may take several hours. No attempt should be made to restore normal values of BP as this may cause a deterioration in organ perfusion. The initial rapid reduction of BP may be achieved by the following medications given alone or combined if hypertension persists: intravenous loop diuretics, particularly if the patient is clearly fluid overloaded with a long history of CHF; intravenous nitroglycerin or nitroprusside to decrease venous preload and arterial afterload and increase coronary blood flow; a calcium-channel blocker (such as nicardipine) may be considered as these patients usually have diastolic dysfunction with an increased afterload. Nicardipine has a similar spectrum of use as nitrates, but may cause adrenergic activation (tachycardia), an increase in intrapulmonary shunt (hypoxaemia), and central nervous system complications.

Among the medications usually given to treat hypertensive crisis, b-blockers should not be advised in cases of concomitant pulmonary oedema. However, in some cases, and particularly in hypertensive crisis related to phaeochromocytoma, intravenous labetalol given as slow boluses of 10 mg while monitoring heart rate and blood pressure and followed by an infusion of 50–200 mg/h can be effective. Acute pulmonary oedema associated with hypertension, and in the absence of other complications, is often very easily treated and does not necessarily need admission to an intensive care unit.

Renal failure

Heart failure and renal failure frequently co-exist, and either one of them may cause the other. Heart failure causes renal hypoperfusion both directly and through the activation of neurohumoral mechanisms. Concomitant therapies (e.g. diuretics and ACE-inhibitors through efferent glomerular artery dilatation, and nonsteroid anti-inflammatory agents through inhibition of afferent glomerular artery dilatation) may

also contribute to the development of renal failure. Initially, the autoregulation of renal blood flow and the constriction of the efferent glomerular artery may compensate for renal hypoperfusion but, at later stages renal function becomes critically dependent on afferent glomerular flow so that renal failure and oliguria are a common finding in patients with severe acute heart failure. Urinalysis may vary depending on the cause of renal failure. When renal failure is secondary to hypoperfusion, the urinary sodium/potassium ratio is characteristically less than 1. Acute tubular necrosis may be diagnosed on the basis of an increase in urinary sodium, reduction in urine nitrogen concentration and typical urinary sedimentation findings.

A mild-to-moderate impairment in renal function is generally asymptomatic and well tolerated. However, even a mild-to-moderate increase in serum creatinine and/or decrease in GFR are independently associated with a worse prognosis.

Concomitant acute renal failure requires the recognition and treatment of its associated disorders. The prevalence of anaemia, electrolyte abnormalities, and metabolic acidosis is greater in patients with concomitant renal failure. Electrolyte abnormalities (hypo- and hyperkalaemia, and hypo- and hypermagnesaemia) and metabolic acidosis should be corrected as they may cause arrhythmias, reduce the response to treatment, and worsen the prognosis.

Renal failure also influences the response and tolerability of heart failure treatments, namely, digoxin and ACE-inhibitors, angiotensin receptor blocking agents, and spironolactone. Also pre-renal arterial stenosis and post-renal obstruction should be assessed. Administration of ACE-inhibitors is associated with an increased incidence of severe renal failure and hyperkalaemia in patients with concomitant renal failure. An increase in serum creatinine of more than 25-30% and/ or achievement of levels ≥3.5 mg/dL (≥266 mmol/L) are relative contraindications to the continuation.

ACE-inhibitor treatment

Moderate-to-severe renal failure [e.g. a serum creatinine 2.5–3 mg/dL (190–226 mmol/L)] is also associated with a reduced response to diuretics—a significant predictor of mortality in HF patients. In such patients, it may be necessary to progressively increase the dose f the loop diuretics and/or add a diuretic with a different me-

chanism of action (e.g. metozalone). This may, however, be associated with hypokalaemia and a further decline in GFR.

In patients with severe renal dysfunction and refractory fluid retention, continuous veno-venous hemofiltration (CVVH) may become necessary. Combined with a positive inotropic agent this may increase renal blood blow, improve renal function, and restore diuretic efficiency. This has been associated with an increase in urine output, a reduction in symptoms, and in the left and right ventricular filling pressures and sympathetic stimulation and with an improvement in lung mechanical function, laboratory abnormalities (hyponatremia), and the response to diuretic therapy. Loss of renal function may require dialysis treatment, especially in the presence of hyponatremia, acidosis, and overt uncontrolled fluid retention. The choice between peritoneal dialysis, haemodialysis, or filtration, is usually dependent on technical availability and on baseline blood pressure.

Pulmonary diseases and bronchoconstriction

When bronchoconstriction is present in patients with AHF, bronchodilators should be used. This is often the case in patients with concomitant lung problems, e.g. asthma, chronic obstructive bronchitis, and lung infections. Bronchodilators may improve cardiac function, but should not be used instead of relevant AHF treatment. Commonly, initial treatment consists of 2.5 mg albuterol (salbutamol) (0.5 mL of a 0.5% solution in 2.5 mL normal saline) by nebulization over 20 min. This may be repeated hourly during the first few hours of therapy and thereafter as part of individual therapy as indicated.

Arrhythmias and AHF

There are no extensive reports on the prevalence of arrhythmias either as a cause or as a complicating factor in decompensated AHF. In the Euroheart Failure Survey, rapid atrial fibrillation was observed at index hospitalization in 9% of patients and 42% had a history of chronic or paroxysmal atrial fibrillation. The prevalence of all atrial tachyarrhythmias was 44%. Life-threatening ventricular arrhythmias were seen at index hospitalization in 2% and in the whole study population they were found as a concomitant early or acute problem in 8% of patients.

Bradyarrhythmias.

Bradycardia in AHF patients occurs most often in AMI, particularly with right coronary artery occlusion. The treatment of bradyarrhythmias is usually initially with atropine 0.25–0.5 mg intravenously, repeated when needed. Isoproterenol 2–20 mg/min can be infused in cases of AV dissociation with low ventricular response, but should be avoided in ischaemic conditions. Slow ventricular rhythm in atrial fibrillation can be improved by intravenous theophylline 0.2–0.4 mg/kg/h as a bolus and then by infusion. A temporary pacemaker should be inserted if no response is achieved with medical therapy. Ischaemia should be treated as soon as possible before or after inserting a pacemaker as indicated.

Recommendations for treatment of SVTs in AHF.

The control of the ventricular rate response is important in patients with atrial fibrillation and AHF, particularly in patients with diastolic dysfunction. Patients with restrictive physiology or tamponade, however, may suddenly deteriorate with rapid heart rate reduction. Rapid rate control or cardioversion on clinical demand should be achieved. The therapy of atrial fibrillation depends on the duration of the atrial fibrillation. Patients with AHF and atrial fibrillation should be anticoagulated. When atrial fibrillation is paroxysmal medical or electrical cardioversion should be considered after initial work-up and stabilization of the patient. If the duration of the atrial fibrillation is more than 48 h, the patient should be anticoagulated and optimal rate control achieved medically for 3 weeks before cardioversion. If the patient is haemodynamically unstable, urgent cardioversion is clinically mandatory, but atrial thrombus should be excluded by transesophageal echocardiography prior to cardioversion. Verapamil and diltiazem should be avoided in acute atrial fibrillation as they may worsen heart failure and cause third degree AV block. Amiodarone and b-blocking agents have been successfully used in atrial fibrillation for rate control and prevention of recurrence.

Rapid dizitalization should be considered especially when atrial fibrillation is secondary to AHF. Verapamil can be considered in the treatment of atrial fibrillation or narrow complex supraventricular tachycardia in patients with only slightly reduced

ventricular systolic function. Class I anti-arrhythmic agents should be avoided in patients with low ejection fraction and particularly in patients who have a wide QRS complex. Dofetilide is a new drug with promising results in medical cardioversion in one study and prevention of new atrial fibrillation, but further studies are needed to evaluate its safety and efficacy in AHF. Beta-blocking agents can be tried in supraventricular tachycardias when tolerated. In wide complex tachycardia, intravenous adenosine can be used in an attempt to terminate the arrhythmia. Electrical cardioversion of SVT with sedation should be considered in AHF with hypotension. AHF patients with AMI and heart failure, and patients with diastolic heart failure, do not tolerate rapid supraventricular arrhythmias. Plasma potassium and magnesium levels should be normalized particularly in patients with ventricular arrhythmias.

Treatment of life-threatening arrhythmias.

The importance of ventricular tachycardia or fibrillation as a cause of, or related to, AHF is unclear. VF and VT require immediate cardioversion, with ventilator assistance if required, and in the case of a conscious patient with sedation. Amiodarone and b-blocking agents can prevent repetition of these arrhythmias. In the case of recurrent ventricular arrhythmias and haemodynamically unstable patients, immediate angiography and electrophysiological testing should be performed. In cases of a localized arrhythmic substrate radiofrequency ablation may eliminate the arrhythmic tendency although the long term effect cannot be ascertained.

Surgical treatment of AHF

AHF is a severe complication of many cardiac disorders. In some of them surgical therapy improves prognosis if performed urgently or immediately. Surgical options include coronary revascularization, correction of the anatomic lesions, valve replacement or reconstruction, as well as temporary circulatory support by means of mechanical assist devices. Echocardiography is the most important technique in the diagnostic work-up.

AHF related to complications of AMI

Free wall rupture. Free wall rupture is documented in 0.8–6.2% of patients after AMI. Usually sudden death occurs within minutes due to cardiac tamponade and

electromechanical dissociation. The diagnosis is rarely established before the patient's death. However, in some cases the presentation of free wall rupture is subacute (thrombus or adhesions seal the rupture) giving an opportunity for intervention if the condition is recognized. Most of these patients have signs of cardiogenic shock, sudden hypotension, and/or loss of consciousness. In some patients rupture is preceded by chest pain, nausea, emesis, new ST segment elevation in the infarct related leads, or T-wave changes. All these patients should undergo immediate echocardiography. The clinical presentation, with a pericardial effusion of 0.1 cm depth and echo densities in the effusion confirm the diagnosis. Temporary haemodynamic stabilization can be obtained by pericardiocentesis, fluids, and positive inotropes. The patient should be immediately transferred to the operating room without any further investigation. Free wall rupture has been also described as a rare complication of dobutamine stress echocardiography after AMI.

Post-infarction ventricular septal rupture. Ventricular septal rupture (VSR) occurs in 1–2% of patients with AMI. Recent data suggest a lower incidence and an earlier presentation in the thrombolytic era. VSR usually occurs in the first 1–5 days after MI. The first sign of VSR is a pansystolic murmur usually at the left lower sternal border in a patient with acute deterioration and signs of AHF/cardiogenic shock after an AMI. Echocardiography will confirm the diagnosis and allow assessment of ventricular function, define the site of the VSR, the size of the left-to-right shunt, and the co-existence of mitral incompetence.

PAC oximetry with O_2 step-up will allow estimation of the pulmonary-to-systemic blood flowratio (usually 2 or more).

There is a developing consensus that surgery should be performed as soon as the diagnosis is made, because the rupture can abruptly expand resulting in cardiogenic shock, the most important determinant of adverse outcome. The patients with VSR should be operated on urgently if they are in haemodynamically stable condition and immediately if they are in cardiogenic shock.

Trans-catheter VSR occlusion has been used to stabilize critically ill patients with good results but more experience is needed before it can be recommended. Re-

cently, left ventricular outflow tract (LVOT) obstruction with compensatory hyperkinesis of the basal segments of the heart has been described in some patients with apical anterior myocardial infarction as a cause of a new systolic murmur and cardiogenic shock. It persists until appropriate therapy decreases the LVOT obstruction.

Acute mitral regurgitation. Acute severe mitral regurgitation (MR) is found in about 10% of patients with cardiogenic shock after AMI. The prevalence is uncertain in the general population of patients with AMI. It occurs 1–14 days (usually 2–7 days) after the infarction. In acute MR from complete papillary muscle rupture most of the non-operated patients die in the first 24 h.

Partial rupture of one or more papillary muscle heads is more common than complete rupture and has a better survival. In most patients the acute MR is secondary to papillary muscle dysfunction rather than to rupture. Endocarditis may also be a cause for severe MR and requires reparatory surgery.

Acute severe MR is manifested by pulmonary oedema and/or cardiogenic shock. The characteristic apical systolic murmur may be absent in patients with severe MR due to the abrupt and severe elevation of left atrial pressure. Chest radiography shows pulmonary congestion (this may be unilateral). Echocardiography will establish the presence and severity of MR and permit assessment of LV function. The left atrium is usually small or slightly enlarged. In some patients transesophageal echocardiography may be needed to establish the diagnosis.

Mechanical assist devices and heart transplantation Temporary mechanical circulatory assistance may be indicated in patients with AHF who are not responding to conventional therapy and where there is the potential for myocardial recovery, or as a bridge to heart transplant or interventions that may result in significant recovery of the heart function. Improvement in the design and function of the devices will increase the number of potential candidates for its short- and long-term use in the future.

Intra-aortic balloon counter-pulsation pump. Counter-pulsation has become a standard component of treatment in patients with cardiogenic shock or severe acute left heart failure that do not respond rapidly to fluid administration, vasodilatation,

and inotropic support; is complicated by significant MR or rupture of the interventricular septum, to obtain haemodynamic stabilization for definitive diagnostic studies or treatment; or is accompanied by severe myocardial ischaemia, in preparation for coronary angiography and revascularization.

Synchronized intra-aortic balloon counter-pulsation (IABC) is performed by inflating and deflating a 30-50 mL balloon placed in the thoracic aorta through the femoral artery. The inflation of the balloon in diastole increases aortic diastolic pressure and coronary flow while the deflation during systole decreases afterload and facilitates LV emptying. IABC may dramatically improve haemodynamics but its use should be restricted to patients whose underlying condition may be corrected (by, e.g. coronary revascularization, valve replacement, or heart transplant) or may recover spontaneously (e.g. myocardial stunning very early after AMI or open heart surgery, myocarditis). IABC is contraindicated in patients with aortic dissection or significant aortic insufficiency. It should not be used in patients with severe peripheral vascular disease, uncorrectable causes of heart failure, or multi-organ failure.

Selection of candidates for device therapy. Only patients with severe heart failure—not responding to conventional treatment of AHF including the appropriate use of fluids, diuretics, intravenous inotropics, and vasodilators, as well as IABC and possibly mechanical ventilation - should be considered as potential candidates for mechanical support. Although transient haemodynamic and clinical improvement can be obtained in many cases, only patients with potential recovery of cardiac function should be considered as candidates for ventricular assist devices.

These conditions include

- acute myocardial ischaemia or infarction;
- shock after cardiac surgery;
- acute myocarditis;
- acute valvular dysfunction (particularly in the absence of previous chronic heart failure, when improvement in ventricular function is expected after spontaneous recovery or after appropriate interventions such as revascularization or valve replacement);
- candidates for heart transplant.

Patients with permanent end-organ dysfunction, including severe systemic disease, severe renal failure, pulmonary disease, hepatic dysfunction, or permanent central nervous injury should not be considered for device therapy. The selection of the specific device depends on the specific cardiac pathology, device availability, and surgical team experience.

Heart transplantation

Transplantation can be considered as a possibility in severe AHF known to have a poor outcome. This is the case in severe acute myocarditis or in postpuerperal cardiomyopathy or in a patient with major myocardial infarction with an initially poor outcome after revascularization. However, transplantation is not possible until the patient's condition has been stabilized with the aid of devices and artificial pumps.

Summary.

The patient with AHF may recover extremely well, depending on the etiology and the underlying pathophysiology. Prolonged treatment on the ward and expert care are required. This is best delivered by a specialist heart failure team that can rapidly initiate medical management and attend to the information needs of the patient and family.

PART II. CHRONIC HEART FAILURE

Epidemiology.

Much is now known about the epidemiology of heart failure in Europe but the presentation and etiology are heterogeneous and less is known about differences among countries. Estimates of the prevalence of symptomatic heart failure in the general European population range from 0.4 to 2%. The prevalence of heart failure increases rapidly with age, with a mean age of the heart failure population being years and, as the proportion of the population that is elderly is increasing, this partly accounts for the rising prevalence of heart failure. Unlike other common cardiovascular diseases, the age-adjusted mortality attributed to heart failure also appears to be increasing. The ESC represents countries with a population of over 900 million, suggesting that there are at least 10 million patients with heart failure in those countries.

Many patients with heart failure have symptoms and PLVEF. There are also patients with myocardial systolic dysfunction without symptoms of heart failure and who constitute approximately a similar prevalence. The prognosis of heart failure is uniformly poor if the underlying problem cannot be rectified. Half of patients carrying a diagnosis of heart failure will die within 4 years, and in patients with severe heart failure 50% will die within 1 year. Studies have confirmed the poor long-term prognosis. Recently, a report on heart failure in Scotland provided survival rates after hospital discharge from 1986 to 1995 suggesting improved prognosis over time. The accuracy of diagnosis by clinical means alone is often inadequate, particularly in women, elderly, and obese. To study properly the epidemiology and prognosis and to optimize the treatment of heart failure, the uncertainty relating to the diagnosis must be minimized or avoided completely.

Descriptive terms in heart failure

Acute vs. chronic heart failure

The term acute heart failure (AHF) is often used exclusively to mean new onset acute or decompensation of chronic heart failure (CHF) characterized by signs of pulmonary and/or peripheral congestion, including pulmonary oedema and/or peripheral oedema with or without signs of peripheral hypoperfusion. Other forms of AHF include hypertensive AHF, pulmonary oedema, cardiogenic shock, high output failure, and right heart failure. Various other classifications for AHF as a syndrome are utilized in coronary and intensive care units, which guide the treatment or are used in clinical research protocols. CHF, often punctuated by acute exacerbations, is the most common form of heart failure. A definition of CHF is given succeedingly. The present document will concentrate on the syndrome of CHF and leave out aspects on AHF. Thus, heart failure, if not stated otherwise, is referring to the chronic state. Systolic vs. diastolic heart failure As ischaemic heart disease is the commonest cause of heart failure in industrialized societies, most heart failure is associated with evidence of left ventricular systolic dysfunction, although diastolic impairment at rest is a common if not universal accompaniment. Diastolic heart failure is often diagnosed when symptoms and signs of heart failure occur in the presence of a PLVEF

(normal ejection fraction) at rest. Predominant diastolic dysfunction is relatively uncommon in younger patients but increases in importance in the elderly. PLVEF is more common in women, in whom systolic hypertension and myocardial hypertrophy with fibrosis are contributors to cardiac dysfunction. A large proportion of patients with CHF have PLVEF as judged by resting left ventricular ejection fraction (LVEF). Patients with acute pulmonary oedema may also have normal LVEF. However, the pathophysiology of heart failure in patients with normal ejection fraction is probably heterogeneous. In most cases, heart failure may be caused mainly by diastolic dysfunction, but some patients have reduced systolic atrioventricular plane displacement, indicating mild systolic dysfunction; in some other cases excessive arterial stiffening has been reported. Furthermore, most, if not all patients with systolic dysfunction, have associated changes in diastolic function. Therefore, in most cases, diastolic and systolic heart failure should not be considered as separate pathophysiological entities. In some patients, however, it appears that the diastolic dysfunction dominates and may be a more sensitive marker of heart disease than LVEF. The most common etiologies are hypertension, coronary artery disease, or both, whereas hypertrophic cardiomyopathy is a more unusual but important etiology. Other descriptive terms in heart failure Right and left heart failure refer to syndromes presenting predominantly with congestion of the systemic or pulmonary veins. The terms do not necessarily indicate which ventricle is most severely damaged. High- and low-output, forward and backward, overt, treated, and congestive are the other descriptive terms still in occasional use; the clinical utility of these terms is descriptive without etiological information and therefore of little use in determining modern treatment for heart failure. Mild, moderate, or severe heart failure is used as a clinical symptomatic description, where mild is used for patients who can move around with no important limitations of dyspnoea or fatigue, severe for patients who are markedly symptomatic and need frequent medical attention, and moderate for the remaining patient cohort.

Definition of CHF

Many definitions of CHF exist, but only selective features of this complex syndrome are highlighted. None is entirely satisfactory. A simple objective definition of

CHF is currently impossible as there is no cutoff value of cardiac or ventricular dysfunction or change in flow, pressure, dimension, or volume that can be used reliably to identify patients with heart failure. The diagnosis of heart failure relies on clinical judgement based on a history, physical examination, and appropriate investigations.

For practical and operational purposes, the Task Force considers the essential components of heart failure to be a syndrome in which the patients should have the following features: symptoms of heart failure, typically breathlessness or fatigue, either at rest or during exertion, or ankle swelling and objective evidence of cardiac dysfunction at rest (Table 2.1). A clinical response to treatment directed at heart failure alone is not sufficient for diagnosis, although the patient should generally demonstrate some improvement in symptoms and/or signs in response to those treatments in which a relatively fast symptomatic improvement could be anticipated (e.g. diuretic administration). It should also be recognized that treatment may obscure a diagnosis of heart failure by relieving the patient's symptoms. The distinctions between cardiac dysfunction, persistent heart failure, as well as heart failure that has been rendered asymptomatic by therapy and transient heart failure (Figure 2.7). It is important to note that exercise-induced ventricular dysfunction, usually caused by myocardial ischaemia, may cause a rise in ventricular filling pressure and a fall in cardiac output and induce symptoms of heart failure (e.g. breathlessness) in the absence of cardiac dysfunction at rest. However, as both the underlying pathophysiology and the treatment of this condition is generally different from that of heart failure secondary to chronic ventricular dysfunction, such patients should not be diagnosed as having CHF.

Table 2.1.

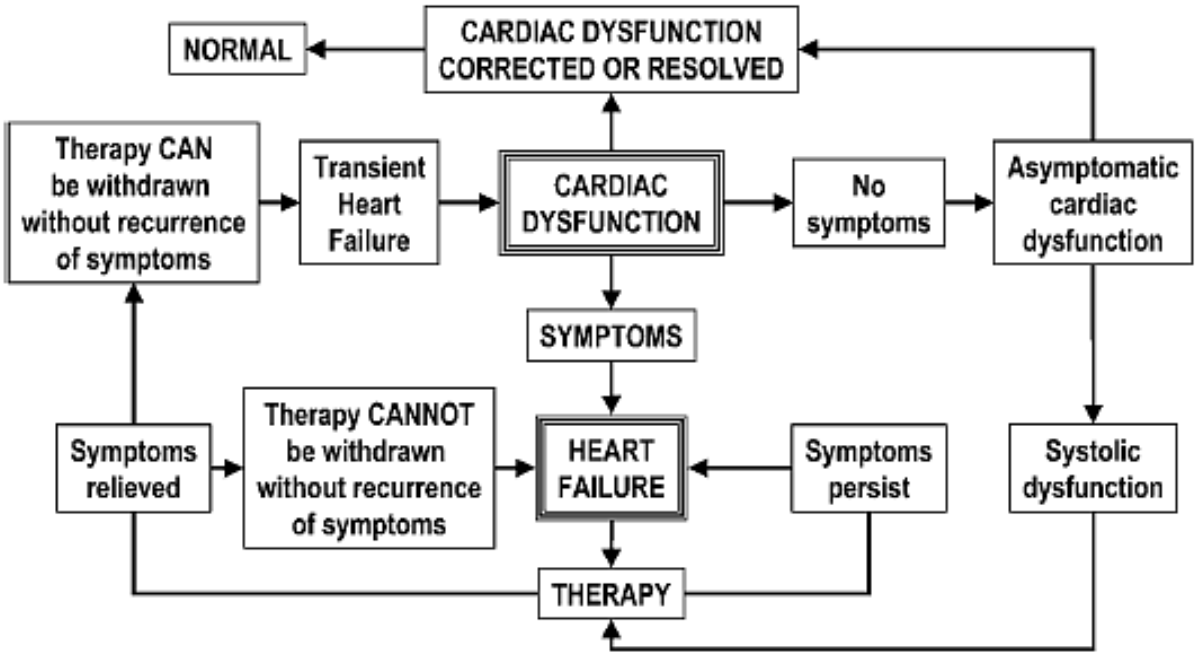
Definition of heart failure

#	Criteria
I	Symptoms of heart failure (at rest or during exercise) and
II	Objective evidence (preferably by echocardiography) of cardiac dysfunction (systolic and/or diastolic) (at rest) and (in cases where the diagnosis is in doubt) and
III	Response to treatment directed towards heart failure

Note: Criteria I and II should be fulfilled in all cases.

Figure 2.7

Relationship between cardiac dysfunction, heart failure, and heart failure rendered asymptomatic.



Asymptomatic left ventricular systolic dysfunction (ALVSD) is considered a precursor of symptomatic CHF and is itself associated with a relatively high mortality and morbidity. Treatments which can improve outcome in ALVSD are available, so this condition is included in these guidelines.

An etiology of heart failure in Europe.

Heart failure should never be the only diagnosis. The etiology of heart failure and the presence of exacerbating factors or other diseases that may have an important influence on management should be carefully considered in all cases. The extent to which the cause of heart failure should be pursued by further investigation will depend on the resources available and the likelihood that diagnosis will influence management. CHF may be caused by myocardial dysfunction, valve abnormalities, pericardial disease, or it may be induced by rhythm disturbances. Acute ischaemia, anaemia, renal or thyroid dysfunction, and cardio-depressant drugs may exacerbate, or more rarely, cause heart failure. Acute pulmonary oedema and cardiogenic shock have a similar etiological spectrum as CHF, though pulmonary oedema may be more often associated with a hypertensive crisis and normal left ventricular systolic function. Standard textbooks of cardiology should be consulted for a more extensive list

of the causes of heart failure. In Europe, myocardial dysfunction secondary to coronary artery disease, usually as a consequence of myocardial infarction, is the most common cause of heart failure among patients under the age of 75 years and clear abnormalities in systolic function are usually present. Concomitant hypertension is the most important condition in this context for the development of heart failure. Among elderly patients who are often less intensively investigated, an accurate diagnosis of the presence and the etiology of heart failure is more difficult and obscured by multiple other diagnoses. Systolic hypertension and cardiac hypertrophy, as well as cell loss and fibrosis may be more important causes of heart failure in the elderly and may be more likely to manifest predominantly as abnormalities of diastolic function. Importance of identifying potentially reversible exacerbating factors In patients with pre-existing cardiac dysfunction, symptoms of CHF may be caused or exacerbated by poor compliance to treatment, myocardial ischaemia, hypertension, tachy- or bradyarrhythmia, changes in valvular regurgitation, pulmonary embolism, aortic dissection, infection, renal dysfunction, side effects of drug therapy, and excessive fluid or sodium intake. It is important to identify any reversible factors in order to treat heart failure optimally.

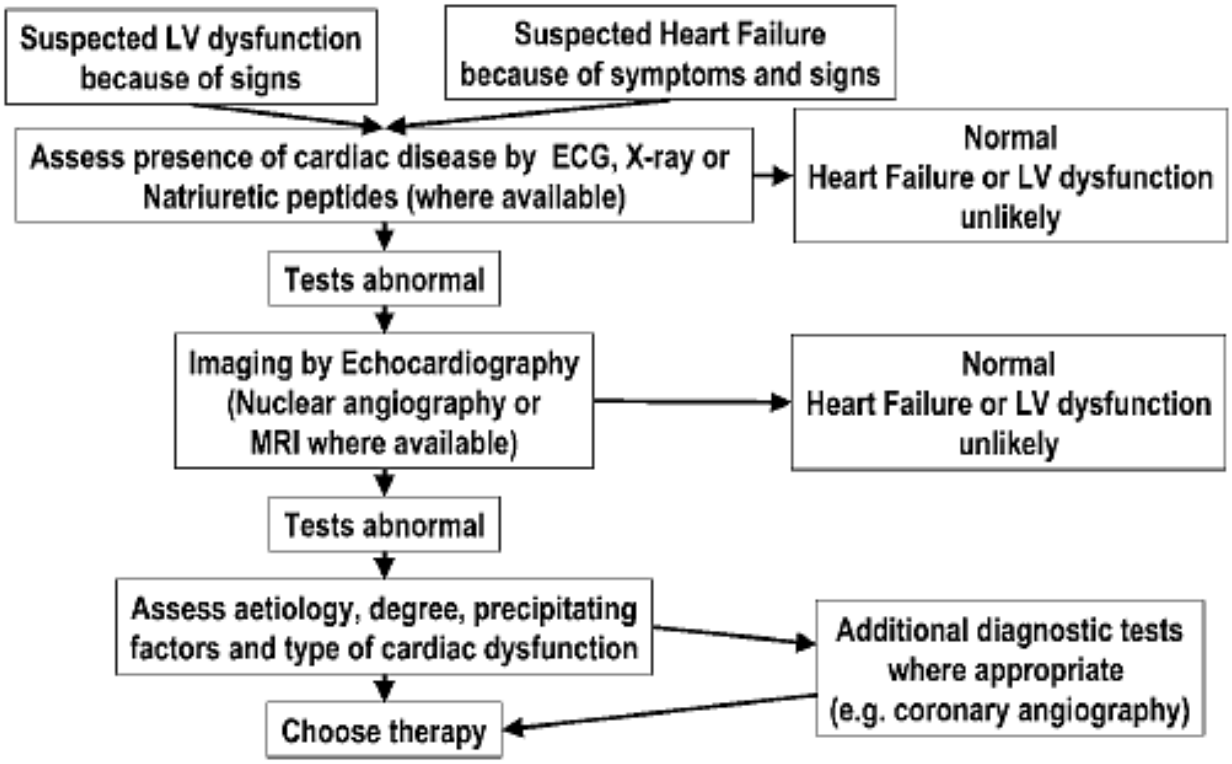
Aspects of the pathophysiology of the symptoms of heart failure relevant to diagnosis The origin of the symptoms of heart failure is not fully understood. Increased pulmonary capillary pressure is undoubtedly responsible for pulmonary oedema in part, but studies conducted during exercise in patients with CHF demonstrate only a weak relationship between capillary pressure and exercise performance. This suggests that raised pulmonary capillary pressure is not the only factor responsible for exertional breathlessness. In this context, variation in the degree of dynamic mitral regurgitation will influence breathlessness. Abnormalities of alveolar-capillary gas diffusion, peripheral or respiratory skeletal muscle deconditioning, and non-cardiac causes of dyspnoea, such as obesity or pulmonary disease, should always be considered. Peripheral oedema is poorly related to right heart pressures: capillary permeability for fluid and small proteins may be important additional factors. Venous insufficiency and drug therapy (calcium channel blockers) should be considered.

Although impairment of cardiac function is central to the development of heart failure, altered peripheral blood flow, especially to the kidney and skeletal muscle, is typical and probably of major pathophysiological importance. Similarly, activation of a number of neuroendocrine systems is characteristic of heart failure. Baroreceptor dysfunction is an important link between vasomotor and neuroendocrine dysfunction. The understanding of CHF has moved from a haemodynamic concept into accepting the importance of neuroendocrine pathophysiological changes as important for the progression as well as the treatment of heart failure. Activation of various inflammatory pathways may also contribute to cardiac dysfunction and to the clinical syndrome, particularly in more advanced stages.

Possible methods for the diagnosis of heart failure in clinical practice Symptoms and signs in the diagnosis of heart failure. Symptoms and signs are important as they alert the observer to the possibility that heart failure exists. The clinical suspicion of heart failure must be confirmed by more objective tests particularly aimed at assessing cardiac function (Figure 2.8).

Figure 2.8

Algorithm for the diagnosis of heart failure or left ventricular dysfunction.



Breathlessness, ankle swelling, and fatigue are the characteristic symptoms and signs of heart failure but may be difficult to interpret, particularly in elderly patients, the obese, and in women. It should be interpreted carefully and different modes (e.g. effort and nocturnal) should be assessed. Fatigue is also an essential symptom in heart failure. The origins of fatigue are complex, including low cardiac output, peripheral hypoperfusion, as well as skeletal muscle deconditioning and confounded by difficulties in quantifying this symptom. Extracardiac causes of oedema not related to heart failure are common. Inter-observer agreement on the presence or absence of symptoms of heart failure may be low, notably in the days following a myocardial infarction. There is no standard questionnaire available for the diagnosis of heart failure. In the context of clinical or epidemiological studies, several scoring systems are available that await proper validation and cannot be recommended for clinical practice at present.

Peripheral oedema, raised venous pressure, and hepatomegaly are the characteristic signs of congestion of systemic veins. Clinical signs of heart failure should be assessed in a careful clinical examination, including observing, palpating, and auscultating the patient. Unfortunately, clinical examination is often replaced by various investigations, which reduce the experience in bedside medicine among physicians. Peripheral oedema and hepatomegaly have low positive predictive value and without the determination of the jugular venous pressure may be difficult. Peripheral oedema is usually absent in well-treated heart failure and primarily left ventricular systolic dysfunction, even if severe. Although cardiologists attain a high agreement on the presence of an elevated jugular venous pressure under study conditions, the reproducibility is much lower among non-specialists. Moreover, many patients, even with well-documented heart failure, do not have an elevated jugular venous pressure, even if severe. Tachycardia is non-specific and may be absent even in severe heart failure, particularly in the presence of beta-blocker therapy. Other signs of heart failure require considerable expertise for their detection. A third heart sound is usually considered to be present in patients with severe heart failure and left ventricular systolic dysfunction, but it is not specific to heart failure and may be averted by medical ther-

apy. Although cardiology specialists may attain a high agreement for the presence of a third heart sound under study conditions, the inter-observer agreement is, 50% among non-specialists and probably even lower in clinical practice.

Pulmonary crepitations also have low positive predictive value and inter-observer differences in eliciting this sign are notably high. When cardiac murmurs are present, their origin and role in the symptomatology should be identified. In particular, mitral regurgitation is often present and may be dynamic, which would influence symptoms during exercise. When multiple signs of heart failure are present, including a displaced apex beat, pitting oedema, a raised venous pressure, and increased P2 and when a third heart sound is heard, then in the presence of appropriate symptoms, a clinical diagnosis of heart failure may be made with some confidence. Although a clinical diagnosis reached in this way may be specific enough, it will fail to identify many patients who might benefit from treatment. The subjective component of the examination and the inability to make a permanent direct record are further weaknesses of a diagnosis made solely on the basis of clinical features. Symptoms and the severity of heart failure. There is a poor relationship between symptoms and the severity of cardiac dysfunction. However, symptoms may be related to prognosis particularly if persisting after therapy. Once a diagnosis of heart failure has been established, symptoms may be used to classify the severity of heart failure and should be used to monitor the effects of therapy. However, as noted subsequently, symptoms cannot guide the optimal titration of neurohormonal blockers. The New York Heart Association (NYHA) classification is in widespread use (Table 2.2).

Table 2.2.

New York Heart Association classification of heart failure

#	
Class I	No limitation: ordinary physical exercise does not cause undue fatigue, dyspnoea, or palpitations
Class II	Slight limitation of physical activity: comfortable at rest but ordinary activity results in fatigue, palpitations, or dyspnoea
Class III	Marked limitation of physical activity: comfortable at rest but less than ordinary activity results in symptoms
Class IV	Unable to carry out any physical activity without discomfort: symptoms of heart failure are present even at rest with increased discomfort with any physical activity

The use of examples such as walking distance or number of stairs climbed is recommended. In other situations, the classification of symptoms into mild, mod-

erate, or severe is used. Patients in NYHA class I classification would have to have objective evidence of cardiac dysfunction, have a past history of heart failure symptoms, and be receiving treatment for heart failure in order to fulfill the basic definition of heart failure. In acute myocardial infarction, the classification described by Killip to describe symptoms and signs has been used. The value of questionnaires for the measurement of quality of life in the context of classification of severity is still being heavily debated.

Frequently used questionnaires are the Minnesota Living with Heart Failure, the SF 36, and the Kansas City Cardiomyopathy Questionnaire. It is important to recognize the common dissociation between symptoms and cardiac dysfunction. Symptoms are also similar in patients across different levels of ejection fraction. The severity of symptoms is highly dependent on the efficacy of therapy, patient expectation, and medical interpretation. Mild symptoms should not be equated with minor cardiac dysfunction.

Electrocardiogram

A normal electrocardiogram (ECG) suggests that the diagnosis of CHF should be carefully reviewed. Electrocardiographic changes in patients with heart failure are frequent. The negative predictive value of normal ECG to exclude left ventricular systolic dysfunction exceeds 90%. On the other hand, the presence of anterior Q-waves and a left bundle branch block in patients with ischaemic heart disease are good predictors of a decreased ejection fraction. ECG signs of left atrial overload or left ventricular hypertrophy may be associated with systolic as well as isolated diastolic dysfunction, but they have a low predictive value. A QRS width .120 ms suggests that cardiac dyssynchrony may be present and a target for treatment. The ECG is crucial for detecting atrial fibrillation or flutter, and sometimes ventricular arrhythmia, all of which are considered causative or contributing factors for heart failure. The diagnostic contribution of ECG anomalies markedly increases if clinical symptoms and signs of heart failure co-exist. ECG recordings do not need to be repeated in the absence of changes of clinical status.

The chest X-ray

The chest X-ray should be part of the initial diagnostic work-up in heart failure. A high predictive value of X-ray findings is only achieved by interpretation of the X-ray in the context of clinical findings and ECG anomalies. The investigation is useful in detecting the presence of pulmonary congestion. Importantly, pulmonary disease contributing/causing dyspnoea can be detected. Cardiomegaly is frequently absent not only in patients with AHF but also in cases with diastolic as well as systolic dysfunction. However, in patients with CHF, an increased cardiac size, as judged by a cardiothoracic ratio >0.50, and the presence of a pulmonary venous congestion are useful indicators of abnormal cardiac function with decreased ejection fraction and/or elevated left ventricular filling pressure. Pleural effusion is also common.

Interstitial and alveolar pulmonary oedemas are also reliable and important signs of severe left ventricular dysfunction. However, in individual patients, the radiographic findings alone do not allow a reliable estimation of the pulmonary capillary pressure and are therefore not suitable as the only basis for therapeutic decisions. There may also be inter-observer variations in the interpretation of chest X-ray changes. The relationship between radiological signs and haemodynamic findings may depend on the duration as well as the severity of cardiac dysfunction.

Hematology and biochemistry

The following laboratory investigations are recommended as part of a routine diagnostic evaluation of patients with CHF: complete blood count (Hb, leukocytes, and platelets), S-electrolytes, S-creatinine, S-glucose, S-hepatic enzymes, and urinanalysis. Additional tests to consider include C-reactive protein, thyroid stimulating hormone (TSH), S-uric acid, and S-urea. In acute exacerbations, it is important to exclude acute myocardial infarction by myocardial biomarkers. Anaemia may exacerbate pre-existing heart failure and is associated with increased risk for morbidity and mortality. A raised haematocrit suggests that breathlessness may be caused by pulmonary disease, cyanotic congenital heart disease, or a pulmonary arteriovenous malformation.

Elevated serum creatinine can be caused by primary renal disease, which may induce all the features of heart failure by volume overload. Heart failure and renal

dysfunction often coincide because of the underlying diseases, such as diabetes and hypertension, or as a consequence of impaired kidney perfusion by reduction in cardiac output during the progression of heart failure. Treatment with diuretics and/or ACE-inhibitors sometimes together with potassium-sparing diuretics is another reason for a high S-creatinine value. Further, age alone can be a cause of reduced creatinine clearance.

Concomitant administration of ACE-inhibitors and potassium-sparing diuretics may lead to hyperkalaemia. Untreated heart failure is rarely associated with major electrolyte disturbances, but such disturbances are quite common in patients on diuretics. Liver enzymes may be poor by hepatic perfusion.

Urine analysis is useful in detecting proteinuria and glycosuria, alerting the clinician to the possibility of underlying renal problems or diabetes mellitus, conditions that may contribute to, or complicate, heart failure.

Hyponatraemia and renal dysfunction in the setting of heart failure indicate a bad prognosis. Heart failure due to thyrotoxicosis is frequently associated with rapid atrial fibrillation, which may be the presenting feature of thyrotoxicosis in the elderly. Hypothyroidism may also present as heart failure.

Natriuretic peptides

Plasma concentrations of certain natriuretic peptides or their precursors, especially BNP and NT-proBNP, are helpful in the diagnosis of heart failure. A low-normal concentration in an untreated patient makes heart failure unlikely to be the cause of symptoms.

BNP and NT-proBNP have considerable prognostic potential though evaluation of their role in treatment monitoring remains to be determined. Several clinical and epidemiological studies have demonstrated a direct relationship between increasing plasma concentrations of natriuretic peptides and decreasing cardiac (usually left ventricular) function. Although this applies to atrial natriuretic peptides (ANP), B-type natriuretic peptide (BNP) and its precursor NT-proBNP, for which there are now commercially available assays, have been much more extensively characterized in clinical practice. Conclusive evidence of diagnostic accuracy is now available from

well-conducted clinical trials. Patients who were referred to a rapid access heart failure clinic from primary care BNP performed extremely well when compared with the gold standard diagnoses made by a panel of three cardiologists with all available clinical information. In particular, the negative predictive accuracy was 97%, i.e. to rule out the diagnosis, whereas this population with a high a priori likelihood of heart failure, the positive predictive value was also high at 70%. Thus, the diagnostic potential of both BNP and NT-proBNP in primary care is high, a setting in which only about one-third of patients with suspected heart failure has the presence of heart failure subsequently confirmed. A large study has recently confirmed that BNP could help differentiate cardiac from respiratory acute breathlessness in the emergency room setting in the United States. The predictive accuracy of BNP for heart failure was similar to or better than other clinical variables, including the chest X-ray.

Although the diagnostic potential of natriuretic peptides is less clear-cut when systolic function is normal, there is increasing evidence that their elevation can indicate that diastolic dysfunction is present. Other common cardiac abnormalities that may cause elevated natriuretic peptide levels include left ventricular hypertrophy, valvular heart disease, acute or chronic ischaemia, hypertension, and pulmonary embolism. Although rarely, a high BNP may also signify noncardiac disease with the most common being renal impairment.

It is important to recognize that female gender and increasing age also elevate the plasma levels, factors that must be taken into account when setting cut points. It needs also to be stressed that, as with troponin measurements, these values are assay specific and not interchangeable among assays.

In considering the use of BNP and NT-proBNP as diagnostic aids, it should be emphasized that a ‘normal’ value cannot completely exclude cardiac disease, but a normal or low concentration in an untreated patient makes heart failure unlikely as the cause of symptoms. Nevertheless, values in the normal range are associated with an excellent prognosis and alternative causes of the symptoms should be sought in the first instance. Most importantly, it must be recognized that elevated levels are powerful predictors of death and future major cardiac events. Therefore, such an observa-

tion confers ‘high risk’ status and mandates further cardiological investigation to elucidate the cause. In the first instance, this is likely to be an ECG, which may provide the explanation and indicate a management plan. In clinical practice today, the place of BNP and NTproBNP is as ‘rule out’ tests to exclude significant cardiac disease. Particularly in primary care but also in certain aspects of secondary care (e.g. the emergency room and clinics), the cost-effectiveness of the test suggests that a normal result should obviate the need for further cardiological tests such as in the first instance, echocardiography as well as more expensive investigations.

Echocardiography

Echocardiography is the preferred method for the documentation of cardiac dysfunction at rest. The most important measurement of ventricular function is the LVEF for distinguishing patients with cardiac systolic dysfunction from patients with preserved systolic function. The access to and use of echocardiography is encouraged for the diagnosis of heart failure. Transthoracic Doppler echocardiography (TDE) is rapid, safe, and widely available. It is a non-invasive technique that allows the assessment of chamber dimensions, wall thicknesses and geometry, indices of regional and global, systolic and diastolic ventricular function.

Echocardiography also provides rapid and semi-quantitative assessment of valvular function, especially of mitral, tricuspid and aortic stenosis and regurgitation, grading of mitral regurgitation and the velocity of secondary tricuspid regurgitation for the estimate of systolic pulmonary artery pressure. Although M-mode measurements benefit from high temporal resolution, they are inaccurate in patients with spherical ventricles and regional dysfunction. The apical biplane summation of discs method - modified Simpson’s method - is validated but relies on accurate endocardial definition. Although quantitative visual assessment has been shown to detect low LVEF with good sensitivity and specificity, this procedure is reliable only with experienced observers. Other measurements include fractional shortening, sphericity index, atrioventricular plane displacement, myocardial performance index, and left ventricular wall motion index.

The interpretation of ejection fraction with any technique shortly after an acute myocardial infarction or in the context of a mitral regurgitation is more uncertain. Reproducibility of ejection fraction among different observers is poor, even when the same techniques are used.

Assessment of LV diastolic function

Assessment of diastolic function may be clinically useful in detecting abnormalities of diastolic function in patients who present with CHF and normal LVEF, in determining prognosis in heart failure patients, in providing a non-invasive estimate of left ventricular diastolic pressure, and in diagnosing constrictive pericarditis and restrictive cardiomyopathy also.

Diagnostic criteria of diastolic dysfunction

According to recommendations from the ESC Working Group on Myocardial Function, a diagnosis of primary diastolic heart failure requires three conditions to be simultaneously satisfied:

- presence of signs or symptoms of CHF,
- presence of normal or only mildly abnormal left ventricular systolic function (LVEF $\leq$ 45–50%),
- evidence of abnormal left ventricular relaxation, diastolic distensibility, or diastolic stiffness.

The third criterion may be the most difficult to satisfy because of limitations in the diagnostic methods. Furthermore, it is essential to exclude pulmonary disease. The two hallmarks of left ventricular diastolic dysfunction are impaired relaxation and decreased diastolic compliance. Quantification of rate of relaxation and compliance requires invasive methods and is therefore not practical in clinical routine. Instead, different echocardiography indices of diastolic filling may be used. Importantly, these indices do not directly measure diastolic function, but serve as markers of impaired diastolic function. The approaches which are most useful are the measurement of transmitral and pulmonary venous flow velocities by pulsed Doppler echocardiography and mitral annular velocities by tissue Doppler imaging (TDI). The peak early diastolic mitral flow velocity (E) is directly related to the transmitral pressure gra-

dient and left atrial pressure and is therefore markedly load-dependent. The peak early diastolic mitral annular velocity (E0) is less load-dependent and is related to the rate of left ventricular relaxation. One should also look for cardiac structural changes that may be consistent with diastolic dysfunction, in particular, left atrial enlargement and left ventricular hypertrophy. Filling patterns and staging of diastolic dysfunction In patients with cardiac disease, three abnormal left ventricular filling patterns have been described. At an early stage of diastolic dysfunction, there is typically a pattern of impaired myocardial relaxation with a decrease in peak transmitral E-velocity, a compensatory increase in the atrial-induced (A) velocity, and therefore a decrease in the E/A ratio. In patients with advanced cardiac disease there may be a pattern of 'restrictive filling', with an elevated peak E-velocity, a short E-deceleration time, and a markedly increased E/A ratio. The elevated peak E-velocity is due to elevated left atrial pressure that causes an increase in the early-diastolic transmitral pressure gradient. The short E-deceleration time is due to reduced left ventricular chamber compliance that leads to rapid deceleration of transmitral flow.

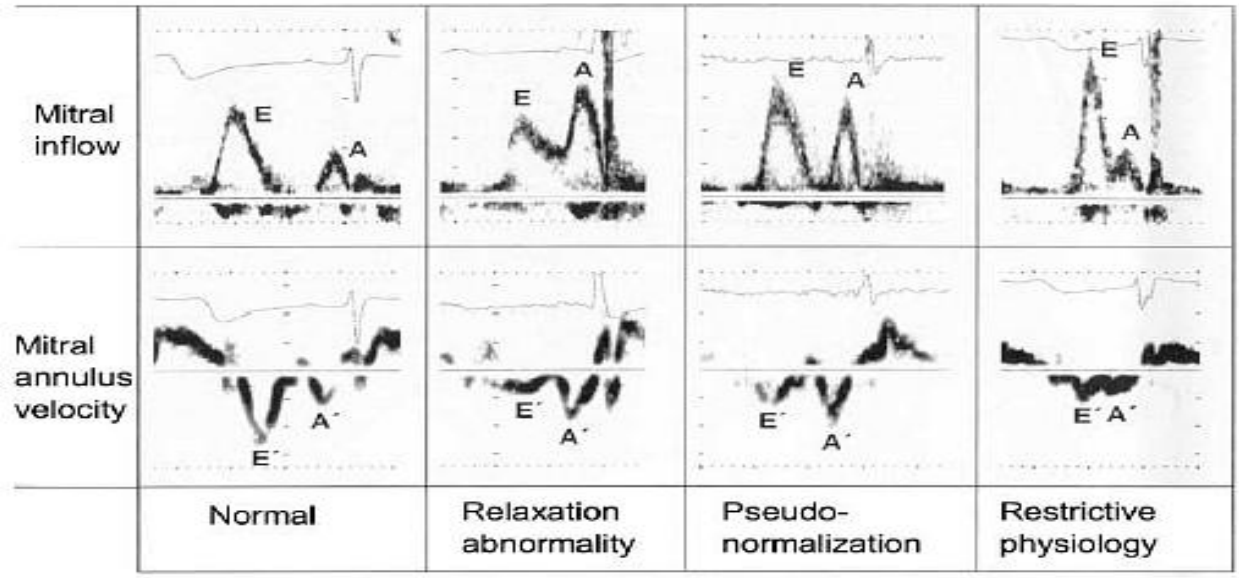
In patients with an intermediate pattern between impaired relaxation and restrictive filling, the E/A ratio and the deceleration time may be normal, a so-called 'pseudonormalized filling pattern'. This pattern may be distinguished from normal filling by the demonstration of reduced peak E_1-velocity by TDI and by some other diagnostic approaches.

The three filling patterns 'impaired relaxation', 'pseudonormalized filling', and 'restrictive filling' represent mild, moderate, and severe diastolic dysfunction, respectively. Thus, by using the combined assessment of transmitral blood flow velocities and mitral annular velocities, it becomes possible to perform staging of diastolic dysfunction during a routine echocardiographic examination (Figure 2.9). In a given patient, however, the pattern may change over time because of changes in intrinsic myocardial function and in response to medication that modifies loading conditions. Importantly, the absolute value of E0 is dependent on the equipment that is used and instrument settings. Furthermore, transmitral velocities and mitral annular velocities are age-dependent, and any given value should be compared with age-adjusted refer-

ence values. We still lack prospective outcome studies that investigate if assessment of diastolic function by these criteria may improve management of heart failure patients.

Figure 2.9.

The three filling patterns ‘impaired relaxation’, ‘pseudonormalized filling’, and ‘restrictive filling’ represent mild, moderate, and severe diastolic dysfunction, respectively



Estimation of LV diastolic pressure

The marked sensitivity of left ventricular filling velocities to loading conditions represents a limitation when Doppler velocities are used as markers of diastolic function. The load sensitivity, however, makes it possible to estimate left ventricular diastolic pressure from the Doppler indices of filling. One of the most useful of these approaches is to compare the durations of antegrade transmitral flow with reversed pulmonary venous flow during atrial contraction. A pulmonary venous reverse A-wave duration that exceeds transmitral A-wave duration by 0.30 ms is a marker of elevated LV EDP. Because peak early mitral annular velocity is less preload-dependent than peak early transmitral velocity, the E/E0 ratio can be used to estimate left ventricular filling pressure. Persistence of a restrictive filling pattern of left ventricular filling after medical treatment is associated with increased mortality. Transoesophageal echocardiography is not recommended routinely and can only be advocated in patients who have an inadequate echo window, in complicated valvular pa-

tients, in patients with suspected dysfunction of mechanical mitral valve prosthesis, or when it is mandatory to identify or exclude a thrombus in the atrial appendage. Repeated echocardiography can be recommended in the follow-up of patients with heart failure only when there is an important change in the clinical status suggesting significant improvement or deterioration in cardiac function.

Additional non-invasive tests to be considered In patients in which echocardiography at rest has not provided enough information and in patients with coronary artery disease (e.g. severe or refractory CHF and coronary artery disease) further non-invasive imaging may include the following techniques.

Stress echocardiography

Exercise or pharmacological stress echocardiography may be useful for detecting ischaemia as a cause of reversible or persistent dysfunction and in determining the viability of akinetic myocardium. Graded dobutamine infusion may be used to recruit contractile reserve. Sustained contractile improvement is observed when flow reserve is appropriate, in the presence of stunning or nontransmural infarction. A biphasic response indicates that flow reserve is blunted and suggests the presence of myocardial hibernation. Although several noncontrolled studies have shown that revascularization can improve regional function, clinical status, and survival in patients with a significant amount of hibernating myocardium, a systematic assessment of myocardial viability in patients with coronary artery disease and heart failure with systolic dysfunction cannot yet be recommended.

Nuclear cardiology

Radionuclide angiography (RNA) provides reasonably accurate measurements of left and, to a lesser extent, right ventricular ejection fraction (RVEF) and cardiac volumes. Left ventricular filling dynamics can also be analysed. In none of these are the measurements reliable in the presence of atrial fibrillation. Planar myocardial scintigraphy or single photon emission computed tomography (SPECT) can be performed at rest or during stress using infusion of different agents, such as thallium^{201} or ^{99} technetium sestamibi. The presence and extent of ischaemia can be evaluated. Although each of these imaging modalities may have certain diagnostic and prognos-

tic value, the routine use of nuclear cardiology cannot be recommended. As with echocardiography, values of ejection fraction vary with the technique used. Thus, analysis using a single region of interest gives values significantly lower than when two regions are used. However, reproducibility is better than with echocardiography.

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (CMR) is a versatile, highly accurate, and reproducible imaging technique for the assessment of left and right ventricular volumes, global function, regional wall motion, myocardial thickness, thickening, myocardial mass, and cardiac valves. The method is well suited for detection of congenital defects, masses and tumours, and valvular and pericardial diseases. Additional information can be obtained when CMR is used with paramagnetic contrast agents. Bolus injection of a gadolinium–chelate can be used to assess myocardial perfusion at rest or during pharmacological stress and, combined with regional assessment of myocardial thickening and excursion, can be used to assess myocardial ischaemia and new infarction. Imaging 10–20 min after an injection of gadolinium can identify areas of delayed hyper-enhancement which are thought to reflect regions of acute infarction or chronic scar. Delayed hyper-enhancement can be used to identify and distinguish full and partial-thickness scar and thus differentiate regions of contractile dysfunction due to loss of myocardium from those that are likely to reflect stunning or hibernation. Marked thinning of the myocardium is also likely to reflect extensive scar. Magnetic resonance angiography with or without paramagnetic contrast also allows imaging of many vascular beds of clinical interest (e.g. aorta, carotid, pulmonary, renal, and peripheral arteries), avoiding invasive tests and the use of potentially nephrotoxic X-ray contrast agents.

There are a few contra-indications that should be considered absolute, such as the presence of metal in the eye or brain (clips or foreign bodies) and cochlear implants. Most angioplasty stents are compatible with CMR. Pacemakers, defibrillators, and other implanted medical devices have generally been considered as a contraindication to CMR but carefully selected cases have been imaged safely and effectively.

The major limitation of CMR for patients is claustrophobia. This may be reduced by new technologies and managing patients' anxiety.

Scan times until now have typically taken <30 min without and 60 min with an acute and delayed scan with gadolinium enhancement and pharmacological stress. New ultra-fast technologies can reduce scan times to 2–3 min. CMR has several advantages over other imaging techniques. CMR has become the gold standard of accuracy and reproducibility against which other techniques for the assessment of volumes, mass, and wall motion should be compared. There is less operator dependence when compared with echocardiography and images can be obtained when echo proves sub-optimal because of a poor acoustic window. There is better spatial resolution when compared with conventional nuclear imaging. There is no radiation or nephrotoxic contrast involved. CMR may be inferior to fast electronbeam CT techniques for the non-invasive assessment of coronary arteries. However, CMR is expensive, a relatively rare resource and, in terms of practical management of most patients with heart failure, it has not been shown to be superior to echocardiography.

Pulmonary function

Measurements of lung function are of little value in diagnosing CHF. However, they are useful in excluding respiratory causes of breathlessness. Spirometry can be useful to evaluate the extent of obstructive airways disease, which is a common comorbidity in patients with heart failure. Epidemiological studies suggest a strong association between chronic obstructive airways disease and ischaemic heart disease, one of the principal causes of heart failure. Peak expiratory flow rate (PEFR) and forced expiratory volume in 1s (FEV1) are reduced by CHF but not to the same extent as in symptomatic obstructive airways disease. Alveolar-capillary gas-diffusing capacity is related to exercise capacity, which can provide prognostic information. Other variables have no value in diagnosing or in grading disease progression in patients with CHF. Dyspnoea and fatigue are the two main causes of exercise limitation in patients with CHF. Respiratory muscle dysfunction may also play an important role.

Exercise testing . In clinical practice, exercise testing is of limited value for the diagnosis of heart failure. However, a normal maximal exercise test in a patient not

receiving treatment for heart failure excludes heart failure as a diagnosis. The main applications of exercise testing in CHF are focused more on functional and treatment assessment and on prognostic stratification. Recommendations for exercise testing in heart failure patients have been released by the Working Group on Cardiac Rehabilitation and Exercise Physiology and the Working Group on Heart Failure of the ESC. In recent years, exercise testing has been used for prognostic purposes and exercise capacity with on-line gas exchange measurements has proved to be an important component of the risk profile in CHF. A peak VO_2 <10 mL/kg per min identifies high risk and a peak VO_2 >18 mL/kg per min identifies low risk patients. Values between these cut-off limits define a 'grey' zone of medium risk patients without further possible stratification by VO_2. The available prognostic data for women are inadequate. Assessment of the ventilatory response to exercise, measured as the slope of the relation between minute ventilation and carbon dioxide production during exercise, has been shown to have an independent prognostic value in CHF. Its prognostic value has been superior to that of peak VO_2 in recent studies. To date, there have been no reports of serious problems related to exercise testing in CHF. The 6 min walk test has been widely implemented in clinical trials. The 6 min walk test may provide useful prognostic information when walking distance is about 300 m. However, for use in the clinical setting, the value of the 6 min walk test is unclear.

Invasive investigation is generally not required to establish the presence of CHF but may be important in elucidating the cause or to obtain prognostic information. Three diagnostic tools may be helpful in different situations: coronary angiography, haemodynamic monitoring, and endomyocardial biopsy. None of them is indicated as a routine procedure.

Cardiac catheterization. Coronary angiography should be considered in patients with acute or acutely decompensated CHF and in patients with severe heart failure (shock or acute pulmonary oedema) who are not responding to initial treatment. Coronary angiography should also be considered in patients with angina pectoris or any other evidence of myocardial ischaemia if they are not responding to appropriate anti-ischaemic treatment. However, revascularization of hibernating or ischaemic myo-

cardium in heart failure has not been shown to improve outcome in controlled trials. Angiography can be used to exclude coronary artery disease when a diagnosis of idiopathic dilated cardiomyopathy is considered. Coronary angiography is also indicated in patients with refractory heart failure of unknown aetiology and in patients with evidence of severe mitral regurgitation or aortic valve disease. Monitoring of haemodynamic variables by means of a pulmonary arterial catheter is indicated in patients who are hospitalized for cardiogenic shock or to direct treatment of patients with CHF not responding promptly to initial and appropriate treatment. Routine right heart catheterization should not be used to tailor chronic therapy.

Endomyocardial biopsy may be useful in selected patients with unexplained (myocardial ischaemia excluded) heart failure. Furthermore, biopsy may help to differentiate between constrictive and restrictive aetiologies.

Tests of neuroendocrine evaluations other than natriuretic peptides. Tests of neuroendocrine activation are not recommended for diagnostic or prognostic purposes in individual patients. Although there are no doubts about the importance of neuroendocrine mechanisms in the pathogenesis of heart failure, the role of neuroendocrine factors in the diagnosis is less clear. In large cohorts of patients there is good evidence that circulating levels of noradrenaline, renin, angiotensin II, aldosterone, vasopressin, endothelin-1, and adrenomedullin are related to the severity and prognosis of heart failure, but in individual patients these predictors are inaccurate and difficult to interpret.

Diuretics, vasodilator agents, ACE-inhibitors, and beta-blockers alter plasma concentrations of neuroendocrine substances in a complex fashion which limits diagnostic use. Plasma noradrenaline increases with age and healthy subjects over the age of 75 years may have plasma concentrations of noradrenaline in the heart failure range.

Holter electrocardiography: ambulatory ECG, and longtime ECG recording

Conventional Holter monitoring is of no value in the diagnosis of CHF, though it may detect and quantify the nature, frequency, and duration of atrial and ventricular arrhythmias which could be causing or exacerbating symptoms of heart failure. Long-

time ECG recording (LTER) should be restricted to patients with CHF and symptoms suggestive of an arrhythmia.

The high prevalence of ventricular ectopy and ventricular tachycardia is well recognized, but it remains unclear whether ventricular arrhythmias identify patients at high risk of sudden death. Ambulatory electrocardiographic monitoring alone seems not to provide additional prognostic information. Furthermore, the finding of asymptomatic non-sustained ventricular arrhythmias on LTER does not identify specific candidates for anti-arrhythmic or device therapy. Heart rate variability Heart rate variability (HRV) is a marker of autonomic balance, a balance that is characterized by an increased sympathetic activation and reduced vagal stimulation in patients with heart failure. The diagnostic and prognostic utility of this observation has been extensively investigated. A correlation between time and frequency domain HRV measures and clinical and haemodynamic variables exists, and time domain variables can predict survival independently from clinical and haemodynamic data. The value of this technology in clinical practice, however, still remains to be determined.

Requirements for the diagnosis of heart failure in clinical practice

To satisfy the definition of heart failure, symptoms of heart failure and objective evidence of cardiac dysfunction must be present (Table 2.1). The assessment of cardiac function by clinical criteria alone is unsatisfactory. Cardiac dysfunction should be assessed objectively.

The echocardiogram is the single most effective tool in widespread clinical use. Other conditions may mimic or exacerbate the symptoms and signs of heart failure and therefore need to be excluded. An approach (Figure 2.8) to the diagnosis of heart failure in symptomatic patients should be performed routinely in patients with suspected heart failure in order to establish the diagnosis. Additional tests should be performed or re-evaluated in cases in which diagnostic doubt persists or clinical features suggest a reversible cause for heart failure. Coronary artery disease is a common, and probably underdiagnosed, cause of heart failure. If there is reason to believe that the patient will benefit from revascularization, then an angiogram and additional tests as appropriate should be done.

Figure 2 represents a simplified plan for the evaluation of a patient presenting with symptoms suggestive of heart failure or signs giving suspicion of left ventricular systolic or diastolic dysfunction. The symptoms are similar in heart failure because of systolic and diastolic dysfunction. Accordingly, the same criteria should be used for the diagnosis of both conditions with the application of the assessment of LV myocardial function as described previously.

Prognostication

Prognosis

The problem of defining prognosis in heart failure is complex for many reasons: several aetiologies, frequent comorbidities, limited ability to explore the paracrine pathophysiological systems, varying individual progression and outcome (sudden vs. progressive heart failure death), and efficacy of treatments. Moreover, several methodological limitations weaken many prognostic studies. The imprecision in making the diagnosis of CHF does not help in defining the prognosis of this syndrome. The problem has become more complex since the recognition of heart failure with a preserved left ventricular systolic function. Considering that a correct diagnosis of heart failure required evidence of left ventricular systolic dysfunction—in practice a low ejection fraction - prognostic stratification needs to be re-considered.

However, prognostic analyses have been predominantly carried out on populations enrolled in trials and because an enrolment criterion in most trials published so far has been a reduced LVEF, there are few data on which to base a stratification analysis of heart failure with preserved systolic function. For this reason, what can be said thus far concerns mainly patients with proven left ventricular systolic dysfunction. Our ability to explore the functional alterations of many biological systems is limited by the available access to the body investigation which, apart from the imaging techniques, is the blood. This precludes from the analysis all short-living paracrine mediators which do not enter the circulation or pass into the blood in small amounts not representing the level of activity of the specific function that they mediate.

Although heart failure is a chronic syndrome, it does not evolve gradually. Periods of relative stability alternate with acute destabilizations. The prognostic stratification should, therefore, be different in relation to the goal. Stratification during an acute unstable phase should have a short-term aim and should guide immediate decisions. Stratification during a stable phase could have a long-term aim and should predict and, hopefully help to prevent, destabilizations and death in the mid-term and long-term. Moreover, the activation of the biological systems involved in the pathophysiology of heart failure can occur at different times during the course of the syndrome. Consequently, the prognostic significance of several variables can change according to the evolutionary stage of the disease.

About half of all deaths from heart failure are sudden, frequently, but not always, of an arrhythmic origin. Sudden death may occur at any stage of the syndrome in patients with very different conventional risk profiles. Introduction of new treatments can modify the prognostic weight of the same variable over time. For example, beta-blockers influence left ventricular function more than exercise capacity.

Thus, the predictive power of these two factors can differ in patients treated or not treated with beta-blockers. Relatively weak prognostic power of many variables is also explained by a series of methodological flaws. These include small, selected samples, short duration of follow-ups, spot (non-sequential) determination of the potential indicators, few and selected variables included in the multivariate analyses which should (but do not) produce ‘independent’ prognostic indicators. Numerous prognostic algorithms have been reported. Usually the independent prognostic predictors considered are clinical variables, chest X-rays, ECG, and echocardiographic parameters. Indicators that can only be measured with sophisticated techniques and/or invasive methods can only be recommended in specific situations in which they have been demonstrated to be of important benefit in making decisions concerning the use of life-saving drugs or devices or submission to demanding therapeutic strategies such as heart transplantation. Excellent reviews of the prognostic value of different variables and algorithms in heart failure have been published. Prognostic stratification must be useful for making therapeutic decisions. Similarly, volume changes over

time and the onset or worsening of mitral regurgitation have important decisional implications because they should lead to further diagnostic investigations and/or intensification of therapy. In contrast, with the exception of brain natriuretic peptide, degree of neurohormonal activation cannot guide the initiation of treatment with ACE-inhibitors or beta-blockers.

Both neurohormonal activation and left ventricular systolic dysfunction tend to fall into a uniformly reduced range in advanced heart failure, such that their incremental value in prognostic stratification tends to decrease as the heart failure worsens. In contrast, central haemodynamic patterns and right ventricular function take on prognostic importance in severe heart failure. If right ventricular function deteriorates, the clinical situation can dramatically worsen and alternative treatments (e.g. transplantation) should be considered. The predictive importance of haemodynamic data is greatest when the data are collected after therapy maximization: in this way the haemodynamic indicator is linked to two other indicators, namely, current therapy and exhausted response to therapy. This is also true for other functional parameters whose relevance lies not so much in an absolute value, but in a capacity to change following acute interventions and chronic therapy. When making decisions, parameters indicating organ damage such as elevated blood levels of creatinine, bilirubine, neurohormonal activation and hyponatremia acquire relevance in advanced heart failure that they do not have in mild to moderate failure. In the last few years, renal dysfunction has emerged as one of the most potent risk markers in heart failure, with a predictive value not lesser than the degree of left ventricular dysfunction. Similarly, pulmonary resistance is of considerable significance (though only in a restricted subset of patients) when it must be decided whether to use ventricular assistance or replacement therapies. A markedly reduced exercise capacity in optimized therapy is a parameter traditionally used in heart failure as an indicator of irreversible cardiovascular compromise and as an indication for heart transplant.

However, the subjective components of both the doctor and the patient in deciding to interrupt the exercise may make the exercise capacity sometimes uncertain. Other exercise parameters seem complementarily valuable, in particular the

VE/VCO2 slope, which appears more objective and physiologically comprehensive. It includes a measure of the effects of musculoskeletal dysfunction on the central nervous system and was proven to be an excellent prognostic marker. New validated information and more integrated approaches may offer, in the future, prognostic algorithms that are more robust for prognostication in heart failure. Genomics and proteomics may offer novel disease markers and risk (or protecting) factors. However, to date, no tests can overcome the clinical judgement in grading risk and guiding therapy in heart failure patients.

Treatment of heart failure

Introduction

Throughout the past 10–15 years, the therapeutic approach to heart failure has undergone considerable change. Current treatment not only concerns symptomatic improvement, but also increasingly focuses on preventing the transition of asymptomatic cardiac dysfunction to symptomatic heart failure, preventing worsening of symptoms/functional limitations of heart failure and reducing mortality. As this is likely to be a slow process, the effects of novel preventive therapies may, in contrast to the often more rapid effects of pure symptomatic treatment, only become apparent after time. Thus, short- and long-term objectives with individualized therapies should be identified. In addition to improvements in symptoms, well-being (quality of life) and survival, important treatment targets include cardiac remodelling, neuroendocrine activation, fluid retention, and renal dysfunction. Accordingly, because heart failure is a complex syndrome, the therapeutic approaches may need several strategies in combination to target different mechanisms. However, as the therapeutic approaches to heart failure are multiple, including general measures, pharmacological therapy, mechanical devices and surgical interventions, they will not always be applicable in each patient. Adverse effects and interaction between different forms of treatment may preclude their use in some. Moreover, rapid deterioration of the clinical condition can require modification of the therapeutic approach.

There are regional differences in the approach to heart failure treatment in Europe. These differences are attributable to variations in aetiology and in health re-

sources. Of more importance, perception and acceptance of the usefulness and need to prescribe therapies proven to be effective in large controlled trials by the different physicians taking care of heart failure patients are slow. Continuous education is clearly needed.

Aims of treatment in heart failure

The aims of heart failure management are those of the treatment of any disease in general and consist of several components.

Prevention of heart failure

The development of heart failure may be delayed or prevented by early management of conditions leading to heart failure, in particular in high risk patients with hypertension and/or coronary artery disease. The prevention of heart failure should always be a primary objective. Many potential causes of myocardial damage can be treated and the extent of myocardial damage reduced. Examples include management of risk factors for coronary heart disease, treatment of ischaemia, early triage of acute myocardial infarction, prevention of reinfarction, accurate identification, and aggressive treatment of hypertension and some causes of specific heart muscle disease, timely correction of valve disorders, and congenital heart disease.

Population-based studies clearly demonstrate that hypertension is a major risk factor for CHF and contributes a large proportion of heart failure patients, suggesting that early and aggressive blood pressure control is a promising strategy for preventing CHF. These epidemiologic studies also point to coronary heart disease as a major contributor to the development of CHF particularly in men.

In hypertension, angiotensin-converting enzyme inhibitors (ACE-inhibitors), angiotensin receptor blockers or a combination of diuretics/beta-blockers, reduces the incidence of heart failure death or hospital admissions for heart failure.

Management of CHF

In CHF that is caused by systolic cardiac dysfunction the therapeutic approach consists of general advice and other non-pharmacological measures, pharmacological therapy, mechanical devices, and surgery. The approach to the treatment of specific patient subgroups, i.e. the elderly or heart failure that is caused by predominant dias-

tolic dysfunction, is addressed in special sections of these guidelines. The treatment of AHF, pulmonary oedema, and cardiogenic shock has been presented in a separate document.

Non-pharmacological management

General advice and measures

Educating patients and family

Patients with CHF and their close relatives should receive general advice for life style modification.

Weight monitoring. Patients are advised to weigh themselves on a regular basis to monitor weight gain (preferably as part of a regular daily routine, for instance after morning toilet) and, in case of a sudden unexpected weight gain of 0.2 kg in 3 days, to alert a health care provider or adjust their diuretic dose accordingly (e.g. to increase the dose if a sustained increase is noted).

Dietary measures

Sodium. Controlling the amount of salt in the diet is a problem that is more relevant in advanced than in mild heart failure. Salt substitutes must be used with caution as they may contain potassium. In large quantities, in combination with an ACE-inhibitor, they may lead to hyperkalaemia.

Fluids. Instructions on fluid control should be given to patients with advanced heart failure, with or without hyponatraemia. However, the exact amount of fluid restriction remains unclear. In practice, a fluid restriction of 1.5–2 L/day is advised in advanced heart failure.

Alcohol.

Moderate alcohol intake (one beer or 1–2 glasses a wine/day) is permitted. Alcohol consumption must be prohibited in suspected cases of alcoholic cardiomyopathy.

Obesity Treatment of CHF should include weight reduction in obese patients. The patient is overweight if his/her body mass index (BMI) (i.e. the actual weight in kilograms divided by height in metres squared) lies between 25 and 30, and obese if it is 0.30.

Abnormal weight loss Clinical or sub-clinical malnutrition is present in <50% of patients with severe CHF. The wasting of total body fat and lean body mass that accompanies weight loss is called cardiac cachexia. Cardiac cachexia is an important predictor of reduced survival.

Consider the possibility of abnormal weight loss when:

- a body weight <90% of ideal body weight or
- a documented non-intentional weight loss of 5 kg or 7.5% of the previous normal non-oedematous weight in the previous 6 months and/or
- BMI (weight/height) < 22 kg/m^2.

The aim of treatment is to achieve an increase in non-oedematous body weight, preferably by increasing muscle mass through adequate physical exercise. Small, frequent meals are indicated when reduced food intake results from nausea, dyspnoea, or a feeling of bloatedness.

Smoking should always be discouraged. The use of smoking cessation aids should be actively encouraged and may include nicotine replacement therapies.

Travelling. High altitudes, very hot or humid places should be discouraged. In general, short air flights are preferable to long journeys by other means of transport. In patients with severe heart failure, long air flights can cause problems (e.g. dehydration, excessive limb oedema, and deep venous thrombosis) and patients should be cautioned. It is also worth discussing potential effects of changes in diet during journeys and actions in cases of acute gastro-enteritis. The use of diuretics and vasodilators may have to be adapted in case of excessive sodium and fluid loss in hot, humid climates.

Sexual activity. It is not possible to dictate guidelines about sexual activity counselling. Recommendations are given to reassure the not severely compromised, but frightened patient, to reassure the partner who is often even more frightened, and perhaps refer the couple for specialist counselling. If appropriate, advise the use of sublingual nitrates before sexual activity and discourage major emotional involvements. PDE5-inhibitors are not recommended in advanced heart failure. If used, it

should be avoided within 24–48 h of nitrate intake depending on agent. Patients in the NYHA class II are at intermediate risk and patients in class III–IV are at high risk of cardiac decompensation triggered by sexual activity. Little is know about the effects of treatments for heart failure on sexual function.

Advice on immunizations. There is no documented evidence of the effects of immunization in patients with heart failure. Pneumococcal and influenza immunization may reduce the incidence of respiratory infections that may worsen heart failure. Immunization for influenza is widely used.

Drug counseling. Self-management (when practical) of the dose of the diuretic, based on changes in symptoms and fluid balance, should be encouraged. Within prespecified and individualized limits, patients are able to adjust their diuretics. Desired effects and side effects of all drugs should be thoroughly explained. Increased patient involvement (concordance) in chronic disease should be the background for the counselling. With this in mind, the following information on drugs could be provided: improvement may be gradual and only complete after several weeks and with some drugs months of treatment; the need for gradual titration with ACE-inhibitors, angiotensin receptor blockers, and beta-blocking drugs to a desired dosage level, which will not directly improve the patient's symptoms; in case dehydration occurs (diarrhoea, profuse sweating in hot climates) to reduce the dose of diuretics; how to act if symptomatic hypotension occurs (reduction of the diuretic and, if necessary, temporary reduction of the dose of the ACE-inhibitor, angiotensin receptor blocker, or beta-blocker); that coughing might occur with the use of ACE-inhibitors as well as an alteration in taste; to avoid non-steroidal inflammatory agents (including coxibs) in combination with ACE-inhibitors (remark over the counter access); possible use of nitrates, in sublingual or spray form, as a transitory symptomatic treatment, administered at the onset of acute dyspnoea or as prevention in certain situations.

Drugs to avoid or beware. The following drugs should be used with caution when co-prescribed with any form of heart failure treatment or avoided:

- Non-steroidal anti-inflammatory drugs (NSAIDS) and coxibs
- Class I anti-arrhythmics drugs

- Calcium antagonists (verapamil, diltiazem, shortacting dihydropyridine derivatives
- Tricyclic anti-depressants
- Corticosteroids
- Lithium.

Rest, exercise, and exercise training

Rest. In AHF or destabilization of CHF physical rest or bed rest is necessary. Passive mobilization exercises are carried out to prevent untoward effects resulting from prolonged bed rest and to attenuate the risk of venous thrombosis. As the clinical condition of the patient improves, respiratory exercises and active mobilization can be carried out.

Exercise. In order to prevent muscle de-conditioning the patient, if in a stable condition, should be encouraged to and advised on how to carry out daily physical and leisure time activities that do not induce symptoms. Strenuous or isometric exercises and competitive and tiring sport should be discouraged. If the patient is employed, their work tasks must be assessed and advice given on whether they can be continued.

Exercise training programs are encouraged in stable patients in NYHA class II–III. In clinical practice, exercise intolerance in CHF has a multi-factorial aetiology. Changes in the periphery rather than left ventricular performance itself are important determinants of exercise capacity. Several small clinical and mechanistic studies and some randomized trials have shown that regular exercise can safely increase physical capacity by 15–25%, improve symptoms and perception of quality of life in patients with stable class II and III heart failure. No significant deleterious effects or significant deterioration in central haemodynamics have been reported with exercise training.

Exercise training can be performed by either interval or steady state exercise, applying intensities of 60–80% of the predetermined peak heart rate. Interval training methods may allow for more intense exercise stimuli on peripheral muscles than obtained during steady-state training, but without inducing greater cardiovascular stress. Titration of exercise training should be performed in the following order: duration, then frequency, and then intensity.

Pharmacological therapy

Angiotensin-converting enzyme inhibitors

ACE-inhibitors are recommended as first-line therapy in all patients, with or without symptoms, who have reduced LVEF expressed as a reduced LVEF, i.e. 40–45% to improve survival, symptoms, functional capacity, and reduction of hospitalizations. ACE-inhibitors should be given as the initial therapy in the absence of fluid retention. In patients with fluid retention ACE-inhibitors should be given together with diuretics. . ACE-inhibition should be initiated in patients with signs or symptoms of heart failure, even if transient, after the acute phase of myocardial infarction, even if the symptoms are transient to improve survival, reduce reinfarctions and hospitalizations for heart failure. ACE-inhibitors should be uptitrated if possible to the dosages shown to be effective in the large, controlled trials in heart failure, and not titrated based on symptomatic improvement alone.

ACE-inhibitors in asymptomatic left ventricular dysfunction. Asymptomatic patients with a documented left ventricular systolic dysfunction benefit from long-term ACE inhibitor therapy. ACE-inhibition markedly enhances survival in patients with signs or symptoms of heart failure after the acute phase of myocardial infarction, even if the symptoms are transient. In addition to these effects on mortality, ACE-inhibitors in general improve the functional status of patients with heart failure. In contrast, only small benefits in exercise capacity occur.

ACE-inhibitors should always be uptitrated to the target dose used in large controlled clinical trials, if tolerated, to reduce long-term morbidity and mortality. ACE-inhibitors should not be titrated based on symptomatic improvement. Important adverse effects associated with ACE inhibitors are cough, hypotension, renal insufficiency, hyperkalaemia, angioedema, and syncope. Although cough may often be due to heart failure or concomitant diseases (e.g. respiratory disease), dry cough is a side effect of ACE-inhibitors. Severe cough may lead to discontinuation of ACE-inhibitor therapy. Some patients may tolerate re-institution of the ACE-inhibitor after a drug-free period. The substitute for ACE-inhibitors when not tolerated should be an angiotensin receptor antagonist.

Changes in systolic and diastolic blood pressure and increases in serum creatinine are usually small in normotensive patients. Moderate renal insufficiency and a relatively low blood pressure (serum creatinine up to 250 mmol/L and systolic blood pressure as low as 90 mmHg) are not contraindications to ACE-inhibitor treatment.

The risk of hypotension and renal dysfunction increases in patients with severe heart failure, those treated with high doses of diuretics, elderly patients and patients with renal dysfunction or hyponatraemia. Changes in serum potassium are usually small (0.2 mmol/L). Whereas mild hyperkalaemia is not a contraindication to use ACE-inhibitors, serum potassium levels >5.5 mmol/L are. If potassium-sparing diuretics were prescribed to correct serum potassium levels, they should be discontinued during initiation of ACE inhibitor therapy. ACE-inhibitor treatment is contraindicated in the presence of bilateral renal artery stenosis and angioedema during previous ACE-inhibitor therapy.

The effect of ACE-inhibition in heart failure has been documented in target doses that are usually higher than those used in clinical practice. Furthermore, in the ATLAS trial the first secondary endpoint was death or all-cause hospitalization which was reduced in patients with a higher than a lower dose regimen. The dose of ACE-inhibitors should always be initiated at the lower dose level and titrated to the target dose.

Initiating ACE-inhibitor therapy

The dose of the chosen ACE-inhibitor should be titrated up to the maximum target dose used in clinical trials (Table 2.3).

Table 2.3

ACE-inhibitors and their dosage in heart failure treatment

ACEI	Dosage, route, duration	
	Initial	Target
Enalapril	2.5 mg OD or BID.	10-20 mg BID
Captopril	6.25 mg TID.	25-50 mg TID
Lisinopril	2.5 mg OD	20-40 mg OD
Ramipril	1.25-2.5 mg OD.	5 mg BID
Trandolapril	1 mg OD	4 mg OD
Fosinopril	5 mg x OD	40 mg OD

When initiating therapy, careful attention should be given to the locally approved prescribing information. Regular monitoring of renal function is recommended:

- before, 1–2 weeks after each dose increment and at 3–6-months interval,
- when the dose of an ACE-inhibitor is increased or other treatments, which may affect renal function, are added e.g. aldosterone antagonist or angiotensin receptor blocker,
- in patients with past or present renal dysfunction or electrolyte disturbances more frequent measurements should be made,
- during any hospitalization.

Care should be taken in patients with low systolic blood pressure or serum creatinine above 250 mmol/L. Patients with a systolic level below 100 mmHg should have therapy initiated under specialist medical care. Modest, orthostatic hypotension may occur. Low blood pressures (<90 mmHg) during ACE-inhibitor treatment are acceptable if the patient is asymptomatic.

Diuretics

Loop diuretics, thiazides, and metolazone. Diuretics are essential for symptomatic treatment when fluid overload is present and manifest as pulmonary congestion or peripheral oedema. The use of diuretics results in rapid improvement of dyspnoea and increased exercise tolerance. Loop diuretics, thiazides, and metolazone are all used at various stages in the treatment of heart failure. Patients with severe heart failure often require increasing doses of loop diuretics. This may be caused by worsening renal function or decreased gastrointestinal absorption of furosemide. In such cases, replacement of furosemide by torasemide can be a solution because the bio-availability of the latter loop diuretic is not reduced in patients with heart failure. Because of the better absorption of torasemide, a more stable diuretic treatment may be achieved with a reduction of re-admissions for heart failure.

Intravenous drug administration, and in particular continuous intravenous infusion of a loop diuretic, also often overcomes the diuretic resistance.

Worsening renal function and hyponatraemia may occur as a consequence of overuse of loop diuretics or diuretic combinations.

Potassium-sparing diuretics should only be prescribed if hypokalaemia persists despite ACE-inhibition, or in severe heart failure despite the combination ACE-inhibition and low-dose spironolactone. Most patients on diuretics for heart failure will also be treated with an ACE-inhibitor. Until recently, the combination of potassium sparing diuretics and ACE-inhibitors was regarded as potentially dangerous. At present, potassium-sparing diuretics, such as triamterene, amiloride, and relatively high dosages of spironolactone, should only be considered if there is persisting diuretic-induced hypokalaemia despite concomitant ACE-inhibitor therapy, or in severe heart failure despite concomitant ACE-inhibition plus low-dose spironolactone. Similar restrictions also pertain in case of intolerance of ACE-inhibition and replacement therapy with angiotensin receptor blockers. Oral potassium supplements are less effective in maintaining body potassium stores during diuretic treatment. In general, the use of all potassium-sparing diuretics should be monitored by repeated measurements of serum creatinine and potassium.

A practical approach is to measure serum creatinine and potassium every 5–7 days after initiation of treatment until the values are stable. Thereafter, measurements can be made every 3–6 months.

Beta-adrenoceptor antagonists. Beta-blocking agents are recommended for the treatment of all patients (in NYHA class II–IV) with stable, mild, moderate, and severe heart failure from ischaemic or non-ischaemic cardiomyopathies and reduced LVEF on standard treatment, including diuretics and ACE-inhibitors, unless there is a contraindication. Beta-blocking therapy reduces hospitalizations (all, cardiovascular and heart failure), improves the functional class and leads to less worsening of heart failure. This beneficial effect has been consistently observed in subgroups of different age, gender, functional class, LVEF, and ischaemic or non-ischaemic aetiology. In patients with left ventricular systolic dysfunction, with or without symptomatic heart failure, following an acute myocardial infarction long-term beta-blockade is recommended in addition to ACE-inhibition to reduce mortality. However, the improved

left ventricular systolic function does not constantly result in a better exercise capacity probably because of the negative chronotropic effects of beta-blockers.

A reduction in mortality and hospitalization has been demonstrated with several beta-blockers in CHF, although the size of the treatment effect can differ between agents. Accordingly, only bisoprolol, carvedilol, and metoprolol succinate can be recommended at present (Table 2.4). A further argument for a more consequent use of beta-blockers is the observation that they have an additive effect to ACE-inhibitors and the combination reduces cardiovascular mortality and hospitalizations for heart failure more than ACE-inhibitors alone.

Table 2.4

Flow-chart regarding treatment of heart failure with beta-blockers

Drugs	Initial dose, mg	Target dose, mg	Duration of titration
Bisoprolol	1.25 OD	10	Some months
Carvedilol	3.125 BID	50	
Metoprolol SR/ER	12.5 OD	200	
Nebivolol	1.25 OD	10	

Initiation of therapy. As beta-blocker action may be biphasic with long-term improvement, possibly preceded by initial worsening, beta-blockers should be initiated under careful control. The initial dose should be small and increased slowly and progressively to the target dose used in the large clinical trials. Up-titration should be adapted to individual responses. Therefore, it is evident that even a low dose of a beta-blocker is superior to a treatment without beta-blocker administration. The introduction of beta-blockers should, therefore, always be attempted even if the titration period has to be prolonged. Beta-blockers may reduce heart rate excessively, may temporarily induce myocardial depression and precipitate heart failure. In addition, beta-blockers may initiate or exacerbate asthma and induce peripheral vasoconstriction.

Aldosterone receptor antagonists. Aldosterone antagonists are recommended in addition to ACE-inhibitors, beta-blockers, and diuretics in moderate-to-advanced heart failure (NYHA II–IV) to improve survival and morbidity. Although spironolactone was developed as a diuretic agent at a higher dose level, it is now understood that aldosterone has an important role in the pathophysiology of heart failure. It pro-

motes vascular and myocardial fibrosis, potassium and magnesium depletion, sympathetic activation, parasympathetic inhibition, and baroreceptor dysfunction. ACE-inhibitors insufficiently suppress circulating aldosterone levels.

Angiotensin II receptor blockers. For patients with left ventricular systolic dysfunction: angiotensin II receptor blockers (ARBs) can be used as an alternative to ACE-inhibition in symptomatic patients intolerant to ACE-inhibitors to improve morbidity and mortality. . In acute myocardial infarction with signs of heart failure or left ventricular dysfunction ARBs and ACE inhibitors have similar or equivalent effects on mortality. ARBs can be considered in combination with ACE-inhibitors in patients who remain symptomatic to reduce mortality. In NYHA class III patients remaining symptomatic despite therapy with diuretics, ACE-inhibitors, and beta-blockers, there is no definite evidence as to whether the addition of an ARB or aldosterone antagonist will further reduce hospitalization for heart failure or mortality.

Cardiac glycosides are indicated in atrial fibrillation and any degree of symptomatic heart failure, whether or not left ventricular dysfunction is the cause. Cardiac glycosides slow the ventricular rate, which improves ventricular function and symptoms. A combination of digoxin and beta-blockade appears superior to either agent alone in patients with atrial fibrillation. Digoxin has no effect on mortality but may reduce hospitalizations and, particularly, worsening heart failure hospitalizations, in the patients with heart failure caused by left ventricular systolic dysfunction and sinus rhythm treated with ACE-inhibitors, beta-blockers, diuretics and, in severe heart failure, spironolactone. Furthermore, a small decrease in the risk of death from heart failure was offset by an increase in the risk of death from other causes. A significant reduction, however, was observed for hospitalizations for worsening heart failure as well as all-cause hospitalizations and total number of hospitalizations per patient.

Thus, the primary benefit and indication of digoxin in heart failure is the reduction of symptoms and improvement of the clinical status, and thereby to decrease the risk of hospitalization for heart failure without an impact on survival. Contraindications to the use of cardiac glycosides include bradycardia, second- and third-degree AV block, sick sinus syndrome, carotid sinus syndrome, Wolff–Parkinson–White

syndrome, hypertrophic obstructive cardiomyopathy, hypokalaemia, and hyperkalaemia, as this may increase malignant arrhythmias.

Digoxin. The usual daily dose of oral digoxin is 0.125–0.25 mg if serum creatinine is in the normal range (in the elderly 0.0625–0.125 mg, occasionally 0.25 mg). No loading dose is needed when treating chronic conditions. The treatment can also be initiated with 0.25 mg bid for 2 days. Renal function and plasma potassium should always be measured before starting treatment. In renal failure, the daily doses should be reduced accordingly.

As the digoxin clearance closely approximates to the creatinine clearance, the latter should be measured or calculated as provided in Table 3. Vasodilator agents in CHF. There is no specific role for direct-acting vasodilators in the treatment of CHF (Class of recommendation III, level of evidence A).

Hydralazine-isosorbide dinitrate. Vasodilator agents may be used as adjunctive therapy in the management of heart failure. In case of intolerance of ACE-inhibitors and ARBs, the combination hydralazine/nitrates can be tried. Relatively high doses of hydralazine (up to 300 mg) in combination with high-dose isosorbide dinitrate (up to 160 mg) without ACE-inhibition may have some beneficial effects on mortality, but not on hospitalization for heart failure. At these doses, the combination increased exercise performance more when compared with enalapril. In African-American patients the administration of 1–2 tablets tid of the fixed doses combination of isosorbide dinitrate (20 mg) and hydralazine (37.5 mg) reduced mortality and morbidity and improved quality of life.

Nitrates may be used as adjunctive therapy for angina or relief of dyspnea. Evidence that oral nitrates improve symptoms of heart failure chronically or during an acute exacerbation is lacking. Early development of haemodynamic tolerance (tachyphylaxis) to nitrates may occur with frequent dosing (every 4–6 h), but is less with intervals of 8–12 h245 or in conjunction with ACE-inhibitors or hydralazine.

Alpha-adrenergic blocking drugs

There is no evidence to support the use of alpha-adrenergic blocking drugs in heart failure.

Calcium antagonists

In heart failure caused by systolic dysfunction, calcium antagonists are not recommended for the treatment of heart failure. Diltiazem- and verapamil-type calcium antagonists in particular are not recommended in heart failure because of systolic dysfunction; they are contraindicated in addition to beta-blockade. Newer calcium antagonists (felodipine and amlodipine) in addition to baseline therapy, including ACE-inhibitors and diuretics, do not provide a better effect on survival when compared with placebo. As long-term safety data with felodipine and amlodipine indicate a neutral effect on survival, they may be considered as additional therapy for concomitant arterial hypertension or angina not controlled by nitrates and beta-blockers.

Nesiritide

Recently, nesiritide, a new class of vasodilator, has been developed for the treatment of decompensated heart failure. Nesiritide is a recombinant human brain or B-type natriuretic peptide that is identical to the endogenous hormone produced by the ventricle. Nesiritide has venous, arterial, and coronary vasodilatory properties that reduce preload and afterload, and increase cardiac output without direct inotropic effects. The drug has been shown to be efficacious in improving subjective dyspnoea score as well as inducing significant vasodilation when administered intravenous to patients with acute heart failure (AHF). Clinical experience with nesiritide is still limited. Nesiritide may cause hypotension and some patients are non-responders. Effects of nesiritide has not been demonstrated on clinical outcome.

Positive inotropic therapy

Repeated or prolonged treatment with oral inotropic agents increases mortality and is not recommended in CHF. Intravenous administration of inotropic agents is commonly used in patients with severe heart failure with signs of both pulmonary congestion and peripheral hypoperfusion. However, treatment-related complications may occur and their effect on prognosis is uncertain; depending on agent level of evidence and strength of recommendation varies.

Intravenous inotropic therapy is used to correct the haemodynamic disturbances of severe episodes of worsening heart failure. The agent most often used in this set-

ting is dobutamine. However, its use has been insufficiently documented in controlled trials and the effects of dobutamine on prognosis are not well characterized.

Problems related to use of dobutamine are tachyphylaxis, increase in heart rate, induction of malignant tachyarrhythmias, and/or myocardial ischaemia. Its mechanisms of action through beta-adrenergic receptor stimulation also makes it less effective in the patients on concomitant beta-blocker treatment. Phosphodiesterase inhibitors like milrinone or enoximone may be more effective in the patients on concomitant beta-blocker treatment and have a peripheral and coronary vasodilating activity which may have favorable effects (i.e. greater decline in pulmonary pressures, lower incidence of myocardial ischaemia). However, they also are associated with atrial and ventricular tachyarrhythmias and an increase in myocardial oxygen consumption. Excessive peripheral vasodilation may cause hypotension. In AHF intravenous milrinone does not reduce the number of hospitalizations or cardiovascular events, but leads to a higher incidence of treatment-related complications (e.g. atrial fibrillation and hypotension) when compared with placebo. The newer calcium sensitizer levosimendan is indicated in patients with symptomatic low cardiac output secondary to cardiac systolic dysfunction without severe hypotension compared with phosphodiesterase inhbitors, levosimendan has peculiar calcium sensitizing and peripheral vasodilator activities. It has been shown to have greater haemodynamic efficacy and to better affect outcome in a double-blind comparison trial with dobutamine.

Anti-thrombotic agents

In CHF associated with atrial fibrillation, a previous thromboembolic event or a mobile left ventricular thrombus, anti-coagulation is firmly indicated. There is little evidence to show that anti-thrombotic therapy modifies the risk of death or vascular events in patients with heart failure. Oral anti-coagulants should be preferred in patients with previous myocardial infarction and a left ventricular mural thrombus. After a prior myocardial infarction, either aspirin or oral anti-coagulants are recommended as secondary prophylaxis.

Aspirin should be avoided in patients with recurrent hospitalization with worsening heart failure. Patients with CHF are at high risk of thromboembolic events. Fac-

tors predisposing to thromboembolism are low cardiac output with relative stasis of blood in dilated cardiac chambers, poor contractility, regional wall motion abnormalities, and atrial fibrillation, if present. Ischaemic heart disease is the commonest cause of heart failure and coronary vascular occlusion is the commonest vascular event in this population. The annual risk of myocardial infarction in CHF is estimated from 2 to 5.4 %. The reported annual risk of stroke in controlled heart failure studies is between 1 and 2% vs. an annual risk of stroke ≥0.5% in the general population aged 50–75 years. However, the rates of thromboembolic complications in heart failure are sufficiently low to limit the evaluation of any potential beneficial effect of anti-coagulation/anti-thrombotic therapy in these patients.

Anti-arrhythmics drugs other than beta-blockers are generally not indicated in patients with CHF. In patients with atrial fibrillation (rarely flutter) or non-sustained or sustained ventricular tachycardia treatment with anti-arrhythmic agents may be indicated.

Class I anti-arrhythmics should be avoided as they may provoke fatal ventricular arrhythmias, have an adverse haemodynamic effect and reduce survival in heart failure (Class of recommendation III, level of evidence

Class II anti-arrhythmics. Beta-blockers reduce sudden death in heart failure. Beta-blockers may also be indicated alone or in combination with amiodarone or non-pharmacological therapy in the management of sustained or nonsustained ventricular tachy-arrhythmias.

Class III anti-arrhythmics. Amiodarone is effective against most supraventricular and ventricular arrhythmias. It may restore and maintain sinus rhythm in patients with heart failure and atrial fibrillation even in the presence of enlarged left atria, or improve the success of electrical cardioversion. Amiodarone is the preferred treatment in this condition. Amiodarone is the only anti-arrhythmic drug without clinically relevant negative inotropic effects.

Routine administration of amiodarone in patients with heart failure is not justified. The risk of organ toxicity, such as hyperand hypothyroidism, hepatitis, pulmonary fibrosis, and neuropathy, although shown to be relatively low in recent, large,

placebo-controlled trials, must be weighed against the potential benefits of amiodarone. Lower doses (100–200 mg/day) may reduce the risk.

Dofetilide, a new class III agent, was found to be safe in heart failure patients as no modification of total mortality was noted. However, the incidence of torsades de pointe was increased.

Oxygen therapy. Oxygen is used for the treatment of AHF, but in general has no application in CHF. Oxygen supplementation may lead to haemodynamic deterioration in patients with heart failure who are free of pulmonary oedema. In patients with cor pulmonale, long-term oxygen therapy has been shown to reduce mortality.

Surgery and devices. Revascularization procedures, mitral valve surgery, and ventricular restoration . If clinical symptoms of heart failure are present, surgically correctable pathologies must always be considered.

Revascularization. There are no data from multicentre trials to support the use of revascularization procedures for the relief of heart failure symptoms. Single centre, observational studies on heart failure of ischaemic origin, suggest that revascularization might lead to symptomatic improvement.

Until the results of randomized trials are reported, revascularization (surgical or percutaneous) is not recommended as routine management of patients with heart failure and coronary disease.

Mitral valve surgery. Mitral valve surgery in patients with severe left ventricular systolic dysfunction and severe mitral valve insufficiency due to ventricular dilatation may lead to symptomatic improvement in selected heart failure patients.

Left ventricular restoration. Anatomically, LV enlargement represents a key feature in patients with heart failure. Irrespective of the aetiology - dilative vs. ischaemic–the pathophysiology of LV enlargement results in increased wall tension, higher oxygen demand, and a tendency to ongoing dilatation. Surgical reduction of the size of the left ventricle has therefore been attempted by a variety of approached aiming at decreasing LV diameters and improving ejection fraction. Among these surgical techniques, myocardial resection can be distinguished from mitral valve repair techniques and external compression.

LV aneurysmectomy is indicated in patients with large, discrete left ventricular aneurysms who develop heart failure. In the past, many patients with ischaemic cardiomyopathy have profited from LV aneurysmectomy, and the technique of Vincent Dor with resection of akinetic zones and not only diskynetic area (aneurysm), has been applied worldwide with improvement, also regarding of LV function and heart failure symptoms. Cooley's endoaneurysmorraphy has been shown in uncontrolled clinical series to improve symptoms and ventricular function in patients with dilated ischaemic heart disease. A registry of 662 left ventricular restoration procedures performed in 13 centres worldwide has recently showed favourable results in terms of hospital and mid-term mortality. More recently, a scientifically more sophisticated approach of "ventricular restoration" has been introduced into clinical practice by Buckberg.

Cardiomyoplasty cannot be recommended for the treatment of heart failure or as a viable alternative to heart transplantation. Cardiomyoplasty has only been applied in a very limited number of patients and is still undergoing investigation.

Partial left ventriculectomy (Batista operation). Currently, partial ventriculectomy cannot be recommended for the treatment of heart failure or as an alternative to heart transplantion. Partial, lateral resection of the left ventricle plus or minus mitral valve surgery initially gained interest for treatment of end-stage heart failure patients. However, in recent studies a number of patients required ventricular assist devices or subsequent transplantation for failed surgery.

External ventricular restoration. Currently, external ventricular restoration cannot be recommended for the treatment of heart failure. Preliminary data suggest an improvement in LV dimensions and NYHA class with some devices. Two devices aiming at restricting enlargement of the failing heart and reducing wall stress have entered the clinical arena. Based on several successful animal experiments as well as a clinical study, the myosplint technique was used in an early clinical study. Bisection of the left ventricle and creation of a smaller LV chamber resulted in significantly reduced LV wall stress.

Pacemakers. Conventional right ventricular pacing has no established role in the treatment of heart failure except for conventional bradycardia indication. Resynchronization therapy using bi-ventricular pacing can be considered in patients with reduced ejection fraction and ventricular dyssynchrony (QRS with ≥120 ms), who remain symptomatic (NYHA III–IV) despite optimal medical therapy to improve symptoms, hospitalizations and mortality. Bi-ventricular pacing improves symptoms, exercise capacity, and reduces hospitalizations. A beneficial effect on the composite of long-term mortality or allcause hospitalization has recently been demonstrated, as well as a significant effect on mortality.

Conventional indication. Pacemakers have been used in patients with heart failure to treat bradycardia when conventional indications exist. Pacing only of the right ventricle in patients with systolic dysfunction will induce ventricular dyssynchrony and may increase symptoms. In retrospective studies, lower morbidity and prolonged survival by atrioventricular (AV) synchronous pacing have been reported in patients with chronic high degree AV block or sinus node disease and concomitant heart failure. However, prospective randomized controlled trials have not shown a reduction in the development of heart failure with AV synchronous pacing compared with only ventricular pacing.

Resynchronization therapy. Approximately 20% of patients with severe heart failure will have a broad QRS complex (≥120 ms) suggesting intra- or interventricular conduction disturbances. A large proportion of such patients will exhibit inter- or intraventricular dyssynchrony in ventricular contraction. Some patients with narrow QRS width will also have dyssynchrony. Many of these patients will have important mitral regurgitation. Bi-ventricular pacing stimulates both ventricles nearsimultaneously, improving the co-ordination of ventricular contraction, and reducing the severity of mitral regurgitation. Successful implantation of the device requires considerable skill and the procedure carries some hazard to the patient. Procedure-related mortality should be ≥1%.

Implantable cardioverter defibrillators. Implantation of an implantable cardioverter defibrillator (ICD) in combination with bi-ventricular pacing can be consi-

dered in patients who remain symptomatic with severe heart failure NYHA class III–IV with LVEF <35% and QRS duration >120 ms to improve morbidity or mortality. ICD therapy is recommended to improve survival in patients who have survived cardiac arrest or who have sustained ventricular tachycardia, which is either poorly tolerated or associated with reduced systolic left ventricular function. ICD implantation is reasonable in selected symptomatic patients with LVEF <30–35%, not within 40 days of a myocardial infarction, on optimal background therapy including ACE-inhibitor, ARB, beta-blocker, and an aldosterone antagonist, where appropriate, to reduce sudden death. In patients with documented sustained ventricular tachycardia or ventricular fibrillation, the ICD is highly effective in treating recurrences of these arrhythmias, either by anti-tachycardia pacing or cardioversion/defibrillation, thereby reducing morbidity and the need for rehospitalization. The ICD is effective in patients at high risk of sudden death, i.e. with a history of myocardial infarction and reduced systolic left ventricular function.

Radiofrequency catheter ablation. Catheter ablation may be indicated in patients with heart failure and reciprocating tachycardias. However, there are insufficient data on the role of ablation on sustained ventricular tachycardias in patients with heart failure or selected patients with AF. It may be an adjunctive therapy to ICDs in some patients. Heart replacement therapies: heart transplantation, ventricular assist devices, and artificial heart.

Heart transplantation. Heart transplantation is an accepted mode of treatment for end stage heart failure.

Ventricular assist devices and artificial heart. Current indications for ventricular assist devices and artificial heart include bridging to transplantation, acute severe myocarditis, and in some permanent haemodynamic support. At present, biventricular support is only possible with external blood pumps. This approach is of limited duration due to infectious complications and is therefore used for short-term bridging (months) until cardiac transplantation.

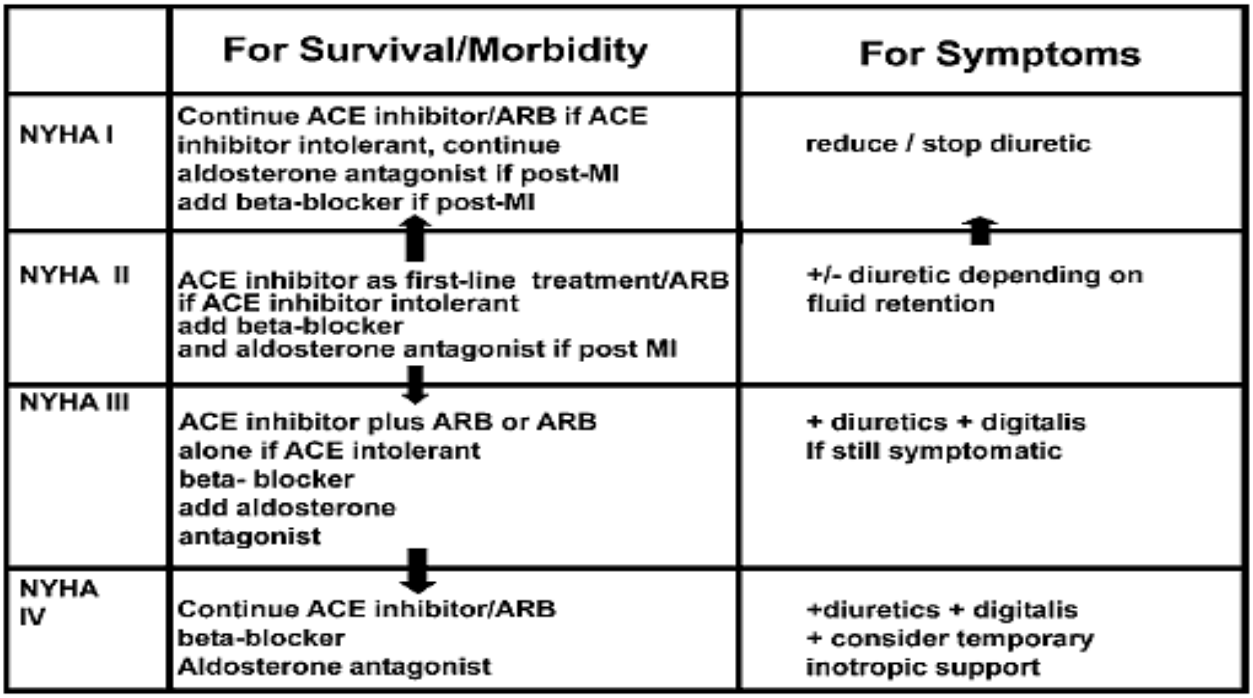
Indications for patients beyond those fulfilling the criteria for heart transplantation may be possible in the future, and first small clinical series with implantation of

such univentricular devices as destination therapy are being released. Complications are mainly of infectious or thromboembolic nature and would currently limit broader application of this technology as longterm implants.

Ultrafiltration has been used for patients with pulmonary for peripheral oedema and/or severe congestive heart failure refractory to diuretics. Ultrafiltration can resolve pulmonary oedema and overhydration in case of refractoriness to pharmacological therapies. In most patients with severe disease the relief is temporary.

Choice and timing of pharmacological therapy. The choice of pharmacological therapy in the various stages of heart failure that is caused by systolic dysfunction is displayed in Figure 2.10

Figure 2.10.
Pharmacological therapy of symptomatic CHF that is due to systolic left ventricular dysfunction.



Note: The algorithm should primarily be viewed as an example of how decisions on therapy can be made depending on the progression of heart failure severity. A patient in NYHA Class II can be followed with proposals of decision-making steps. Individual adjustments must be taken into consideration.

Pharmacological therapy of heart failure with PLVEF or diastolic dysfunction. The recommendations provided below are largely speculative in that limited data exist in patients with PLVEF or diastolic dysfunction; the reason for the sparsity of

data is that patients are excluded from nearly all large controlled trials in heart failure. Presently, we do not have clear evidence that patients with primary diastolic heart failure benefit from any specific drug regimen.

Because heart failure is most often due to coronary artery disease and/or hypertension, it is most logical to search for these conditions by appropriate tests and then to treat the patients according to general principles for managing these disorders.

1. ACE-inhibitors may improve relaxation and cardiac distensibility directly and may have long-term effects through their anti-hypertensive effects and regression of hypertrophy and fibrosis.
2. Diuretics may be necessary when episodes with fluid overload are present, but should be used cautiously so as not to lower preload excessively and thereby reduce stroke volume and cardiac output.
3. Beta-blockade could be instituted to lower heart rate and increase the diastolic period.
4. Verapamil-type calcium antagonists may be used for the same reason. Some studies with verapamil have shown a functional improvement in patients with hypertrophic cardiomyopathy.
5. A high dose of an ARB may reduce hospitalizations.

In general, the treatment of PLVEF/diastolic dysfunction remains difficult and often unsatisfactory. One of the main problems is that isolated diastolic dysfunction may be rare, the condition often occurring in conjunction with some degree of systolic dysfunction. As conditions under which PLVEF/diastolic dysfunction occur vary between patients and no controlled data from studies exist, straightforward therapeutic algorithms are not easy to provide for the individual.

Heart failure treatment in the elderly. Heart failure occurs predominantly among elderly patients with a median age of about 75 years in community studies. Ageing is frequently associated with comorbidity. Frequent concomitant diseases are hypertension, renal failure, obstructive lung disease, diabetes, stroke, arthritis, and anaemia. Such patients also receive multiple drugs, which includes the risk of unwanted inte-

ractions and may reduce compliance. In general, these patients have been excluded from randomized trials. In addition, elderly patients with heart failure have reduced cognitive function compared with healthy individuals. Accordingly, the approach to the elderly patient with heart failure must include the understanding of several associated conditions in the therapeutic decision. The therapeutic approach to systolic dysfunction in the elderly should be principally identical to that in younger heart failure patients on the choice of drug treatment. Altered pharmacokinetic and pharmacodynamic properties of cardiovascular drugs in the elderly necessitate that therapy should be applied more cautiously. Sometimes reduced dosages are necessary. Renal dysfunction is of special importance because some cardiovascular drugs that are used frequently, such as most ACE-inhibitors and digoxin, are excreted in active form in the urine.

Other complicating factors include diastolic dysfunction, blunting of baroreceptor function, and orthostatic dysregulation of blood pressure. A sedentary lifestyle with deconditioning and reduced skeletal mass, as well as changes in nutritional habits leading to reduced calorie/protein intake are further complicating factors in the management of elderly heart failure patients.

ACE-inhibitors and ARBs are effective and well tolerated in elderly patients in general. Because of a greater likelihood for hypotension and a delayed excretion rate of most ACE-inhibitors, low-dose titration is advisable. Initiation of ACE-inhibitor/ARBs therapy should be supervised, if possible, with monitoring of supine and standing blood pressure, renal function, and serum potassium levels. With such precautions, treatment can be introduced in the outpatient setting.

Diuretic therapy. In the elderly, thiazides are often ineffective because of reduced glomerular filtration rate. Reduced absorption rate and bio-availability of drugs or an increased excretion rate of thiazides or loop diuretics may lead to delayed onset, prolonged duration or sometimes reduced drug action. On the other hand, diuretics often cause orthostatic hypotension and/or further reduction in renal function. In elderly patients, hyperkalaemia is more frequently seen with a combination of aldosterone antagonsist and ACE-inhibitors or NSAIDs and coxibs.

Beta-blockers. Beta-blocking agents are surprisingly well tolerated in the elderly if patients with such contraindications as sinoatrial disease, AV-block and obstructive lung disease are excluded. Currently used beta-blockers in heart failure are eliminated by hepatic metabolism and do not require dosage reduction in patients with decreased renal function. Initiation of beta-blockade, however, should be carried out with low dosages and prolonged periods of titration. Beta-blockade should not be withheld because of increasing age alone.

Cardiac glycosides. Elderly patients may be more susceptible to adverse effects of digoxin. This glycoside is mainly eliminated in active form by the kidney and therefore half-lives increase up to two- to three-fold in patients aged over 70 years. Initially, low dosages are recommended in patients with elevated serum creatinine.

Vasodilator agents. Venodilating drugs, such as nitrates and the arterial dilator hydralazine and the combination of these drugs, should be administered carefully because of the risk of hypotension.

Arrhythmias. In the approach to arrhythmia, it is essential to recognize and correct precipitating factors, improve cardiac function and reduce neuroendocrine activation with beta-blockade, ACE-inhibition, and possibly, aldosterone receptor antagonists. Both supraventricular and ventricular arrhythmias occur frequently in heart failure. Sudden death accounts for ≤ 40–50% of all deaths, decreasing in relative proportion in advancing stages of heart failure. Various mechanisms, i.e. structural cardiac changes, myocardial ischaemia and neurohormonal activation, may play a role. Further precipitating factors for arrhythmias include electrolyte disturbances (hypokalaemia, hypomagnesaemia, and hyperkalaemia), drug interaction with cardiac pump function or electrical stability, such as some calcium antagonists and some anti-arrhythmic agents, digitalis toxicity, and inter-current diseases (e.g. hyperthyroidism and respiratory diseases).

Ventricular arrhythmias. In patients with ventricular arrhythmias, the use of anti-arrhythmic agents is only justified in patients with severe, symptomatic, ventricular tachycardias and where amiodarone should be the preferred agent. The routine use of anti-arrhythmic agents for asymptomatic premature ventricular complexes or nonsus-

tained ventricular tachycardias is not justified. ICD implantation is indicated in patients with heart failure and life threatening ventricular arrhythmias (i.e. ventricular fibrillation or sustained ventricular tachycardia) and in selected patients at high risk of sudden death.

Atrial fibrillation. For persistent (non-self-terminating) atrial fibrillation, electrical cardioversion could be considered, although its success rate may depend on the duration of atrial fibrillation and left atrial size. In patients with atrial fibrillation and heart failure and/or depressed left ventricular function, the use of antiarrhythmic therapy to maintain sinus rhythm should be restricted to amiodarone and, if available, to dofetilide. In asymptomatic patients beta-blockade, digitalis glycosides or the combination may be considered for control of ventricular rate. In symptomatic patients with systolic dysfunction digitalis glycosides are the first choice. In PLVEF verapamil can be considered. Anti-coagulation in persistent atrial fibrillation with warfarin should always be considered unless contraindicated. Management of acute atrial fibrillation is not dependent on previous heart failure or not. Treatment strategy is dependent on symptoms and haemodynamic stability. There is no evidence in patients with persistent atrial fibrillation and heart failure that restoring and maintaining sinus rhythm is superior to control of heart rate, particularly in severe heart failure. The development of atrial fibrillation in CHF is associated with worse prognosis. Amiodarone may convert atrial fibrillation to sinus rhythm and improve the success rate of electrical cardioversion. In permanent atrial fibrillation, (cardioversion not attempted or failed) rate control is most important. If digoxin or warfarin is used in combination with amiodarone, their dosages may need to be adapted.

Symptomatic systolic left ventricular dysfunction and concomitant angina or hypertension. Specific recommendations in addition to general treatment for heart failure because of systolic left ventricular dysfunction.

If angina is present

- optimize existing therapy, e.g. beta-blockade;
- add long-acting nitrates;
- add amlodipine or felodipine, if not successful;
- consider coronary revascularization

If hypertension is present

- optimize the dose of ACE-inhibitors, beta-blocking agents, and diuretics;
- add spironolactone or ARBs if not present already;
- try second generation dihydropyridine derivatives if not successful.

Care and follow-up

An organized system of specialist heart failure care improves symptoms and reduces hospitalizations and mortality of patients with heart failure.

Summary.

Many common clinical problems encountered in patients with heart failure remain unresolved. The role of anticoagulant therapy in patients with systolic dysfunction and sinus rhythm is unclear; neither the type of therapy needed nor the appropriate duration of treatment is known. There may be an important adverse interaction between aspirin and ACE inhibitors that will be clarified in upcoming trials. The optimal care for patients with heart failure and preserved systolic function (diastolic heart failure) awaits further research. The value of revascularization in patients with symptoms of heart failure but without angina will be explored in an important trial that is slated to begin soon. How will we identify patients with familial cardiomyopathy at an earlier stage? How do we identify patients with the greatest risk of sudden death? What is the best way to prevent sudden death in a cost-effective manner? Who will be best served by mechanical cardiac-support devices? Can we afford optimal care for the growing number of patients with heart failure? These questions and many others will undoubtedly be answered in the years to come. Perhaps our most intensive investigations, however, should be reserved for efforts that have been shown to prevent this cardiac plague - the control of hypertension and vascular risk factors. So, at the moment we had known that aggressive prevention and of cause treatment of heart failure can dramatically improve both short and long-term prognosis.

SQUEEZES

SQUEEZE FOR PRIMARY AND SECONDARY ARTERIAL HYPERTENSION

1. Why does blood pressure remain elevated in patients with essential hypertension without treatment
    a. Due to all mentioned causes
    b. Due to increase in peripheral arterial resistance
    c. due to inappropriate renal retention of salt and water
    d. due to increased endogenous pressure activity
    e. due to simpatico-adrenal system activation
2. What the main causes of secondary hypertension onset are?
    a. all mentioned causes
    b. Polycystic Kidneys
    c. Renovascular disease
    d. Aortic coarctation
    e. Cushing's syndrome
3. What factors that can contribute to the pathophysiology of hypertension are?
    a. all mentioned causes
    b. Systemic and local renin-angiotensin system
    c. Sympathetic nervous system
    d. Insulin resistance
    e. Obesity
5. What medicines are usually considered as causes of blood pressure elevation? Chose 1 incorrect answer.
    a. Litium derivates
    b. appetite suppressants,
    c. oral contraceptives,
    d. cyclosporine,
    e. tricyclic antidepressants.
6. Family history of high risk regarding onset of arterial hypertension should be included all follow except
    a. locomotorium disturbances
    b. premature coronary heart disease,
    c. stroke,
    d. gout,
    e. dyslipidemia.

7. Evaluation of patients with documented arterial hypertenson has not include one of follow objectives
    a. Genetic examination
    b. Assess lifestyle
    c. identify other CV risk factors or concomitant disorders
    d. Reveal identifiable causes of high BP.
    e. Assess the presence or absence of target organ damage and CVD
8. Prehypertension stage (JNC-7) should be verified after identification follow systolic BP ranges at rest
    a. 120–139 mm Hg
    b. 140-159 mm Hg
    c. 160-179 mm Hg
    d. <120 mm Hg
    e. >180 mm Hg

10. Stage 1 of arterial Hypertension (JNC-7) should be verified after identification follow systolic BP ranges at rest
    a. 140-159 mm Hg
    b. 120–139 mm Hg
    c. 160-179 mm Hg
    d. <120 mm Hg
    e. >180 mm Hg
9. Stage 2 of arterial hypertension (JNC-7) should be verified after identification follow systolic BP ranges at rest
    a. 160-179 mm Hg
    b. 140-159 mm Hg
    c. 120–139 mm Hg
    d. <120 mm Hg
    e. >180 mm Hg
10. High normal level of BP(ESC) should be verified after identification follow diastolic BP ranges at rest
    a. 85-89 mm Hg
    b. 90-99 mm Hg
    c. 100-109 mm Hg
    d. <84 mm Hg
    e. >105 mm Hg
11. Grade 3 of arterial hypertension (ESC) should be verified after identification follow diastolic BP ranges at rest
    a. >110 mm Hg
    b. 85-89 mm Hg

c. 90-99 mm Hg
d. 100-109 mm Hg
e. <84 mm Hg

12. ABPM is recommended for all occasions except
    a. documented white-coat hypertension
    b. Drug-resistant hypertension
    c. Hypotensive symptoms with medications
    d. Episodic hypertension
    e. Autonomic dysfunction
13. Goals of the arterial hypertension management should include all ones except
    a. Achieve normal systolic BP values in all patients
    b. Reduce CVD and renal morbidity and mortality.
    c. Treat to BP <140/90 mmHg in patients with diabetes
    d. Treat to BP <130/80 mmHg in patients with chronic kidney disease.
    e. Achieve systolic BP goal especially in persons ≥50 years of age.
14. Recommended first line drugs for initial treatment of arterial hypertension should include all ones except
    a. Alfa-adreno-blockers
    b. Calcium channel blockers
    c. ACE inhibitors
    d. Diuretics
    e. Angiotensin-2 receptor antagonists

SQUEEZE FOR ACUTE AND CHRONIC HEART FAILURE

1. Determine the most often cause of chronic heart failure in generally population:
    a. Arterial hypertension
    b. Cardiomyopathies
    c. Not rheumatic cardites
    d. Valvular heart diseases
    e. Myocardial infarctio
2. Determine beneficial effects of therapy on outcome of chronic heart failure:
    a. All answers are true
    b. reduction in the duration of intravenous vasoactive therapy
    c. the length of stay both in the intensive care unit and in the hospital,
    d. reduction in the readmission rate with an increase in the time to readmission

e. improve survisal

3. Determine the most important instrumental prognostic features of unfavorable outcome of chronic heart failure:

a. All answers are true
b. Premature contraction / tachyarrhythmia on ECG at rest
c. Low left ventricular ejection fraction
d. Increase heart rate
e. Cardiothoracic index > 0.65

4. Determine indications for Sodium nitroprusside in chronic heart failure:

a. All answers are true
b. severe heart failure
c. predominantly increased afterload
d. acute heart failure due to arterial hypertension crisis
e. cardiogenic shock

5. Determine vasodilators that are not recommended for treatment of chronic heart failure:

a. dihydropyridines calcium antagonists
b. nitrates
c. nesiritide
d. ACE inhibitors
e. Angotensin-receptor blockers

6. Determine indications for diuretics in patients with chronic heart failure:

a. presence of symptoms secondary to fluid retention
b. enhancing the excretion of water
c. increasing both right and left ventricular filling pressures
d. peripheral congestion and pulmonary oedema
e. all answeres are correct

7. Determine indications for inotropic agents in patients with chronic heart failure:

a. presence of peripheral hypoperfusion
b. presence of symptoms secondary to fluid retention
c. increasing both right and left ventricular filling pressures
d. peripheral congestion and pulmonary oedema
e. pulmonary oedema refractory to volume replacement diuretics and vasodilators at optimal doses

8. Determine indications for mechanical assist devices implantation in patients with chronic heart failure:

a. refractory to drug treatment heart failure
b. presence of peripheral hypoperfusion

c. presence of symptoms secondary to fluid retention
d. increasing both right and left ventricular filling pressures
e. peripheral congestion and pulmonary oedema

9. Determine indications for intra-aortic balloon counter-pulsation pump imple-mentstion in patients with acute heart failure

a. cardiogenic shock
b. severe acute left heart failure that do not respond rapidly to fluid administration, vasodilatation, and inotropic support
c. presence of peripheral hypoperfusion
d. presence of symptoms secondary to fluid retention
e. peripheral congestion and pulmonary oedema

10. Determine conditions that could be take into considerations for selection of candidates for device therapy in advance heart failure:

a. refractory to drug treatment of acute heart failure
b. acute valvular dysfunction
c. acute myocarditis
d. acute valvular dysfunction
e. all answeres are correct

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