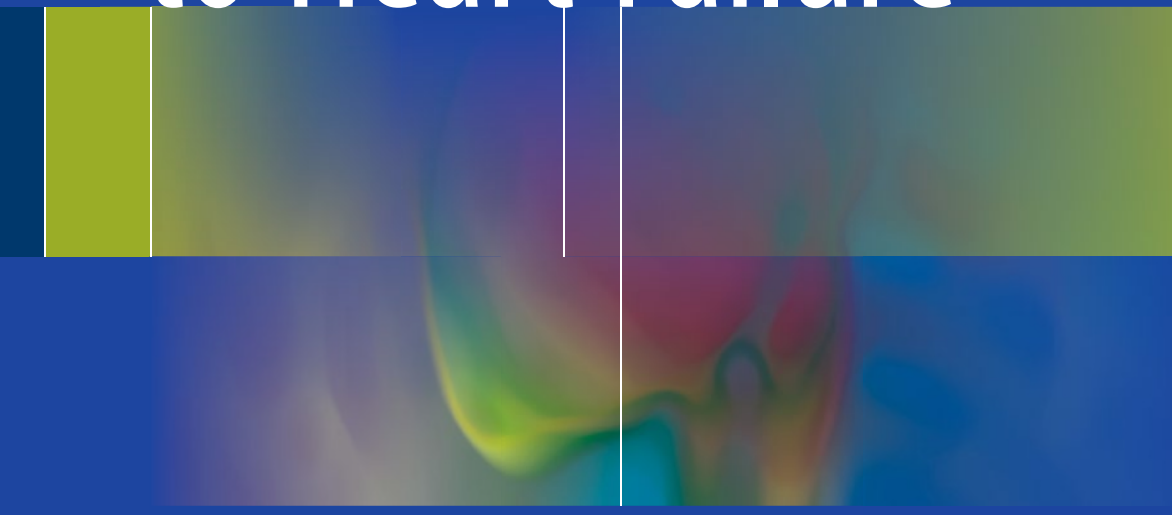
Current Approach to Heart Failure



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ISBN 978-3-319-45236-4 ISBN 978-3-319-45237-1 (eBook)
DOI 10.1007/978-3-319-45237-1

Library of Congress Control Number: 2016960763

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Why do we need another heart failure (HF) book in the context of currently abundant literature on the subject?

At present, HF prevalence is still high, while its morbidity and mortality is highly dependent on the HF type as well as the access to the advanced diagnostic and therapeutic techniques. The pathophysiology is better understood and there is a trend for a better characterization of HF subtypes. Currently, we know that HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF) are two different pathophysiological entities. It is accepted that HFpEF is the consequence of a cluster of comorbidities which promotes a proinflammatory systemic state; this in turn, results in endothelial inflammation in the coronary microcirculation leading to myocardial stiffness and increased collagen synthesis. Furthermore, the 2016 guidelines introduce a new term for patients with HF and a left ventricular ejection fraction that ranges from 40 to 49 %—HF with mid-range ejection fraction—an entity which needs to be better characterized by future research.

The importance of the right ventricle in HF had been studied extensively in the last years. That is why we dedicated two chapters which detail the state of the art regarding the physiology, anatomy, and the assessment of the right ventricle as well as the pathophysiology and treatment of right heart failure. Similarly, a separate is dedicated to the left atrium assessment in HF patients. We emphasize through one of the chapters that the complete HF diagnosis is made through multimodality imaging.

Regarding HF treatment, this book is offering separate chapters related to pharmacological treatment, cardiac resynchronization, mechanical circulatory support, gene therapy, heart transplant, and rehabilitation. Comorbidities such as iron deficiency and electrolytes and kidney imbalances are addressed in separate chapters. Special populations such as oncologic patients are given a great importance, since the awareness of HF in this category of patients is increasing.

We assist to rapidly developing strategies in the field of HF, which fundamentally help in better prognostication and management of HF patients. This is the reason for which we decided to gather the very new knowledge on the topic in this book.

Accordingly, this book is intended to offer in a quick manner the updated information necessary for the modern, correct management of HF patients.

The information is delivered by professionals with a rich experience on each topic. This way, this book is a combination of evidence-based medicine and personal experience, a link between guidelines and clinical practice. This book is a useful tool for professionals from all the fields related to HF: noninvasive cardiology, interventional cardiology, electrophysiology and cardiovascular imaging, cardiac surgery, internal medicine, nephrology, or anesthesiology. Most importantly, our book has a multidisciplinary approach since the frequently encountered clinical situation is represented by HF associated with comorbidities.

Bucharest, Romania Maria Dorobanţu

Contents

Part III Treatment of Heart Failure

Part IV Particular Forms of Heart Failure

Part I
New Concepts on Epidemiology and Mechanisms of Heart Failure

Chapter 1
Prevalence, Incidence and Lifetime Risk of Heart Failure

Tomasz Zdrojewski

Heart failure (HF) is a global public health problem affecting millions of people worldwide. The prevalence of HF in the United States is 5.7 million and there are 670,000 new cases annually [1]. The number of patients with HF in Europe has been estimated at 15 million. The overall medical and economic burden of HF-related care also results from the fact that the annual number of admissions due to HF is more than one million in both the United States and Europe. More older Americans and Europeans are hospitalized for HF than for any other medical condition. However, the socio-economic burden of HF is especially worrisome in the low- and middle-income regions of, e.g., Africa, South America and the Middle East, where the prevalence of HF is rising rapidly and the clinical characteristics, treatment patterns, and outcomes vary substantially. In countries where good quality statistical data are available, HF has been shown to be an important contributor to both the burden and the cost of national healthcare.

Clinical epidemiology of HF has not been clearly appreciated in the context of this burden for healthcare systems over the world. With population aging and improved survival after an acute myocardial infarction, the impact of HF is expected to increase substantially.

In 2013, experts of the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) [2] published results of their analyses to project the epidemiology and future costs of HF from 2012 to 2030. They assumed that HF prevalence will remain constant while rising costs and technological innovations will continue at the same rate. More than eight million people in the United States (1 in every 33 persons) will have HF by 2030. Between 2012 and 2030, real

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M. Dorobanţu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_1

total direct medical costs of HF are projected to increase from 21 to 53 billion US dollars. Total costs, including indirect costs for HF, have been estimated to increase from 31 billion US dollars in 2012 to 70 billion US dollars in 2030. These projections show how much aging of the population will increase the number of patients and the cost of care for HF.

Thus, strategies to prevent HF and improve the efficiency of care should become a major health policy priority. This cannot be achieved without adequate monitoring by epidemiological studies to evaluate the prevalence, incidence and control of, and mortality due to HF.

The incidence and prevalence of HF depends on the definition used. The most recent one is the definition by the European Society of Cardiology (ESC) experts proposed in 2016 [3]. In the new 2016 ESC guidelines, major changes introduced in comparison to the 2012 version include a new term of *HF with midrange ejection fraction (HFmrEF)* to describe patients with HF and left ventricular ejection fraction (LVEF) in the range of 40–49 %. Clear recommendations were also presented in regard to the diagnostic criteria for HF with reduced ejection fraction (HFrEF), HFmrEF, and HF with preserved ejection fraction (HFpEF). In addition, a new algorithm for the diagnosis of HF in the non-acute setting was offered, based on the evaluation of HF probability using clinical symptoms, echocardiographic findings and blood natriuretic peptide levels. What is very important from the health policy point of view, the new recommendations are aimed at prevention or delay of the development of overt HF, and prevention of death before the onset of symptoms.

Obviously, no epidemiologic studies are available yet to evaluate HF prevalence in accordance with these new guidelines. Epidemiological data on HF presented in this chapter refer to chronic heart failure.

Lifetime Risk

Although chronic HF has been described as an emerging cardiovascular disease epidemic, limited studies are available on the lifetime risk of developing CHF. The first European study to assess lifetime HF risk was the Rotterdam survey [4], a prospective population-based cohort study performed in participants aged ≥55 years. The baseline examination was conducted between July 1989 and 1993. Participants were visited at home for evaluation with a standardized questionnaire and subsequently examined at the research center. For estimation of incidence rates and lifetime risks, the study population included 7734 subjects who were free from HF at baseline. Echocardiographic assessment of systolic function was performed and fractional shortening was measured in 2267 subjects (mean age 65.7 years, 1028 men). Subjects were followed from baseline until the first diagnosis of HF, the date of last collection of information for determination of HF, or January 2000. The definition of HF was in accordance with the 2001 ESC criteria [5]. The lifetime HF risk in the Rotterdam Study was 33 % for men and 28.5 % for women at the age of 55 years.

Another important analysis regarding the lifetime risk was performed in the Framingham Heart Study cohort. Lloyd-Jones et al. [6] studied 3757 men and 4472 women free from HF at baseline who were followed up from 1971 to 1996. Thus, the analysis included the period of major changes in the treatment of myocardial infarction, including development of invasive cardiology strategies and introduction of angiotensin-converting enzyme inhibitors to the medical management of HF. At the age of 40 years, the lifetime risk for CHF was 21.0 % in men and 20.3 % in women. The remaining lifetime risk did not change with advancing index age because of rapidly increasing HF incidence rates.

In the second analysis, the authors only considered those patients who developed HF without an antecedent myocardial infarction. At the age of 40 years, the lifetime risk for HF was 11.4 % in men and 15.4 % in women. Thus, in the Framingham Heart Study cohort followed up for 25 years at the end of the twentieth century when established clinical criteria were used to define overt HF, the lifetime risk for HF was approximately one in five in both men and women. As evidenced by these data, HF is overwhelmingly a disease of the elderly and its increasing incidence with advancing age outpaces the increase in mortality from competing causes.

Prevalence of Heart Failure

The most important and widely cited epidemiological studies on the prevalence of HF were conducted in the Western European countries and the United States, mostly in Caucasians. Their results were well summarized in the respective chapters of the 2016 ESC guidelines [3] and the 2013 ACC/AHA guidelines [1].

Major studies to evaluate HF prevalence were undertaken already in the 1990s. However, their results must be interpreted cautiously due to changes in the diagnosis and treatment that have occurred since then. These were Rotterdam [4] and EPICA [7] studies in Europe and a survey performed in Olmsted County, Minnesota, in the United States [8]. The results of these studies, along with others conducted in the early twenty-first century, were appropriately summarized in a 2007 review by Mosterd and Hoes [9].

However, due to differences in the selection criteria and population characteristics, as well as different criteria to assess the presence of HF, comparisons between various investigations are quite difficult. For example, in the Framingham Heart Study [10], clinical criteria were used that did not include evidence of cardiac dysfunction on echocardiography, which is an important tool for the diagnosis of HF in clinical practice. Therefore, the true incidence and prevalence of HF might have been underestimated in the Framingham Heart Study cohort.

As mentioned above, the Rotterdam study [4] was a prospective population-based cohort study performed in participants aged ≥55 years. The prevalence of HF was reported according to the 2001 ESC criteria. In 40 % of all participants, left ventricular (LV) systolic function was assessed by echocardiography. Point prevalence of HF was determined in 1997, 1998 and 1999 and ranged between 6.4 and

7.0 %. The prevalence of HF was 8.0 % in men and 6.0 % in women. The mean age of the study population was 74 years. A sharp rise of HF prevalence estimates with age was noted. For example, point prevalence in 1998 increased from 0.9 % in subjects aged 55–64 years to 4.0 % in subjects aged 65–74 years, 9.7 % in those aged 75–84 years, and 17.4 % in those aged 85 years or older. Left ventricular systolic dysfunction was found to occur more frequently in men than in women (5.5 % vs 2.2 %). Only 35 % of patients survived 5 years after the initial diagnosis of HF.

Another study which is among the most widely cited in the literature was conducted in 1997–2000 in randomly selected residents of Olmsted County, Minnesota, aged 45 years or older. Of 4203 invited eligible residents, 2042 (47 %) participated in this cross-sectional survey by Redfield et al. [8] which was the first population-based study of the prevalence of both systolic and diastolic LV dysfunction based on Doppler echocardiography in relation to the symptoms and signs of HF. In addition to measuring standard transmitral flow parameters, pulmonary venous flow, mitral inflow at peak Valsalva manoeuver, and Doppler tissue imaging of mitral annular motion were used to characterize diastolic function. HF was diagnosed using the slightly modified Framingham criteria [11]. Subjects without the diagnosis of HF but with systolic or diastolic dysfunction were considered as having a preclinical disease.

The prevalence of validated HF was 2.2 % (with LVEF higher than 50 % in 44 % of participants), increasing from 0.7 % in persons aged 45 through 54 years to 8.4 % in those aged 75 years or older. Less than half of those with moderate or severe diastolic or systolic dysfunction had overt HF. The prevalence of LVEF $\leq$40 % was 2.0 %, and moderate or severe diastolic dysfunction was present in 7.3 % of participants. Systolic dysfunction was frequently present in individuals without recognized HF. In addition, diastolic dysfunction defined rigorously by comprehensive Doppler techniques was found to be common, often not accompanied by recognized HF, and associated with a marked increase in all-cause mortality.

The EPICA study [7], carried out in Portugal in 1998, was the first community-based, well-designed epidemiological survey aimed to estimate the prevalence of HF throughout the whole country. The study was characterized by a nation-wide coverage, large sample size, the coverage of institutionalized subjects, direct evaluation by a physician, and the use of two-dimensional (2D) echocardiography. This survey included subjects attending primary care centers selected by a two-stage sampling and stratification procedure. Heart failure cases were identified based on the 1995 ESC guidelines [12]. In order to ensure national coverage of the sample, health care centers were randomly selected from every district by sampling in proportion to the population of the district. The subjects over 25 years of age who attended primary care centers were recruited consecutively, stratified by age, and examined. Overall, 5434 eligible subjects were evaluated by 365 general practitioners. The overall prevalence of CHF in mainland Portugal was 4.4 %. The prevalence was similar in males (4.3 %) and females (4.4 %). Age-specific HF prevalence was 1.4 % in the age group 25–49 years, 2.9 % in the age group 50–59 years, 7.6 % in the age group 60–69 years, 12.7 % in the age group 70–79 years, and 16.2 % among those aged 80 years or older.

Of note, the authors of the EPICA and Rotterdam studies defined LV systolic dysfunction as fractional shortening below 28 % which was assumed to be equivalent to LVEF below 45 %. The Rotterdam, Olmsted and EPICA studies evaluated the prevalence of HF in large Caucasian populations in Europe and the United States. Due to methodological differences in regard to the definition of cases, sample selection, population coverage, and geographic location and/or ethnic background, the results of these three studies cannot be directly compared. However, their agreement regarding the prevalence of symptomatic LV systolic dysfunction is remarkable.

Ten years later, in 2008, Sanches et al. [13] reported on the prevalence of HF in the Spanish general population aged over 45 years. The PRICE study was a population-based survey with participation of 15 healthcare centers throughout Spain. In each area, a random sample of residents was invited and examined (n = 1772, 44 % of males, mean age 64 ± 12 years) by their primary care physicians who used the Framingham criteria. Subjects (n = 242) who fulfilled the criteria of CHF were referred for Doppler echocardiography by a cardiologist. The weighted prevalence of HF was 6.8 %, similar in men (6.5 %) and women (7 %). Age-specific prevalence was 1.3 % in those aged 45–54 years, 5.5 % in those aged 55–64 years, 8 % in those aged 65–74 years, and 16.1 % in those aged over 74 years.

Asymptomatic Left Ventricular Dysfunction

By definition, HF is characterized by its symptoms and signs, and thus asymptomatic left ventricular systolic dysfunction (ALVD) is not equivalent to HF. It is important to establish the role of ALVD in the natural history of HF and potential for any preventive measures because two contemporary trends, aging of industrialized populations and improvements in survival after a myocardial infarction, are expected to cause a substantial increase in the prevalence of HF. Thus, preventing HF by targeting its preclinical stages and treating known risk factors may be the best strategy to reduce the overall societal burden of this disorder. It is widely accepted that individuals may progress through an asymptomatic phase of LV systolic dysfunction before the development of overt HF.

Population-based echocardiographic studies have demonstrated that more than 50 % of participants with LV systolic dysfunction (LVEF <40 %) have no symptoms or signs of HF [8]. Asymptomatic LV systolic dysfunction is found more frequently in subjects with coronary artery disease, hypertension or an abnormal electrocardiogram (ECG).

The analysis by Wang et al. [14] in a cohort of 4257 Framingham Study participants (1860 men) who underwent routine 2D echocardiography was the first study to describe the natural history of ALVD. During up to 12 years of follow-up, the authors showed that subjects with ALVD were at a high risk of CHF and death even if only mild LVEF impairment (≤50 %) was present. After adjustment for cardiovascular disease risk factors, ALVD was associated with a hazard ratio for HF of 4.7 compared to individuals without ALVD. An increased risk of HF was observed even

in individuals with ALVD and no history of myocardial infarction or valvular disease, with an adjusted hazard ratio of 6.5.

Researchers form Vasteras, Sweden assessed the prevalence of LV systolic dysfunction in a population-based random sample of 75-year-old men and women (n = 433; response rate 70.1 %) using 2D echocardiographic examination [15]. The prevalence of LV systolic dysfunction was 6.8 % and was greater in men than in women (10.2 % vs 3.4 %). Clinical evidence of HF was absent in 46 % of the participants with LV systolic dysfunction. Thus, no clinical evidence of HF was present in nearly half of 75-year-old subjects with LV systolic dysfunction.

Heart Failure with Reduced Versus Preserved Ejection Fraction

The proportion of patients with HFpEF ranges from 22 to 73 % depending on the definition used, clinical settings (primary care, hospital clinic, hospitalized patients), age and sex distribution of the studied population, previous myocardial infarction, and the year of publication. Owan et al. [16] studied all consecutive patients hospitalized with decompensated HF at the Mayo Clinic Hospitals in Olmsted County, Minnesota, from 1987 through 2001 and showed that of 4596 patients discharged over the 15-year period, 53 % had reduced ejection fraction (EF) and 47 % had preserved EF. The authors reported that the proportion of patients with the diagnosis of HFpEF increased over time and that prevalence rates of hypertension, atrial fibrillation, and diabetes increased significantly among patients with HF. Survival improved over time in those with reduced EF but not in those with preserved EF.

In the 1998 EPICA Study [7], the prevalence of HF due to systolic dysfunction was 1.3 % and the prevalence of HF with normal systolic function was 1.7 %.

Recently, van Riet et al. [17] reported a cross-sectional selective screening study in patients ≥65 years of age presenting to primary care with shortness of breath on exertion during the previous 12 months. Thirty primary care practices (a representative sample of primary care practices) in the Zeist region (a total practice population of approximately 72,000 subjects) participated in this study between 2010 and 2012. All participants underwent history taking, physical examination, electrocardiography, and a blood test for N-terminal pro-B-type natriuretic peptide (NTproBNP), thus making possible to adopt the approach recommended in the 2012 and 2016 ESC guidelines [3, 18]. Only those with an abnormal electrocardiogram or NTproBNP level above the exclusion cut-off value for non-acute onset HF of >125 pg/mL underwent echocardiography. An expert panel established the presence or absence of HF according to the ESC guidelines criteria [18]. The mean age was 74.1 years, and 54.5 % of the 585 participants were female. Overall, 15.7 % participants had HF: 2.9 % had HFrEF (LVEF ≤45 %), 12.0 % had HFpEF, and 0.9 % had isolated right-sided HF.

The study by Boonman-de Winter et al. [19] published in 2012 was the first epidemiological analysis that provided precise prevalence estimates of previously

unrecognized HF and LV dysfunction in a representative sample of patients with type 2 diabetes. In total, 605 patients aged 60 years or over with type 2 diabetes participated in this cross-sectional study carried out in the south-west of the Netherlands (response rate 48.7 %). Between 2009 and 2010, the patients without known HF underwent a standardized diagnostic work-up including medical history, physical examination, ECG and echocardiography. An expert panel used the ESC criteria to diagnose HF. Of the 581 patients with no prior diagnosis of HF, 27.7 % were found to have previously unrecognized HF: 4.8 % with reduced EF, and 22.9 % with preserved EF. The prevalence of HF increased steeply with age.

The epidemic of HF seems to be changing, but precise prevalence estimates of HF and LV dysfunction in older adults based on adequate echocardiographic assessment are scarce. As systematic reviews that would include recent studies on the prevalence of HF and LV dysfunction were lacking, Riet et al. [20] performed a systematic electronic search of the Medline and Embase databases. The authors included studies that reported prevalence estimates based on echocardiographic examination in community-dwelling people ≥60 years of age. Overall, 28 papers from 25 different study populations were analyzed. The median prevalence of systolic and 'isolated' diastolic LV dysfunction was 5.5 % and 36.0 %, respectively. A peak in the prevalence of systolic dysfunction seemed to have occurred between 1995 and 2000. 'All type' HF had a median prevalence rate of 11.8 % (range 4.7–13.3 %), with fairly stable rates in the last decade and with HFpEF being more common than HFrEF (median prevalence 4.9 % and 3.3 %, respectively). The authors concluded that both LV dysfunction and HF remained common in the older population and that prevalence of diastolic dysfunction was on the rise and higher than that of systolic dysfunction. The prevalence of the latter seems to have decreased in the twenty-first century. These findings are in accordance with the results published by other groups between 2006 and 2012 [21–24].

Incidence of Heart Failure

Reliable estimates of HF incidence are available from the Rotterdam study performed in the 1990s. Cases of incident HF were obtained by continuously monitoring the Rotterdam study participants [4] for the occurrence of HF during the follow-up through automated linkage with files from general practitioners. In the Rotterdam study, the incidence of HF increased from 2.5/1000 person-years in the age group 55–64 years to 44/1000 person-years among those 85 years or older. Heart failure occurred more frequently in men than in women (an incidence of 15 and 12 per 1000 person-years, respectively).

Among Framingham Heart Study participants followed up for up to 12 years (mean 5 years), Wang et al. [14] noted that overt HF developed in overall 4 % of subjects, including 26 % of subjects with ALVD at baseline. The crude HF incidence rate among subjects with ALVD was 5.9 per 100 person-years, compared with 0.7 per 100 person-years in those without ALVD. The incidence of HF was

nearly identical in men and women with ALVD. Of ALVD subjects who developed HF, 29 % suffered an interim myocardial infarction (between baseline and occurrence of HF). Overall, 62 % of ALVD subjects who developed HF had a history of baseline or interim myocardial infarction.

As far as HF incidence trends are concerned, an important paper based on the population-based study in Olmsted County, Minnesota was published by Roger et al. [25] in 2004. The authors examined trends in HF incidence between 1979 and 2000 (4537 HF patients, 42 % of whom were diagnosed as outpatients). Findings of this study indicate that HF incidence did not change during that period. We clearly need similar studies with follow-up duration of least 15–20 years in the era of primary percutaneous coronary interventions. The reduction of post-myocardial infarction HF is consistent with the declining severity of myocardial infarction in the era of modern revascularization therapy. However, it seems that aging of the population in combination with improved prognosis will increase the number of patients and the burden of HF epidemic. It clearly follows that prevention of the occurrence of HF is needed to stem this epidemic.

One can also expect that the prevalence of HFpEF may be changing as a result of changes in population demographics and the prevalence and treatment of risk factors for HF. Changes in the prevalence of HFpEF may contribute to changes in the natural history of HF.

An important appraisal of the contemporary HF epidemic has been recently presented by Gerber et al. [26] based on the data from the Olmsted County study. The aim of this analysis was to evaluate trends in HF incidence and outcomes overall and by HFpEF or HFrEF between 2000 and 2010. Patients with incident HF (n = 2762, mean age 76.4 years, 43.1 % male) were followed up for all-cause and cause-specific hospitalizations and deaths. The age- and sex-adjusted HF incidence declined substantially from 316 per 100,000 in 2000 to 219 per 100,000 in 2010 (annual percentage change −4.6), equating to a rate reduction of 37.5 % over the decade. The decline in incidence was greater for HFrEF (−45.1 %) than for HFpEF (−27.9 %). Mortality was high (24.4 % for age 60 years and 54.4 % for age 80 years at 5 years of follow-up) and did not decline over time. The risk of cardiovascular death was lower for HFpEF than for HFrEF (multivariable-adjusted HR, 0.79; 95 % confidence interval [CI], 0.67–0.93) while the risk of non-cardiovascular death was similar (1.07; 95 % CI, 0.89–1.29). The authors concluded that the incidence of HF declined substantially in the period examined, particularly for HFrEF, but these findings contrasted with no apparent change in mortality. Importantly, they demonstrated that non-cardiovascular conditions had an increasing role in hospitalizations and remained the most frequent cause of death. Thus, disease-centric management approaches with holistic strategies are necessary to reduce the population burden of HF.

In the meta-analysis of Global Group in Chronic Heart Failure (MAGGIC) [27] published in 2012, the authors analyzed the survival of patients with HFpEF or HFrEF. Patients with HFpEF had lower mortality than those with HFrEF when adjusted for age, gender, etiology, and history of hypertension, diabetes, and atrial fibrillation (HR 0.68, 95 % CI 0.64–0.71). The risk of death did not increase notably

until LVEF fell below 40 %. However, absolute mortality is still high in patients with HFpEF, highlighting the need for better treatment strategies to improve outcomes.

Future Directions
The epidemiologic data highlight the need for better HF treatment strategies to improve outcomes. It is also important to establish the role of asymptomatic left ventricular dysfunction in the natural history of HF and potential for any preventive measures in this regard.

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Chapter 2
Evolving Concepts on the Basic Mechanisms of Heart Failure

Maria Dorobanţu and Sebastian Onciul

Abbreviations

ADH	Antidiuretic hormone
CFR	Coronary flow reserve
CKD	Chronic kidney disease
CRS	Cardio-renal syndrome
CSA	Central sleep apnea
ECM	Extracelullar matrix
GWA	Genome-wide association
HF	Heart failure
HfmEF	Heart failure with mid-range ejection fraction
HfpEF	Heart failure with preserved ejection fraction
HfrEF	Heart failure with reduced ejection fraction
LV	Left ventricle
MP	Metalloproteinase
NP	Natriuretic peptide
OSA	Obstructive sleep apnea
RAAS	Renin angiotensin aldosterone system
RHF	Right heart failure
RyR	Ryanodine receptors
SDB	Sleep disordered breathing
SNP	Single nucleotide polymorphisms
SR	Sarcoplasmic reticulum
TIMP	Tissue inhibitors of metalloproteinases

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M. Dorobanţu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_2

The Current Heart Failure Mechanisms in Heart Failure with Reduced Ejection Fraction (HFrEF)

Heart failure with reduced ejection fraction (HFrEF) syndrome is the result of the interaction of multiple mechanisms which act interdependently. According to Braunwald [1], currently there are seven major mechanisms which are evidence based and consequently are accepted by the majority of medical community. Each of these mechanisms has a different relative contribution in the pathophysiology of HF in each individual. The first description of some of these mechanisms dates decades ago, while other mechanisms are recently proposed and are currently under further investigation. These fundamental mechanisms constitute the backbone of HF pathophysiology but each of them expands into a cascade of subsequent physiological pathways which individually contribute to HF syndrome. The importance of complete characterization of each of these pathways resides in the concept that every link may be a therapeutic target. Blunting of as many as possible of these pathways may alleviate symptoms and prolong survival of HF patients.

The Pump Failure

Historically, one of the first explanations of the HF syndrome indicated the abnormal pump function of the heart and the consequent peripheral vasoconstriction to be the leading causes of HF syndrome. According to this paradigm the dysfunctional myocardium cannot provide the cardiac output necessary to body's requirements. This mechanism is very easy to understand in the context of HF with reduced ejection fraction (HFrEF), but it might also explain the pathophysiology of some cases of HF with preserved ejection fraction (HFpEF), in which the left ventricular (LV) cavity is small, and the myocardium is thicker and stiffer, and thus dysfunctional.

The Role of Neurohormones

The observation that the pharmacological blockade of certain neurohormonal systems in the body may slow the progression of HF indicated the neurohormonal hyperactivity to be one of the main causes of HF progression. Indeed the activation of several neurohormonal pathways is an important compensatory mechanism of HF, with benefic effects on the short term, but deleterious long-term effects, contributing to progression of HF. The neurohormonal activation in HF consists in the activation of sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS), as well as increased secretion of other endogenous substances such as antidiuretic hormone (ADH), endothelin, natriuretic peptides and inflammatory cytokines.

Sympathetic Overactivity

Sympathetic overactivity is one of the most important compensatory mechanisms in the setting of acute HF, but long term sympathetic activation has deleterious effects in chronic HF patients [2]. In the setting of acute HF, the activation of sympathetic nervous system results in increased heart rate and contractility and peripheral vasoconstriction; the renal effects of sympathetic overactivity consists in sodium retention as well as efferent arteriole vasoconstriction which maintains intraglomerular pressure, despite low renal blood flow. Chronic exposure to high levels of noradrenaline and adrenaline results in cardiac myocytes hypertrophy, apoptosis, as well as changes in the extracellular matrix architecture. Beta−1 receptor stimulation can induce myocardial necrosis, via a pathway involving cellular calcium overload and alterations in mithocondrial membrane permeability [3]. These cellular alterations are clinically expressed as pathologic myocardial remodeling occurring after myocardial injury [4].

Moreover chronic sympathetic hyperactivity results in decreased beta-adrenergic receptor density (down-regulation phenomenon) as well as their functional desensitization [5]. This way the adrenergic reserve of the heart is diminished in chronic HF patients [5].

Chronic HF is characterized by a selective reduction of beta-1 but not beta-2 receptor densities. The result is that the insufficient heart becomes dependent on beta-2 adrenergic receptors inotropic support. Current evidence indicates that beta-2 adrenergic receptors can mediate both beneficial and negative effects contributing to HF pathophysiology. It was shown that this population of receptors is characterized by a high genetic heterogeneity; the most important polymorphism results from substitution of amino acid 164 – threonine with isoleucine (threonine to isoleucine polymorphism). Transgenic mice expressing this polymorphism have depressed cardiac contractile function, both at rest and in response to agonist treatment, compared to mice with the wild-type receptor [6]. This polymorphism may be relevant in states in which cardiac contractility is highly dependent on the sympathetic drive, such as HF.

In addition to the contribution to inotropic response, the beta-2 adrenergic receptors promote anti-apoptotic effects, opposing the pro -apoptotic effects of stimulated beta−1 adrenergic receptors [7].

Renin Angiotensin Aldosterone System

The excess of angiotensin II stimulates renal sodium reabsorption, induces renal and systemic vasoconstriction, induces myocardiocyte hypertrophy as well as apoptosis, and promotes extracellular matrix fibrosis.

Angiotensin II directly stimulates aldosterone secretion by the adrenal gland. In addition, it has been demonstrated that aldosterone is also produced in human heart and its secretion is proportional to heart disease severity [8]. Aldosterone acts at myocardial level by promoting hypertrophy, fibrosis and arrhythmogenesis.

Tissue and plasma concentrations of angiotensin converting enzyme (ACE) and angiotensin II are partly determined by ACE gene. There are several polymorphisms

of this gene manifested in the form of insertion (I) or deletion (D), resulting three major genotypes (DD, ID and II). The homozygous DD genotype was associated with decreased survival in patients with idiopathic congestive HF [9, 10]. The negative effect on survival in HF patients with genotype DD seems to be related to progression of pump failure rather than sudden cardiac death [11].

Antidiuretic Hormone

The ADH secretion is stimulated by the activation of aortic arch and carotid sinus baroreceptors secondary to decreased cardiac output and blood pressure. There are three types of ADH receptors: V1a which are present in the arterial wall smooth muscle cell and are responsible for arterial vasoconstriction; V1b are primarily responsible for stimulating adrenocorticotropin release; V2 are responsible for the antidiuretic effect by increasing water reabsorption in the collecting tubules.

The antidiuretic effect combined with increased water intake (secondary to thirst stimulation by ADH) leads to decreased plasma sodium concentration. These effects are proportional to HF severity. As a consequence, the degree of hyponatremia is an important prognostic marker of survival in patients with HF. However treatments with V2 receptor antagonist tolvaptan didn't improve the long-term survival in HF patients (although the levels of plasma sodium were improved).

The Endothelins

The endothelins are powerful arterial vasoconstrictors but also contribute to vascular remodeling promoting smooth muscle cell proliferation. They also have a proinflammatory role, increasing vascular permeability, cytokine release and adhesion molecules expression in the vascular wall.

The cardiac effects of endothelins are different in healthy subjects and in HF patients. In healthy individuals, the main cardiac effect of endothelin is the positive inotropic effect mediated by increased myofibrillar Ca2+ responsiveness [12]. In opposition, in HF patients, the myocardial effects of endothelins consist in myocite hypertrophy, fibroblast proliferation, negative inotropism as well as proarrhythmogenic effects [13]. Endothelin plasma levels are elevated in HF patients and are related to the severity of the disease. It was demonstrated that the endothelin levels are directly proportional to the NYHA class and inversely proportional to LV ejection fraction [14].

Similarly, the plasma concentrations of endothelin were correlated with the pulmonary arterial pressure and vascular resistance [15]. However, it is unclear whether endothelin directly contributes to the development of pulmonary hypertension or is just a marker of its presence.

The Natriuretic Peptides and the Role of Neprilysin Inhibitors

The natriuretic peptides (NP) such as atrial, brain or C-type NP are hormones which have vasodilator, natriuretic and diuretic actions. They are secreted by ventricular/atrial myocardiocytes in response to hypervolemia and contribute to the homeostatic control of body water, sodium and potassium despite excessive activation of RAAS in HF patients.

The neutral endopeptidase neprilysin is an endogenous enzyme that breaks down the NP molecules, decreasing their bioavailability, and thus limiting their benefic effects in HF. In this context, the neprilysin inhibitors have emerged as potential therapeutic agents which can limit the NPs cleavage, increasing their bioavailability so that they can play their compensatory role in maintaining salt and water homeostasis in HF patients.

The combination of an angiotensin receptor blocker with a neprilysin inhibitor (Angiotensin receptor neprilysin inhibitor, ARNI) proved to be very efficacious in improving the outcomes of HF patients in addition to the benefits of the currently recommended optimal therapy [16].

The Kidney: Responsible for HF

Heart failure and kidney failure are strongly interdependent. They share similar risk factors such as hypertension, diabetes, age, anemia, oxidative stress and history of cardiac or kidney disease. Moreover there are several other risk factors specific to chronic kidney disease (CKD) which may explain the higher cardiovascular mortality in patients with CKD.

A recent meta-analysis showed that the parathormone is associated with an increased risk of cardiovascular events [17]. The parathormone activates cardiac fibroblasts and induces myocardial fibrosis, but also decreases cardiac contractility by altering intracellular calcium homeostasis [18]. Hypophosphatemia, another marker of advanced CKD is also an independent predictor of cardiovascular events [19]. Moreover protein-bound uremic toxins, such as indoxyl sulfate, *p*-cresyl sulfate, and homocysteine which are not effectively removed by dialysis contribute to the increased cardiovascular risk in CKD patients. Indoxyl sulfate, induces vascular inflammation, endothelial dysfunction, and vascular calcification [20]. High *p*-cresyl sulfate levels were associated with an increased risk of cardiovascular events among CKD patients [21]. Similarly the proatherogenic effects of homocysteine are well known.

There are currently accepted 5 subtypes of cardio-renal syndrome (CRS) [22]. This pathophysiological classification of the CRS takes into account whether the heart or the kidney dysfunction is acute or chronic but also which of the two systems is primarily affected and which is secondarily affected; in subtype 5 CRS both the heart and the kidney are simultaneously injured by a systemic condition (e.g. sepsis).

In subtype 2 CRS the chronic heart dysfunction leads to CKD. The mechanisms of this interdependence are complex and contribute to various extents to disease progression. The low cardiac output theory states that the renal hypoperfusion leads to increased renin secretion, RAAS activation, decreased sodium excretion and hypervolemia [23]. However the ESCAPE trial showed that there is no correlation between the renal function and the cardiac index [24].

The increased intraabdominal and central venous pressures hypothesis states that renal venous congestion is being more important than the low blood pressure in

generating chronic kidney injury in HF patients. In this regard, it was demonstrated that the degree of tricuspid regurgitation is directly proportional with the decrease of glomerular filtration in HF patients [25].

The oxidative stress is increased in both HF and CKD and contributes to cellular death both in kidney and in the myocardium. Other mechanisms proposed to contribute to the renal injury in chronic HF patients include the sympathetic and RAAS hyperactivity but also anemia and erythropoietin deficit [23].

Loss of Cardiac Myocytes

Apart of the systemic pathophysiological pathways activation, local myocardial mechanisms also contribute to the progression of HF. These consist in myocardial cell loss, cell dysfunction and alterations in the structure of the extracellular matrix (ECM).

Necrosis, apoptosis and autophagy are all mechanisms of myocardial cell loss. *Necrosis* usually develops secondary to an acute ischemic or inflamatory injury and results in disruption of cell membranes and eflux of cell components in the interstitial space with secondary activation of inflamatory processes. However, myocyte necrosis of a much smaller magnitude takes place continuously during the course of chronic HF, the best evidence being the low levels of troponin detected in the serum of patients with severe chronic HF.

Apoptosis is programmed cell death, which normally doesn't trigger any local or systemic inflammatory process. Apoptosis was identified in all stages of HF, having a role in the thinning of ventricular walls and worsening myocardial dysfunction. Human failing hearts in NYHA classes III–IV typically display apoptotic rates ranging between 0.12 and 0.70 % [26]. Even though, these percentages may seem small, the apoptosis is of significant importance to cardiac remodeling, taking into account that once lost the myocytes cannot be replaced by processes of regeneration. Thus, the subtle but regular cell loss can lead to severe cardiac remodeling in HF. Moreover, some authors consider apoptosis as the mechanism underlying the transition from chronic to acute HF [27].

Autophagy is a relatively newly developed concept in the field of cardiac myocyte biology. The process consists in degradation of proteins, mitochondria and other organelles after their fusion with lysosomal vesicles.

Autophagy is considered to be a protective mechanism against injuries such as ischemia, reperfusion or hemodynamic overload by restoring energy reserves [28]. In the context of acute myocardial infarction, autophagy is stimulated by tissue hypoxia and plays an important role in saving the peri-infarct area; on the other hand, in the context of reperfusion, it seems that the magnitude of autophagy increases excessively, thus becoming a maladaptive mechanism that contributes to the aggravation of reperfusion injury [29].

By whatever mechanism cell death occurs, the final stage is irreversible cardiac remodeling. New therapies based on pluripotent stem cell transplantation may change in the future this irreversibility axiom.

Dysfunctional Cardiac Myocytes due to Abnormal Cytoplasmic Ca^{2+} Homeostasis

Ca^{2+} is the signal for myocyte contraction, which means that an abrupt increase in cytoplasmic Ca^{2+} concentration is necessary for the excitation-contraction process. At the moment of depolarization, Ca^{2+} enters the myocite through transverse tubules localized in the membrane (L-type Ca^{2+} channels). This relatively low quantity of Ca^{2+}, triggers the release of a much larger quantity of Ca^{2+}, from the sarcoplasmic reticulum (SR), through ryanodine receptors 2 (RyR2). This way, the peak cytoplasmic Ca^{2+} concentration becomes ten times higher than the basal level [30], and this activates myocyte contraction. In the relaxation phase, the SR reuptakes Ca^{2+} through specific channels called sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2a (SERCA2a). (Fig. 2.1).

Ca^{2+} cycling refers to the release and reuptake of intracytoplasmic Ca^{2+} that drives muscle contraction and relaxation [30]. In some forms of HF, the abnormal Ca^{2+} cycling is responsible for myocardial dysfunction. These anomalies may imply dysfunctional RyR2 or SERCA2a. A leaky RyR2 means that Ca^{2+} is continuously

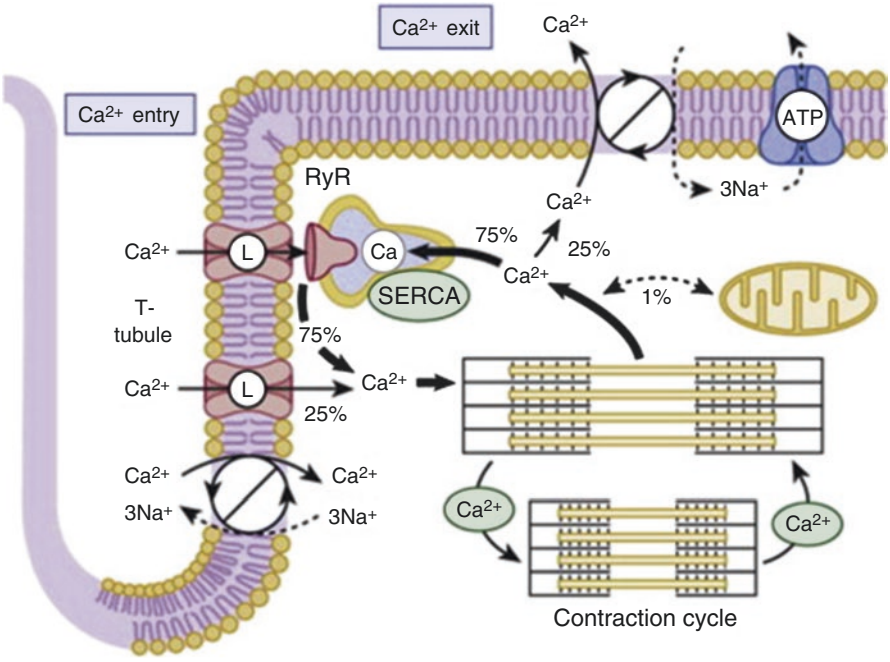

Fig. 2.1 Calcium fluxes in the myocardium. Calcium ions (Ca^{2+}) enter the cell through L-type Ca^{2+} channels (L), which triggers the release of $Ca^{2+}$from the sarcoplasmic reticulum to initiate contraction. Ca^{2+} leaves the myocyte via the Na^{+}/Ca^{2+}exchanger. *RyR* ryanodine receptors (Ca^{2+} release channels), *SERCA* sarcoplasmic reticular adenosine triphosphate (ATP)-driven pump, which returns Ca^{2+} to the sarcoplasmic reticulum (SR) (From Braunwald [1])

released from SR even in the relaxation phase, which lowers the SR Ca^{2+} stores, making them unavailable for signaling contraction, and thus impaired contractility. On the other hand, a dysfunctional SERCA2a, implies a decrease in Ca^{2+} reuptake into the SR, low SR Ca^{2+} stores which is translated in abnormal relaxation and diastolic dysfunction.

When RyR2 is hyperphosphorylated it becomes leaky and it was shown that in various models of HF the degree of RyR2 phosphorylation correlates with the degree of cardiac dysfunction [31]. Excessive catecholaminergic activation results in hyperphosphorylation of RyR2 [31, 32], rendering it leaky. This may be an explanation for the benefits of beta blockers in HF: β-blockers inhibit RyR2 phosphorylation and thereby reduce SR Ca^{2+} leak in HF patients, resulting in improved contractility [30].

New HF therapies oriented to restoration of both RyR2 and SERCA2a function are currently under development [30].

The Myocardial Extracellular Matrix

The changes in the composition of myocardial extracellular matrix (ECM) represent another mechanism that contributes to HF. It might be one of the causes of HF progression, despite adequate treatment of salt and water retention.

The largest myocardial cell population is represented by fibroblasts (almost two thirds of all myocardial cells). Fibroblasts maintain ECM homeostasis by regulating the synthesis of its constituent proteins. Generally, fibroblasts synthetize the ECM proteins, the enzymes responsible for their degradation (metalloproteinases, MP) but also the inhibitor factors of these enzymes (tissue inhibitors of metalloproteinases, TIMP). This way, fibroblasts control the ECM's collagen turn-over, but also they have a role in intercellular communication between myocytes, their electric activity, growth factors and cytokines secretion and apoptosis.

If myocardial injury occurs, fibroblasts transform into myofibroblasts, which are cells that are not usually found in healthy myocardium, and which have an increased capacity of ECM proteins synthesis. Myofibroblasts are attracted to the region of myocardial injury where they perform they role as reparatory cells; by secreting MPs and TIMPs they orchestrate the healing process.

The pattern of ECM's architectural disorganization is trigger-dependent. In chronic pressure overload, the fibroblasts synthetize excess collagen which accumulates in the interstitium resulting in stiffer myocardium and diastolic dysfunction. In opposition, chronic volume overload results in MPs overactivity, excess collagen degradation and thus the loss of structural support for myocardiocytes. This process facilitates the myocites slippage and elongation resulting in thin ventricular walls and a dilated cavity. Following myocardial infarction, the lost contractile cells are replaced by fibroblasts which secrete mostly type I collagen, a process often called replacement fibrosis.

Thus, according to the ECM model, fibroblasts and the ballance betwwen MPs and TIMPs regulate the collagen deposition in the myocardium which results in various degrees of myocardial dysfunction.

Genes Contribution

The "candidate gene" approach allowed in the past the identification of a number of important monogenic disorders involved in the cardiomyopathies that lead to HF, such as: hypertrophic cardiomyopathy, familial dilated cardiomyopathy or arrhythmic right-ventricular cardiomyopathy [1].

Currently, the genome-wide association (GWA) approach is the principal method used for the identification of the genetic mechanisms underlying HF. Genome-wide association studies are used to improve the accuracy of prognosis in HF; accordingly, they are able to identify genetic variants associated with an increased risk of death in this patient population. Similarly, GWA studies may identify the genetic variants associated with a response or a resistance to a specific treatment, and thus they open the path to personalized medicine. Another application of GWA studies consists in elucidating pathophysiology; these studies may identify single nucleotide polymorphisms (SNPs), associated with HF, but which are located in genes which are responsible for the encoding of proteins that are implicated in other processes in the body (for example in allergic response), and this may suggest that these specific processes might also contribute to the pathophysiology of HF.

In the field of HF, scientists have identified using GWA studies genetic variants associated with an increased risk of death in HF patients. Recently, it was discovered that a SNP on chromosome 5q22 is associated with 36 % increased risk of death in subjects with HF (rs9885413, P = 2.7 × 10–9) [33]. Furthermore this specific genetic variant was associated with a DNA methylation signature that in turn is associated with allergy and expression of the gene TSLP (Thymic stromal lymphoprotein) in blood [33]. The TSLP gene encodes a cytokine with important chemoattractant and T helper 2 mediated proinflammatory properties. The identification of this particular SNP suggests new targets for novel disease-modifying medications for HF patients.

Heart Failure with Preserved Ejection Fraction (HFpEF)

Heart failure with preserved ejection fraction characterizes the patients with signs and symptoms of HF with normal LV ejection fraction (≥50 %). Recently, those patients with an ejection fraction in the range of 40–49 % were categorized in a new entity – HF with mid-range ejection fraction (HFmEF) [34]. Relevant structural disease (LV hypertrophy or left atrial enlargement) or diastolic dysfunction is necessary for the diagnosis of HFpEF and HFmEF [34]. In opposition, HF with reduced ejection fraction (HFrEF) is characterized by a less than 40 % ejection fraction.

Since currently there is no single specific marker for a positive diagnostic, HFpEF is usually a difficult diagnostic. Diastolic dysfunction characterizes patients with HFpEF but normal LV filling pressures don't exclude HFpEF, especially in patients who have received diuretic treatment; these patients may have normal LV filling pressures at the time of examination (see Chap. 3). Similarly, a normal BNP

level does not exclude HFpEF since almost one third of patients with HFpEF can have normal BNP values.

HFpEF and HFrEF are currently regarded as two distinct entities. There are differences regarding myocardial structure, myocardiocyte function and intramyocardial signaling between the two syndromes.

New important insights into the HFpEF pathophysiology were obtained through recent endomyocardial biopsy studies. Alterations in both ECM and myocytes structure and function result in passive myocardial stiffness which is the hallmark of HFpEF.

Collagen-dependent stiffness results from increase in total collagen and collagen I expression and enhanced collagen crosslinking [35]. The trigger for this process seems to be inflammation: transforming growth factor beta promotes the transformation of fibroblasts into myofibroblasts and the decrease in matrix metalloproteinase 1 activity resulting in increased collagen deposition [36].

On the other hand, the anomalies of myocardiocyte function and structure are secondary to hypophosphorylation of the giant protein titin, a process called titin-dependent stiffness [37]. Titin is considered to be the third myofilament of the sarcomere [38]; it is characterized by high extensibility and functions as a molecular spring that when extended develops passive force. This way, titin is essential for myocyte diastolic recoil in early diastole and distensibility in late diastole [38]. In HFpEF, hypophosphorylation of titin results in higher myocyte resting tension which is reversed by increased protein kinase G (PKG) activity [39].

The modern molecular techniques were able to establish the relative contribution of collagen-dependent versus titin-dependent processes to the development of passive myocardial stiffness. Zile et al. demonstrated for the first time that both collagen-dependent and titin-dependent stiffness contribute to HFpEF [37]. In their endomyocardial study, patients with hypertension but without HFpEF had no change in myocardial passive stiffness, collagen, or titin phosphorylation, while patients with HFpEF had increased total, collagen-dependent and titin-dependent stiffness. This observation made the authors to suggest the idea that changes in collagen and titin constitute mechanisms associated with the transition from hypertension to HFpEF [37].

Currently, HFpEF is regarded to be the consequence of a cluster of multiple comorbidities [40]. According to this paradigm, the aggregation of comorbidities and risk factors such as age, hypertension, metabolic syndrome, diabetes mellitus, obesity, physical inactivity, renal dysfunction or chronic obstructive pulmonary disease promotes a proinflammatory systemic state and increased oxidative stress, resulting in coronary microvascular endothelial inflammation [40]. Similarly, this inflammatory state may result in increased collagen synthesis, leading to myocardial fibrosis. (Fig. 2.2).

Autopsy data support the role of coronary microvascular inflammation in the pathophysiology of HFpEF. Recently, it was shown that patients with HFpEF have lower microvascular density, and more myocardial fibrosis than controls, independent of the severity of epicardial coronary artery disease [41].

Similarly, non-invasive assessment of coronary flow reserve (CFR) indicates the microvascular dysfunction to be one of the mechanisms of HFpEF. Kato et al. used phase contrast cine-magnetic resonance imaging of the coronary sinus for the assessment of CFR in patients with HFpEF, those with hypertensive left ventricular

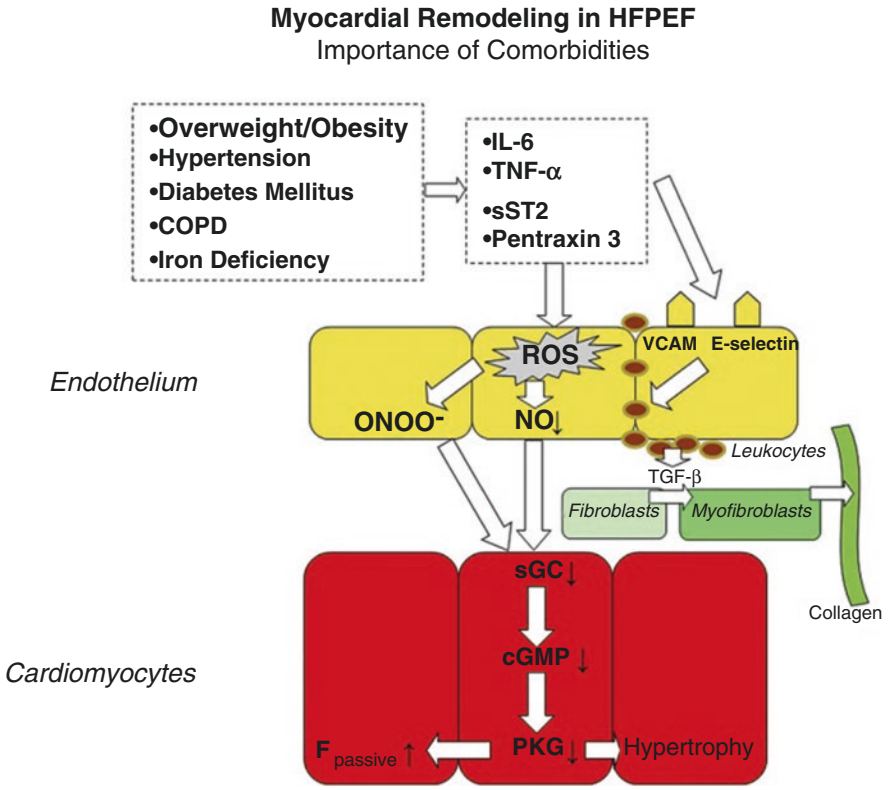

Fig. 2.2 Comorbidities drive myocardial dysfunction and remodeling in HFPEF. Comorbidities induce a systemic proinflammatory state with elevated plasma levels of interleukin (IL)-6, tumor necrosis factor (TNF)-α, soluble ST2 (sST2), and pentraxin 3. Coronary microvascular endothelial cells reactively produce reactive oxygen species (ROS), vascular cell adhesion molecule (VCAM), and E-selectin. Production of ROS leads to formation of peroxynitrite ($ONOO^-$) and reduced nitric oxide (NO) bioavailability, both of which lower soluble guanylate cyclase (sGC) activity in adjacent cardiomyocytes. Lower sGC activity decreases cyclic guanosine monophosphate concentration and protein kinase G (PKG) activity. Low PKG activity increases resting tension ($F_{passive}$) of cardiomyocytes because of hypophosphorylation of titin and removes the brake on prohypertrophic stimuli inducing cardiomyocyte hypertrophy. VCAM and E-selectin expression in endothelial cells favors migration into the subendothelium of monocytes. These monocytes release transforming growth factor β (TGF-β). The latter stimulates conversion of fibroblasts to myofibroblasts, which deposit collagen in the interstitial space. *COPD* chronic obstructive pulmonary disease, *HFPEF* heart failure with preserved ejection fraction (From Paulus and Tschöpe [40])

hypertrophy (LVH), and controls [42]. CFR was significantly lower in patients with HFpEF than in hypertensive LVH patients and controls. These results indicated that impairment of CFR might be a pathophysiological factor for HFpEF and might be related to HFpEF disease severity [42].

In the light of the above mentioned, the current paradigm for the mechanisms of HFpEF implies that this syndrome is a consequence of a cluster of multiple comorbidities, which promotes an inflammatory state, which in turn results in microvascu-

lar endothelial inflammation and loss of compliance of heart and vessels. This is in opposition with HF with reduced ejection fraction in which myocardial cell loss and fibrosis, promotes neurohormonal systemic activation. To best picture the different mechanisms between the two syndromes, it was recently stated that: *"There are two syndromes: one starting from the heart and leading to the periphery, HFrEF; and one starting from the periphery and leading to the heart, HFpEF."* [43] The mechanisms of recently introduced HFmEF are intermediary to HFpEF and HFrEF.

From Left to Right Heart Failure

The increased left ventricular filling pressures are transmitted backwards to the left atrium and subsequently to the pulmonary circulation, resulting in post-capillary pulmonary hypertension [44]. The coexistence of functional mitral regurgitation often augments the pulmonary hypertension. In this pathobiological chain, the left atrium plays a critical role through its distensibility [44].

Some of the patients with left heart failure may develop severe right ventricular failure and their clinical picture may be dominated by signs and symptoms of right heart failure. However, there is another group of patients in which the right ventricular morphology and function remains normal despite very severe left ventricular heart disease. Future research should identify the factors which predispose some patients to severe right heart failure and which are the protective mechanisms against this complication.

The diagnostic process is relatively not difficult in the context of heart failure with reduced ejection fraction, in which the finding of increased pulmonary artery pressure may be easily explained by the left heart pathology. However, pulmonary hypertension and right ventricular dysfunction may also develop secondary to HFpEF [44]. In this scenario, the first in life examination of patient usually reveals the constellation of a dilated, dysfunctional right ventricle combined with pulmonary hypertension and normal left ventricular systolic function. In these cases, a careful strategy combining non-invasive imaging as well as right heart catheterization should be implied in order to establish the causality between the left ventricular diastolic dysfunction and the right heart failure.

Irrespective of the etiopathogeny, pulmonary hypertension is an independent factor of worse prognosis in HF patients [44].

For a detailed discussion regarding the etiology and pathogenesis of right HF in the setting of left heart disease please see Chap. 23.

Noncardiac Comorbidities and HF

Noncardiac comorbidities have a great impact on HF pathophysiology, interfere with HF medication and contribute to the high mortality of this syndrome.

For a detailed discussion on cancer, iron deficiency and anemia, renal failure and electrolyte imbalances in HF patients, please see Chaps. 24, 25 and 26 respectively.

Here we will discuss only the role of sleep-disordered breathing (SDB), an entity which recently proved to have great implications in the pathophysiology of HF.

Sleep-Disordered Breathing in Heart Failure Patients

The incidence of SDB is much higher in HF patients than in general population. More than half of the HF patients (with either preserved or reduced EF) have SDB, either obstructive sleep apnea (OSA) or central sleep apnea (CSA), or both [45, 46].

While CSA may be regarded as a consequence of HF syndrome, the high prevalence of OSA in HF patients comparative with general population may at least partly be explained by the rostral fluid shift from the legs during the night. According to this theory, the volume of fluid accumulated in the legs during the day is displaced to the neck during the night leading to pharyngeal edema, favoring collapse of the pharynx and OSA. Similarly, the nocturnal shift of fluid to the lung interstitium may cause pulmonary irritant receptor stimulation, resulting in hyperventilation, driving the $PaCO_2$ below the apnea threshold and triggering CSA [47].

Obstructive sleep apnea contributes to the pathophysiology of HF through several ways: the negative intrathoracic pressure during the episodes of OSA increases right ventricle preload by augmenting the venous return; the episodes of apnea stimulates the sympathetic nervous activity with deleterious effects on myocardium but also on RAAS activation with subsequent salt and water retention; furthermore the apnea episodes are associated with oscillations in blood pressure and heart rate, which in combination with hypoxia enhance the endothelial dysfunction [48].

Although both CSA and OSA are associated with a worse prognosis for HF patients, CSA should be regarded as a marker of the severity of HF more than an aggravating factor. CSA may manifest as Cheyne–Stokes respiration. The randomized trials didn't show any benefit of CSA treatment in patients with HF. The SERVE-HF investigated the effects of adaptive servo-ventilation in patients who had heart failure with reduced ejection fraction and predominantly central sleep apnea. The primary end point in the time-to-event analysis was the first event of death from any cause, lifesaving cardiovascular intervention, or unplanned hospitalization for worsening heart failure. Adaptive servo-ventilation had no significant effect on the primary end point in patients who had heart failure with reduced ejection fraction and predominantly central sleep apnea, but all-cause and cardiovascular mortality were both increased with this therapy. The risk of cardiovascular death was increased by 34 %, which was sustained throughout the trial, and there was no beneficial effect on quality of life or symptoms of heart failure. These results were seen despite effective control of central sleep apnea during adaptive servo-ventilation therapy. One possible explanation is that central sleep apnea may be a compensatory mechanism in patients with heart failure [49].

The knowledge on HF pathophysiology is evolving and new insights into the mechanisms of this syndrome are continuously discovered. A better understanding of these mechanisms implies novel targets for therapies and a prolonged and a higher quality of life for HF patients. The myriad of systems and pathways implied in HF pathophysiology indicate that the neutralization of a single mechanism is

insufficient for the abolition of HF signs and symptoms and cardiac reverse remodeling. Instead, pharmacological blockage of multiple pathways may result in better control of symptoms, cardiac reverse remodeling and longer survival for HF patients.

Future Directions
The new paradigm of HFpEF pathophysiology which states that this syndrome is the consequence of systemic comorbidities should be verified. Furthermore, future research should identify the factors which predispose some patients with left HF to severe right heart failure and which are the protective mechanisms against this complication. In the field of translational medicine, future studies should evaluate the new HF therapies oriented to restoration of both RyR2 and SERCA2a function. Similarly, the role of genetic mechanisms in HF should be further explored in order to define new therapeutic targets. Pluripotent stem cell transplantation may represent the future of HF therapy.

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Part II
The Role of Cardiac Imaging in the Evaluation of Heart Failure

Chapter 3
Assessment of Left Ventricular Systolic and Diastolic Function by Echocardiography

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Introduction

The diagnosis of heart failure (HF) can be sometimes difficult because symptoms are not specific, especially in the elderly, and signs can be absent, particularly in patients receiving treatment, or may have a low reproducibility. Thus, the key to the diagnosis of HF is the evidence of an underlying cardiac cause. Cardiovascular imaging has a central role in the diagnosis and identification of the HF etiology.

Echocardiography is a diagnostic test that accurately and noninvasively provides information about structural and functional abnormalities and can assess the underlying cause so that an optimal management strategy can be implemented. Due to its accuracy, availability, low cost and safety profile, echocardiography is the imaging method of choice in the evaluation of patients with HF [1].

Transthoracic echocardiography (TTE) is the imaging method that usually underlines the first diagnosis of HF in urgent, elective, or screening settings [2]. TTE can provide a wealth of information about left and right ventricular size, geometry and function, left atrium size, valve function, pulmonary pressures, and the pericardium.

The left ventricular (LV) ejection fraction (EF) is useful to differentiate HF with reduced ejection fraction (HFrEF, when EF < 40 %) from HF with preserved EF (HFpEF, EF ≥ 50 %), and HF with mid-range EF (HFmrEF, EF between 40 and 50 %) [3]. Abnormalities in diastolic function are very common in patients with heart failure and either reduced or preserved LVEF and may have prognostic implications. Around half of all patients with HF have a normal LV EF [4, 5] and the frequency of this syndrome continues to increase as the prevalence of risk factors involved (e.g. older age, female sex, hypertension) is growing.

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M. Dorobanţu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_3

Assessment of Left Ventricular Systolic Function

The most common indication for echocardiography is the evaluation of LV function. Echocardiography offers several methods for assessment of systolic function, most of them being indirect estimates of LV systolic performance. Thus, echocardiography may evaluate the percentage change in LV dimension (e.g. LV fractional shortening, LVFS; or LV ejection fraction, LVEF), parameters of LV myocardial deformation (e.g. LV strain and strain rate), the rate of change in intracavitary pressure (i.e. LV dp/dt), or parameters related to the LV output (e.g. stroke volume, cardiac output).

Left Ventricular Fractional Shortening

Fractional shortening (FS) is a percentage change in LV dimensions that is usually obtained by 2D-guided M-mode imaging. It is calculated as the difference between LV end-diastolic and end-systolic diameters divided by LV end-diastolic diameter:

FS (%) = (LVEDD−LVESD)/LVEDD × 100.

Although easy to measure and widely used, this method has several limitations: it is load dependent, it does not evaluate LV longitudinal function, it may not be representative for the whole ventricle, particularly in the presence of regional wall motion abnormalities (e.g. in patients with coronary artery disease or conduction abnormalities). This parameter is now rarely used for diagnosis or clinical decision making.

Left Ventricular Ejection Fraction

2D Echocardiography

The LVEF is the most commonly used method for assessing LV systolic function [6]. It has proved useful in diagnosis and risk stratification in a variety of cardiovascular diseases and is the basis for recommendations of several important therapies, allocated to patients based on their LVEF [3].

It represents the percentage of LV end-diastolic volume ejected in the following systole. It is therefore calculated as stroke volume divided by LV end-diastolic volume: LVEF = (LVEDV − LVESV)/LVEDV × 100.

Left ventricular volumes may be estimated from 2D echocardiography in different moments of the cardiac cycle. End-diastole is defined as the first frame after mitral valve closure or the frame in which LV volume is the largest [6]. End-systole is defined as the frame after aortic valve closure or the frame in which the LV volume is the smallest. Currently, the recommended 2D method to assess LV EF is the biplane method of

disks (modified Simpson's rule). This technique requires two orthogonal apical views. Reliable visualization of the LV endocardial border is essential for reliable LV volume measurements. When the acoustic window is suboptimal, the use of a trans-pulmonary contrast agent to better delineate the endocardial border is recommended [6]. Also, harmonic imaging may improve the definition of the endocardial border.

The normal values for LVFS and LVEF are included in recommendations documents and may be slightly different between TTE and cardiac magnetic resonance (CMR) imaging [6].

Although LVEF carries important prognostic information and is the basis for many therapeutic decisions, it is not an index of contractility, and it simply reflects the volume changes during the cardiac cycle. Thus, it depends on volumes, preload, afterload, heart rate, and valvular function and it does not describe intrinsic myocardial function [3].

For example, LVEF may be preserved in patients with significant mitral regurgitation, despite a reduced forward stroke volume. Moreover, the stroke volume may be normal in patients with HFrEF because of LV dilation, whereas it may be reduced in patients with HFpEF and severe concentric LV hypertrophy. Therefore, LVEF must always be interpreted in clinical context.

Another limitation of LVEF as a measure of LV systolic function is its late impairment in conditions affecting LV function. Thus, LVEF decreases only late in the course of many diseases being unable to detect early LV dysfunction and to trigger initiation of proper treatment. Thus, it has to be combined with more sensitive measures of LV dysfunction.

From a technical standpoint, the accuracy of LVEF estimation by 2DE is affected by image quality, endocardial border definition, ventricular geometry, and representative orthogonal imaging planes.

2D echocardiography is less accurate compared with the gold imaging standard for quantification of LV volumes and LVEF, cardiac magnetic resonance (CMR) [7]. The reasons for the underestimation of LV volumes and EF by echocardiography involve reliance on geometric assumptions and commonly encountered foreshortening of the LV. This underestimation may be overcome using three-dimensional echocardiography (3DE) [8].

3D Echocardiography

3DE may provide measurements of LV volumes and ejection fraction independent of geometric assumptions about LV shape [9–11]. Experience indicates that LV volume measurements are more reliable and accurate with real-time 3DE than with 2DE and also avoid LV foreshortening and geometric assumptions about LV shape [8, 12]. Comparisons of 3DE LV volume determinations with 2DE and CMR imaging measurements showed that LV volume was significantly underestimated by 2DE, and much less by 3DE [12]. Mor-Avi et al. showed in their study that the accuracy of 3DE in volumetric assessments is similar to that of the gold standard CMR [13].

Also, 3DE has proved accurate in assessing LV volumes in remodeled ventricles after myocardial infarction and in evaluating the global LV dyssynchrony [14]. The LV cavity shape allows the extraction of quantitative information in patients with LV dysfunction (e.g. the 3D sphericity index) [9, 15].

Data Acquisition

There are two different methods for data acquisition using 3DE imaging: real-time and multiple-beat. Real-time refers to the acquisition of multiple pyramidal data sets per second in a single heartbeat. This method is limited by poor temporal and spatial resolution although it overcomes the limitations imposed by rhythm disturbances or respiratory motion. Multiple-beat 3DE refers to multiple acquisitions of narrow volumes of data over several heart beats that are subsequently stitched together to form a single volumetric data set. Therefore, this method provides images of higher temporal resolution, although imaging artifacts due to respiratory motion or irregular cardiac rhythms may limit it [9]. In atrial fibrillation, however, the single-beat acquisition is superior because the absence of stitching artifacts is more important than the image quality.

In clinical practice, to quantify LV volumes, LVEF, and LV shape in patients with heart failure, a gated 3DE full volume data set from the apical window must be acquired. It is best to use a wide-angle acquisition in the apical window so as to include the entire ventricle. The acquisition is obtained during breath hold to minimize the risk of artifacts. In multi-beat acquisitions, stitching artifacts can easily be detected in the transversal plane. The transducer frequency and overall gain should be adjusted accordingly to improve image quality. If the acoustic window is limited, then acquisition may be combined with the infusion of contrast to improve delineation of the endocardial border [9].

Images may be displayed with either orthogonal long-axis views or multiple short-axis views. The examiner may obtain multiple slices from the same volumetric data set and different orientations. An advantage of a 3D data set over 2D is the ability to avoid foreshortening [16, 17].

Analysis

Image analysis may be performed offline, using a dedicated 3D software, or online, with a software intrinsic to the ultrasound machine. Following manual identification of the mitral annulus and LV apex, the program automatically identifies the endocardial surface using a deformable shell model [9]. For the calculation of LV volumes, the LV trabeculae and papillary muscles should be included within the LV cavity. The end-diastolic LV volume will be automatically computed directly from voxel counts. After that, end-systole will be selected by identifying the frame in

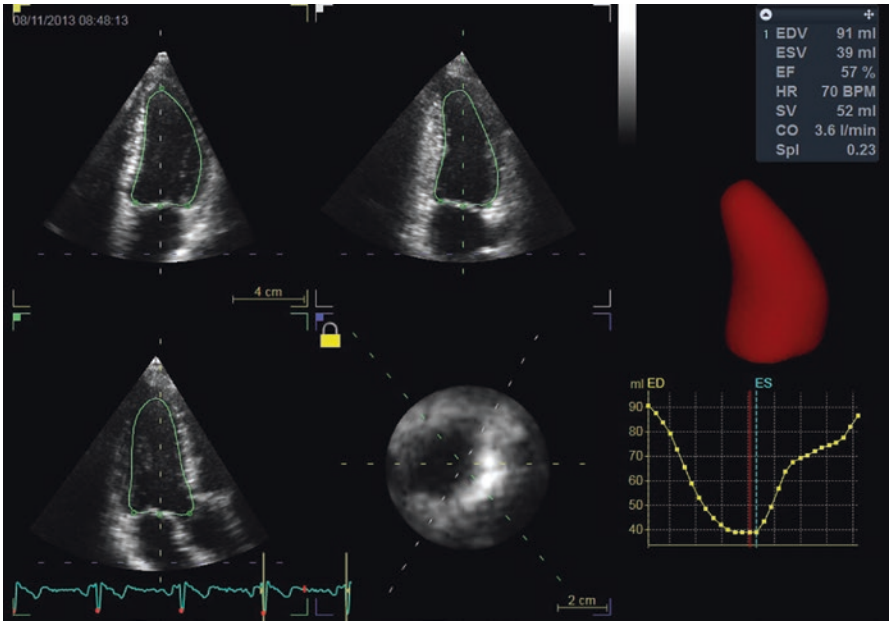


Fig. 3.1 The assessment of LVEF by 3D echocardiography

which the LV volume is smallest. Endocardial border detection, including initialization, will then be repeated on this frame to obtain end-systolic volume. The 3DE LV EF will be calculated from these LV volumes (Fig. 3.1).

Also, the LV volumes can be segmented, which allows for regional LV function assessment. Regional LV volumes are divided into 17 segments, and the relative contribution of each volume segment to the global LV systolic function can be established. Time-volume curves can be generated to evaluate each LV volume segment changes over time and also the presence of dyssynchrony. This may be of particular interest in guiding optimal LV lead placement for cardiac resynchronization therapy (CRT). The accuracy of LVEF measurements may guide a more appropriate selection of patients who are suitable for CRT.

The real-time 3D imaging of the LV may also be used during stress echocardiography. Preliminary clinical studies have confirmed the feasibility of this technique and reported sensitivity and specificity comparable to 2D stress imaging. An advantage of real-time 3D stress echo would be the reduced acquisition time [18, 19].

Stroke Volume and Cardiac Output

Other approaches commonly used to assess LV systolic function are stroke volume (SV) and cardiac output (CO) estimates.

Stroke volume can be determined through volumetric or Doppler methods.

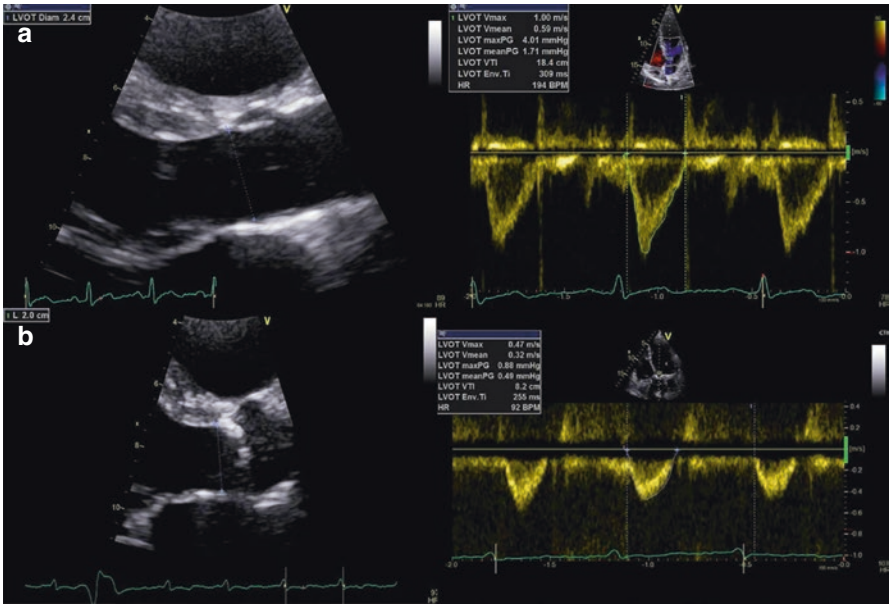


Fig. 3.2 Determination of stroke volume by Doppler method. The first patient (**a**) has a normal SV: LVOT 2.4 cm, LVOT VTI 18.4 cm, SV 83 ml. The second patient (**b**) has a reduced SV due to severe LV systolic dysfunction: LVOT 2 cm, LVOT VTI 8.2 cm, SV 25 ml. *LVOT* left ventricular outflow tract, *VTI* velocity time integral, *SV* stroke volume

Volumetric method SV can be measured by subtracting LV end-systolic volume from LV end-diastolic volume, obtained by the Simpson method or by 3D echocardiography, as previously described. The difference should be equal to the SV across the LVOT if there is no valvular regurgitation.

Doppler method Stroke volume can be measured by multiplying the velocity time integral (VTI) in the LV outflow tract (LVOT) by the LVOT area. The VTI in the LVOT can be measured by PW Doppler from the apical five-chamber/long-axis view, while LVOT diameter (D_{LVOT}) is usually measured in the parasternal long-axis view (Fig. 3.2) and it is used to calculate the LVOT area assuming it has a circular shape.

The formula used is: $SV = \pi \times (D_{LVOT}^2/4) \times \text{LVOT VTI (ml)}$.

Although this is a useful method to estimate cardiac output, it has some limitations. Small errors in the measurement of LVOT diameter lead to significant errors in the calculation of LVOT area (because the radius of the outflow tract is squared). Moreover, the LVOT is often oval, not circular so using the assumption of a circular area implies an inherent error in many cases.

The presence of significant valve regurgitation may affect the use of SV as a measure of LV systolic function. For example, the presence of significant aortic regurgitation would increase the SV, overestimating the LV systolic perfor-

mance. Cardiac output can be calculated multiplying the SV by the heart rate, while the cardiac index can then be obtained dividing the cardiac output by the body surface area [6].

LV Regional Function

Even though measures of global LV function provide quantification of overall cardiac performance, the regional function can vary substantially, such as in ischemic heart disease. Acute myocardial infarction (MI) can cause regional wall motion abnormalities in a specific coronary distribution. Currently, regional wall motion is assessed qualitatively using a scoring system based on a17-segment model. In this system, each segment is scored as normal or hyperkinetic (1 point), hypokinetic (2 points), akinetic (3 points), or dyskinetic (4 points) [6]. The wall motion score index (WMSI) is the average value of all analyzed segments. Therefore, a normokinetic LV has a WMSI score of 1.0, and the index increases as wall motion abnormalities become more severe. This score also has prognostic value and a higher score is an independent predictor of morbidity and mortality, including increased hospitalizations for heart failure following MI [20]. Although MI is the most likely reason for regional wall motion abnormalities, other conditions (such as myocarditis or sarcoidosis) can affect myocardial function regionally, but usually not in a definite coronary distribution.

Doppler Methods of LV Systolic Function Evaluation

Rate of LV Pressure Increase

The rate of LV pressure increase during isovolumic contraction, LV dP/dt, reflects force development and thus represents a parameter of myocardial contractility. There is no significant change in LA pressure during early systole. Therefore, the mitral regurgitation (MR) jet velocity is the instantaneous systolic pressure in the LV and reflects LV dP/dt. According to the simplified Bernoulli equation ($G = 4 \times v^2$), pressure gradients may be estimated from measured velocities. Thus, the pressure change calculated from the slope of the CW Doppler spectrum of MR between 1 m/s (G = 4 mm Hg) and 3 m/s (G = 36 mm Hg) is 32 mm Hg, while the time interval between these two moments is directly measured. Thus, the dP/dt is calculated from the following formula: LV dP/dt = 32 mm Hg/time.

While normal values are usually ≥12,000 mm Hg/s, values less than 1000 mm Hg/s indicate LV systolic dysfunction, and values less than 600 mm Hg/s imply severely impaired LV systolic function and are associated with poor outcome [21] (Fig. 3.3).

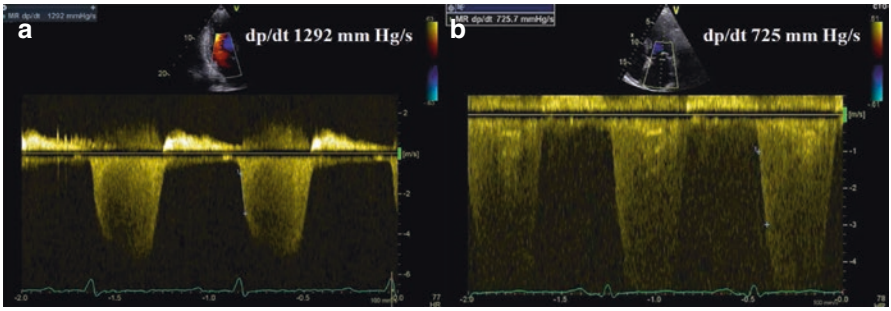


Fig. 3.3 Determination of Doppler-derived LV dP/dt from the continuous-wave Doppler spectrum of the mitral regurgitation jet. The time interval between the moments corresponding to velocities of 1 m/s and 3 m/s, respectively, is directly measured. (**a**). Dp/dt in a patient with normal left ventricular systolic function = 1292 mm Hg/s. (**b**). Dp/dt in a patient with reduced left ventricular ejection fraction of 30 %: dp/dt of 725 mm Hg/s

This parameter is complementary to LVEF and is useful mainly when decreased or increased afterload (e.g. significant MR, significant aortic stenosis, respectively) coexist, and the LVEF over/underestimates the LV contractile function. In these settings, dP/dt may be a useful index of LV contractile reserve.

Although the method is very appealing, it has several limitations: the MR signal is needed; small differences in measuring the time interval will lead to large differences in calculated dP/dt; this parameter cannot be used in the presence of acute MR (due to the very high LA pressure).

Myocardial Deformation Imaging

Novel advanced echocardiographic techniques to image the myocardial mechanics have been developed in the past years. Myocardial deformation imaging is a method for the assessment of intrinsic myocardial function.

The efficient systolic pumping of the LV is a complex process requiring a coordinated contraction of the myocardial fibers. The LV has a complex anatomy with the endocardial and the epicardial fibers orientated in a double helical pattern. The subendocardial fibers have a right-handed orientation, while the subepicardial fibers have a left-handed orientation, forming a helical structure [22]. When it contracts, the LV changes shape and deforms in different directions: it shortens in the longitudinal direction, it thickens in the radial direction, and it shortens circumferentially [22]. Moreover, as the oppositely oriented double helical fibers contract, this leads to a twisting of the LV as the apex rotates in the opposite direction compared to the base. The twisting motion of the LV helps squeezing the blood into the aorta, contributing to a more efficient ejection [23].

During LV ejection, elastic potential energy is stored due to the deformation of the subendocardial fiber matrix. Its subsequent elastic recoil causes rapid untwisting

which is associated with the release of restoring forces, creating suction gradients that contribute to early LV diastolic filling by active suction of blood from the atria [22–24].

This complex deformation of the LV in three directions is, therefore, essential for both LV systolic and diastolic function and its impairment contributes to the occurrence of LV dysfunction as the precursor of HF.

It is known that the impairment of longitudinal function is an early marker of LV dysfunction that precedes the drop in LVEF. The use of advanced echocardiography techniques allows measurements of different parameters describing myocardial mechanics, such as myocardial displacement, velocity, strain, and strain rate, in different directions (e.g. longitudinal, radial, and circumferential). Such measurements can be performed either with tissue Doppler or speckle tracking echocardiography.

Tissue Doppler imaging (TDI) allows the preferential sampling of myocardial motion which has lower velocities and larger amplitudes compared to that of the blood flow. TDI is most often recorded using pulsed-wave (PW) or color Doppler. The recorded waves are then analyzed and used to offer information about the myocardial function. The peak systolic myocardial velocity S recorded at the LV base, reflects longitudinal myocardial fiber shortening and has been used to assess LV systolic function in patients with HF. While S values are uniformly reduced in HFrEF, reduced S-wave values as determined by PW-TDI have been reported in a large proportion (around 50 %) of patients with HFpEF [25, 26]. These findings suggest that TDI may detect impairment of longitudinal function as an early marker of LV dysfunction, that precedes the drop in LVEF.

One major limitation of assessing LV function by measuring myocardial velocities by TDI is that the translational motion of the heart or tethering by adjacent segments may influence the measured velocities. Assessing LV deformation may overcome this limitation.

Strain (deformation) refers to the actual change in length of the myocardium during the cardiac cycle as compared to its initial value and is expressed as a percentage. Therefore, shortening is expressed as negative values, while lengthening/thickening as positive values.

Strain rate is the rate of instantaneous change in deformation, and is calculated as the difference between two velocities (V) normalized to the distance (d) between them: Strain rate = (V1−V2) / d. This parameter is expressed as "s^{-1}" [27].

The measurement of LV strain and strain rate by TDI is limited by the requirement of parallel alignment of the Doppler cursor with the direction of myocardial motion. This limits its application to the segments which can be properly insonated and cannot be applied to the whole ventricle and for all types of myocardial deformation.

In clinical practice, measuring strain and strain rate has proved useful to detect abnormalities of both LV systolic and diastolic function in patients with infiltrative cardiomyopathies [28]. Moreover, it can help to differentiate restrictive cardiomyopathy (reduced early diastolic strain rate) from constrictive pericarditis (increased early diastolic strain rate) [29].

One of the most studied applications of TDI is the evaluation of LV dyssynchrony. Intersegmental delay in peak systolic longitudinal contraction between different segments (abnormal >65 ms), and the standard deviation of time to peak velocity of 12 basal- and mid-LV segments (abnormal>30 ms) are parameters of LV dyssynchrony [30, 31].

Several studies have reported good sensitivity and specificity of TDI techniques in predicting echocardiographic and clinical response after cardiac resynchronization therapy (CRT) [32–34]. However, the negative and/or controversial results of some trials [35] lead to the lack of inclusion of such methods in the recommendations for CRT in HF guidelines [3]. It may be useful in selected cases, in a comprehensive approach, to select borderline candidates, to guide device optimization and to assess response during follow-up.

Doppler-based methods to assess myocardial strain and particularly strain rate are relatively noisy and require dedicated acquisition during scanning, thus limiting their usefulness. The angle-dependent nature inherent to a Doppler technique represents another limitation.

Speckle tracking echocardiography (STE) is a method based on 'speckles' formed by reflection, scattering and interference of the ultrasound beam in the myocardial tissue [36]. The 'speckles' can be tracked frame to frame throughout the entire cardiac cycle and information about tissue motion and its derivatives, including strain and strain rate can be obtained. Strain imaging based on STE has proved to be more reliable and easier to use, although it has poorer temporal resolution than Doppler-based techniques do. Due to its relative angle-independence, STE can be applied to all LV segments, irrespective of the insonation angle. Thus, STE-derived myocardial strain can be measured for all LV segments in the longitudinal, circumferential, and radial directions by using the appropriate imaging plane [28] (Fig. 3.4).

The most robust parameter of LV systolic function assessed by STE is LV global longitudinal strain (GLS), calculated by averaging the different segmental values measured (Fig. 3.5). It has proved useful both for diagnostic purpose in identifying early LV dysfunction in patients with HFpEF [3] and for prognostic purposes in patients with HfrEF [37]. Moreover, the bulls' eye display of individual segmental values allows a rapid identification of LV dysfunction pattern: diffuse in dilated cardiomyopathy, following a specific coronary distribution in patients with coronary disease, or following a specific regional pattern in other disease settings (Fig. 3.5). The latter may be particularly useful in identifying the etiology of LV dysfunction in patients with HFpEF. Thus, apical sparing of longitudinal myocardial deformation has been described in amyloidosis, while regional reductions in LV longitudinal strain in the most hypertrophied areas of the LV has been shown in patients with hypertrophic cardiomyopathy [38]. While strain values are reduced in patients with HFrEF, recent studies have described reductions in myocardial deformation in both longitudinal and circumferential directions in patients with HfpEF [39]. Thus, systolic function abnormalities are quite prevalent in HFpEF, can be detected by echocardiography, and may contribute to the pathophysiology of this syndrome.

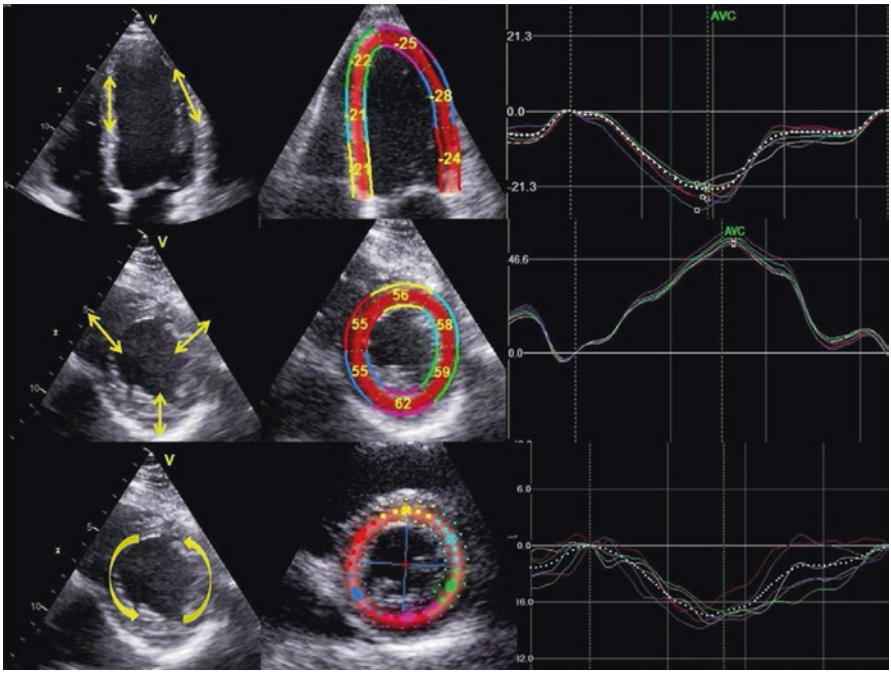


Fig. 3.4 Strain imaging based on 2D speckle tracking echocardiography. On the left column: the directions of myocardial deformation which are assessed (*arrows*): longitudinal deformation (*upper row*), radial deformation (*middle row*), and circumferential deformation (*lower row*). On the middle column: the peak systolic strain values are displayed for each LV segment. On the right column: the color-coded segmental deformation curves for all LV segments in the longitudinal (*upper row*), radial (*middle row*), and circumferential (*lower row*)

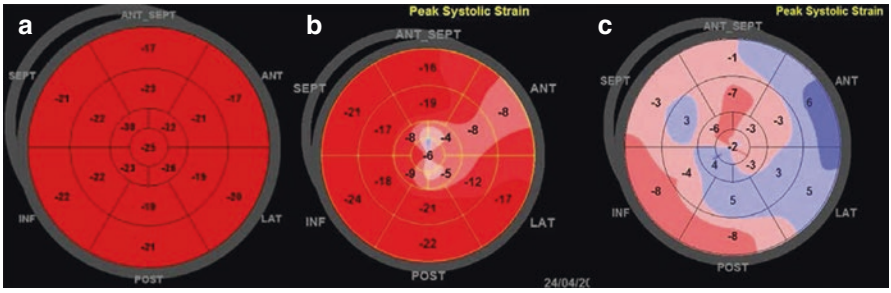
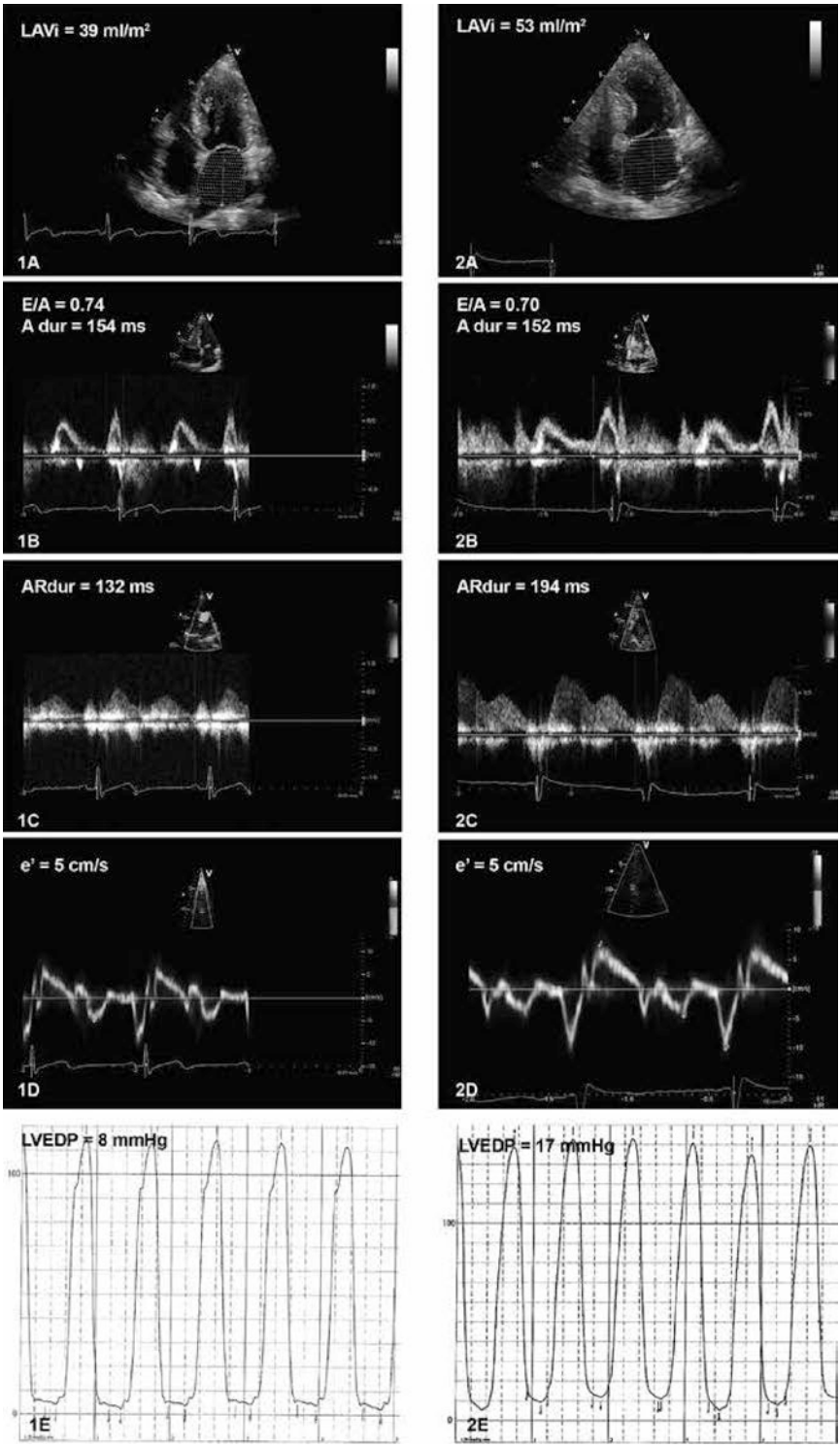


Fig. 3.5 Left ventricular global longitudinal strain (GLS) displayed in the bull's eye format. (**a**) Normal global and regional longitudinal strain in a healthy individual. (**b**) Segmental myocardial dysfunction with a specific coronary distribution (the left anterior descending territory), in a patient with an old anterior myocardial infarction. (**c**) Diffusely reduced global longitudinal strain (not following a specific coronary distribution) in a patient with dilated cardiomyopathy and normal coronary arteries


LAVi = 39 ml/m²
1A
LAVi = 53 ml/m²
2A
E/A = 0.74
A dur = 154 ms
1B
E/A = 0.70
A dur = 152 ms
2B
ARdur = 132 ms
1C
ARdur = 194 ms
2C
e' = 5 cm/s
1D
e' = 5 cm/s
2D
LVEDP = 8 mmHg
1E
LVEDP = 17 mmHg
2E

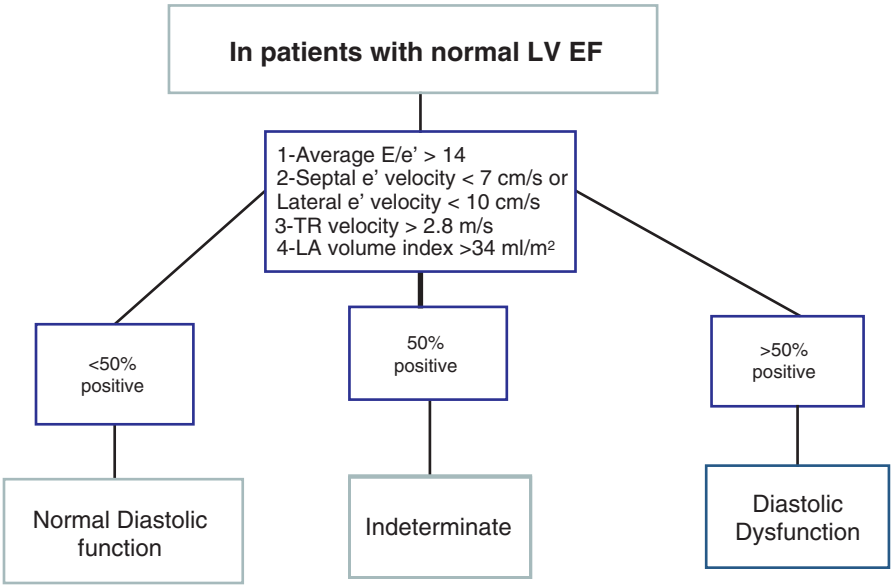


Fig. 3.7 Algorithm for diagnosis of LV diastolic dysfunction in subjects with normal LVEF (Reprinted with permission from Ref. [44])

Fig. 3.6 Echocardiographic findings in two patients with normal LVEF and impaired relaxation pattern, yet significantly different left ventricular end-diastolic pressure (LVEDP) at cardiac catheterization. The figure presents: measurements of left atrial volume from the apical four-chamber view – *first row A*; pulsed wave Doppler tracings of mitral inflow – *second row B*; pulsed wave Doppler tracings of pulmonary venous flow – *third row C*; mitral annulus velocities at the septal site – *fourth row D*; left ventricular pressure curves recorded at cardiac catheterization: *fifth row E* Patient 1 (*left column*) had a normal LVEDP of 8 mm Hg (*1E*) while patient 2 (*right column*), who had LV hypertrophy, had a significantly increased LVEDP of 17 mm Hg (*2E*). Both patients had a very similar impaired relaxation filling pattern (*1B*, *2B*). The impaired LV relaxation was confirmed by the reduced early diastolic velocity e': 5 cm/s in both (*1D*, *2D*). Both patients had a dilated left atrium, but the severity of LA dilation was higher in patient 2 (53 ml/m2, *2 A*) compared to patient 1 (39 ml/m2, *1 A*). Although both patients had an E/e' ratio of 8 and a very similar S/D ratio at pulmonary venous flow (*1C*, *2C*), the time difference between pulmonary vein AR duration and mitral A-wave duration was increased only in patient 2 (42 ms). In patient 1 AR duration was actually shorter than mitral A-wave duration (132 ms vs 154 ms), indicating normal LVEDP. In these patients the careful assessment of AR duration and mitral A-wave duration and the size of the LA suggested a higher LVEDP in patient 2 despite the similarity in all the other echo parameters. This example underlines the importance of a comprehensive multi-parameter approach for the evaluation of LV diastolic function. (Reprinted with permission from Ref. #46).

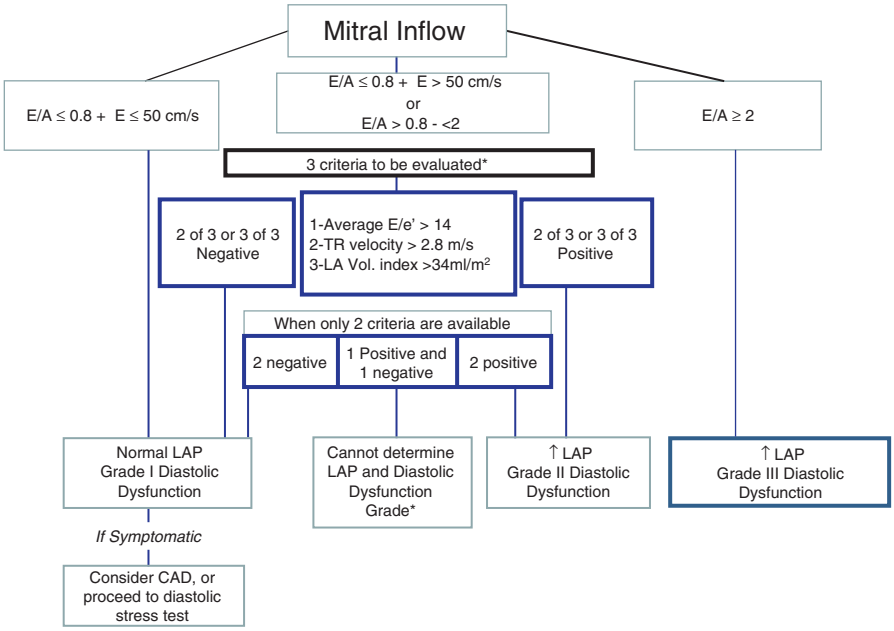


Fig. 3.8 Algorithm for estimation of LV filling pressures and grading LV diastolic function in patients with depressed LVEFs and patients with myocardial disease and normal LVEF after consideration of clinical and other 2D data (Reprinted with permission from Ref. [44])

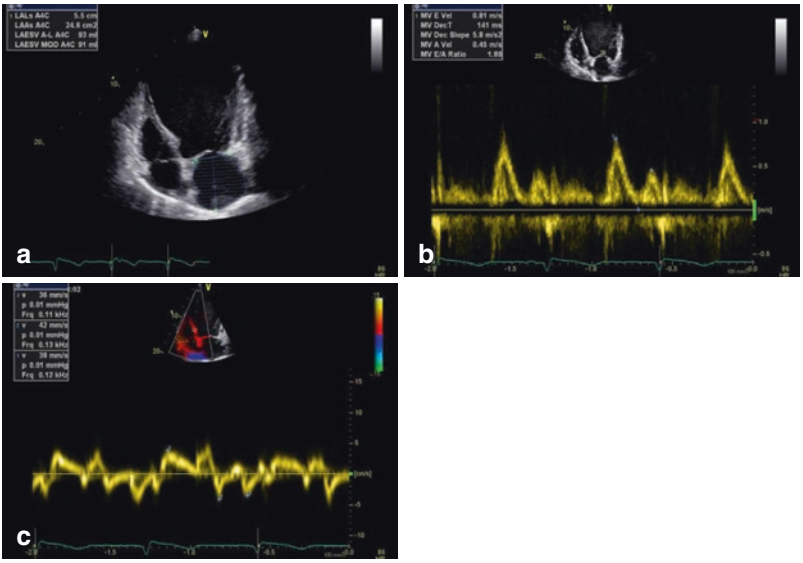


Fig. 3.9 Echocardiographic evaluation of LV diastolic function in a patient with HFrEF: E 81 cm/s, E/A ratio 1.8, EDT 140 ms (**b**), LVEF = 20 % (**a**). The combination of LVEF<35 % and RFP with EDT<150 ms is highly suggestive of increased LVFP. LAVi was 51 ml/m^2 (**a**) and E/e'sep = 20 (**c**), also suggestive of high LVFP. At left heart catheterization the measured LVEDP was 20 mm Hg, confirming the echo estimates

While normal values of the global peak systolic strain are usually higher than 20 % in absolute values, figures less than 16 % are highly sensitive and specific for the identification of patients with prior myocardial infarction [27]. Given the reported inter-vendor variability, for follow-up studies the use of the same software is recommended for a meaningful comparison.

These STE-derived strain measurements, although easier to obtain compared to TDI-derived ones, have the limitation of lack of proper standardization in acquisition and analysis, and both inter-observer and inter-vendor measurement variability [28, 40]. The former is being addressed by attempts to standardize its use in a very practical way [41], the latter by standardization efforts based on synthetic ultrasound data [42]. These improvements lead to the inclusion of newer techniques in the most recent version of the ESC guidelines on HF, receiving a Class IIa indication for the detection of early LV dysfunction [3].

Speckle tracking methods can also be used to assess ventricular rotation and to derive LV twist and torsion. Impaired LV twist has been described in patients with dilated cardiomyopathy, and reversed apical rotation correlated to the severity of LV systolic and diastolic dysfunction [43].

However, the clinical applications of measuring LV rotation and twist are limited because of technical difficulties and high inter observer variability and lack of properly validated normal values.

The routine use of myocardial deformation parameters for the assessment of LV systolic function is likely to increase in the near future, as long as the mentioned limitations will be overcome and clear cut-off values for practical use in different settings will be established.

Assessment of Left Ventricular Diastolic Function

Echocardiographic assessment of left ventricular (LV) diastolic function is an essential component of the comprehensive assessment of patients with heart failure (HF).

LV diastolic dysfunction (LVDD) is usually the consequence of abnormal LV relaxation, reduced restoring forces and increased LV chamber stiffness, leading to increased cardiac filling pressures [44]. With impaired LV relaxation, LV filling progressively shifts from early to late diastole and left atrial (LA) contraction becomes responsible for a substantial proportion of LV diastolic filling and cardiac output. In the early stages, as long as LA function is preserved and with an adequate filling period, LVDD is asymptomatic since LV filling pressure (LVFP) remains normal. With the further deterioration of diastolic function and loss of diastolic reserve, LVFP increases leading to upstream congestion and symptomatic LVDD initially with exercise and eventually at rest [45, 46].

In HF patients with reduced LV ejection fraction (HFrEF), LV diastolic function is virtually always impaired. Thus, when evaluating diastolic function in this setting, the focus is mainly on estimating LVFP, since it can guide therapy, monitor the disease course and improve outcomes. In patients with HFpEF, on the other hand, the focus is on detecting the presence of LVDD which is the likely cause of HF and fundamental to the diagnosis [44].

A broad spectrum of echocardiographic techniques and parameters may be used to reveal impaired LV relaxation, reduced restoring forces, increased diastolic stiffness, increased LA pressure and LV end-diastolic pressure (LVEDP) in patients presenting with symptoms or signs of HF.

Echocardiographic Diagnosis of LVDD in Patients with HFpEF

By demonstrating relevant structural heart disease and LV diastolic dysfunction in patients with clinical features of HF and preserved LVEF, echocardiography can provide key diagnostic criteria for HFpEF [3].

Relevant structural alterations are represented by LV hypertrophy (LVH) and LA dilation, whereas functional abnormalities (e.g. changes in LV relaxation, compliance or stiffness, indices of increased LVFP) are best reflected by mitral flow velocities, mitral annular e' velocity and E/e' ratio. Other echocardiographically derived measurements such as longitudinal strain, or tricuspid regurgitation velocity (TRV) may provide diagnostic features of LVDD in patients with HFpEF. In case of uncertainty, an echocardiographic diastolic stress test may provide additional information to confirm the diagnosis [44].

It should be noted that, according to current guidelines, the term "preserved" LVEF refers to LVEF >50 %. A LVEF between 40 and 50 % in patients with signs and symptoms of HF, along with relevant structural alterations and LVDD has been defined as HF with mid-range LVEF (HFmrEF). Since LVDD is thought to be the main pathophysiological abnormality in patients with HFpEF and perhaps HFmrEF, LV diastolic function evaluation is of utmost importance in both clinical situations and follows the same diagnostic pathway [3].

Two-dimensional echocardiography may reveal structural abnormalities of the heart representing either the cause or the consequence of DD and expressing its severity and duration.

Pathological LVH, defined as abnormally *increased LV mass* in untrained subjects, is a marker of impaired myocardial relaxation and increased stiffness, which strongly suggest the presence of LV DD. It is the most prevalent structural cardiac abnormality reported in patients with HFpEF, and it was independently associated with an increased risk of morbidity and mortality in this setting [6, 47, 48].

The currently recommended method for LV mass estimation in patients without significant cardiac geometry distortions relies on M-mode or 2D echocardiographic linear measurements of LV diastolic diameter and wall thickness as most studies relating LV mass to prognosis are based on this method. However, the linear dimension method using the cubed formula (with LV modeled as a prolate ellipse) may be inaccurate in many HF patients exhibiting asymmetric ventricular hypertrophy. Two-dimensional methods based on either the area-length or truncated ellipsoid technique are less dependent on geometrical assumptions and more suited for LV mass estimation in patients with regional variations in wall thickness. The main limitations of 2D methods are related to methodology, low reproducibility, and limited prognostic data [6].

Three-dimensional echocardiography provides a more accurate estimation of LV mass in patients with remodeled ventricles, since it is free of geometric assumptions. However, prognostic data with 3D methods are still scarce [6, 9].

Uniform reference values for LV mass are difficult to define since LV mass may vary with gender, age, body size, obesity and geographic area. Moreover, there is still a controversy related to the term of LV mass indexing (height, weight or body surface area) [6].

The upper limits for normal LV mass currently recommended with 2D measurements, indexed to BSA, are 88 g/m^2 in women and 102 g/m^2 in men. Left ventricular DD should be suspected when LV mass by linear measurements is >95 g/m^2 in women and >115 g/m^2 in men [3, 6]. There is insufficient available data in healthy subjects to recommend reference values for LV mass with 3D echocardiography.

Different patterns of LV remodeling were reported in patient with HFpEF. While concentric LV remodeling/hypertrophy is common, some patients present with normal LV geometry or even with an eccentric pattern. Thus, further assessment of ventricular geometry and function in broader HFpEF populations will be needed to establish the prevalence, correlates, and prognostic significance of these measures [49].

Left atrial (LA) dilation is an important feature for the diagnosis of HFpEF, suggesting the presence of DD with long standing increased LV filling pressure. Moreover, LA size emerged as an independent outcome predictor in patients with HFpEF [48].

Bradycardia, atrial arrhythmias, significant mitral valve disease, high-output states may lead to LA dilation on their own, altering the relationship between LA size and LV filling pressure [44, 50]. Thus, LA size value as a supportive finding for the diagnosis of HFpEF is limited in these settings.

Two-dimensional echocardiography is currently recommended to assess LA size. The anteroposterior diameter, widely used for LA assessment, often underestimates the real LA size in patients with asymmetric LA remodeling [51]. Thus, LA volume, which provides a more accurate assessment of LA size and has superior prognostic value when compared to area or diameter, should be used to estimate LA dilation [6, 52].

Three-dimensional echocardiography (3DE) allows a better assessment of LA size due to lack of geometric assumptions, higher accuracy than 2D echo in determining LA volume when compared to CMR, and better prognostic value. However, its use for LA size assessment is still limited by the lack of a standardized methodology, variability, and the limited normative data [6].

Scaling LA volume to body size by dividing it to body surface area is recommended. The cut-off value for normal LA volume is 34 ml/m^2 which is also the reference value for the diagnosis of LVDD and for LVFP assessment (44, 3 6). However, a LA volume index <34 ml/m^2 does not rule out the LVDD when other relevant parameters are strongly suggesting it. A normal LA volume has been reported in patients with early stages of diastolic dysfunction or with acute elevations of LVFP [6].

In a study comparing echocardiographic features of patients with HFpEF vs nonfailing hypertensive subjects with LVH, the product of LV mass index and LA

volume emerged as the best predictor of HF-pEF [53]. Thus, the association of LVH and LA dilation in patients experiencing exercise dyspnea increases the likelihood of HFpEF.

Increased LA volume without associated increase of LVFP may be found in athletes, in patients with atrial rhythm disturbances, mitral valve disease, high output states, heart transplants with biatrial technique or in patients with chronic, compensated HF [6].

Conventional Doppler echocardiography is critical to reaching correct conclusions regarding LV diastolic function in patients with HFpEF.

Transmitral flow profile parameters (peak early transmitral filling velocity E, peak atrial contraction velocity A, the E/A ratio, E velocity deceleration time, and isovolumic relaxation time IVRT), continue to play a significant role in the workup of HFpEF patients [44]. However, the age and load dependency of these parameters limit their use as first-line tools in this process [54].

Slowing of LV relaxation and LV pressure decay, in the absence of elevated left atrial pressure, leading to "impaired LV relaxation" pattern, may be encountered in the early stages of LVDD, but also with increasing age, higher heart rate, right ventricular overload, and other conditions [55]. On the other hand, several studies reported cases of patients presenting with acute or chronic HFpEF and „impaired relaxation pattern" and increased LVFP probably due to markedly delayed LV relaxation (Fig. 3.1) [56, 57, 58].

Moreover, a "pseudonormal" filling pattern in patients with progressive LV diastolic dysfunction and increased left atrial pressure which restores the early diastolic gradient between the LA and the LV (E/A ratio>1) may be difficult to differentiate from normal transmitral filling. Further information supporting the presence of LVDD in this setting may be obtained from response to *Valsalva maneuver and pulmonary venous flow analysis*. Thus, a decrease in E/A ratio with Valsalva Maneuver with more than 0.5 in patients with baseline E/A>1 is highly accurate for "pseudonormal filling" due to increased LV filling pressures and supports the presence of LVDD. Likewise, an increase in pulmonary vein atrial reversal wave Ar, with a difference between Ar duration and mitral A in duration >30 ms has a good accuracy in predicting elevated LVEDP in patients with abnormal LV relaxation [44].

Echocardiographic assessment of *pulmonary artery systolic pressure* (PASP) based on Doppler assessment of tricuspid regurgitation jet peak velocity and inferior vena cava evaluation by 2D, should not be overlooked when assessing LV diastolic function in patients with suspected HFpEF. In previous studies, PASP estimated by echocardiography emerged as a better predictor of HFpEF when compared to other echocardiographic parameters associated with DD (E/e' ratio, LA volume, and LV wall thickness). Elevated PASP values can identify patients with increased LV filling pressures due to LVDD provided pulmonary vascular disease or other potential causes of PH such as valvular heart disease, lung disease, chronic thromboembolic disease, and obstructive sleep apnea have been excluded [44, 59, 60].

Mitral annular velocities assessed by **Tissue Doppler** are currently considered key echocardiographic measurements in assessing diastolic dysfunction. The mitral

annulus early diastolic velocity e' is of primary interest for the evaluation of LV diastolic function as it decreases with impaired LV relaxation and it is less preload dependent compared to mitral E wave in patients with myocardial disease [44, 55, 61, 62]. Whereas the E/A ratio of the mitral inflow exhibits a U-shaped relationship with progressive LVDD, the e' velocity decreases in a continuous manner being less affected by the gradual increase in LVFP. It was suggested that the decrease in e' velocity precedes the reduction in E/A ratio with 10–15 years [61, 63]. Therefore, normal e' velocity is unusual in patients with LVDD related to a myocardial abnormality or disease, which is the main reason that the joint Diastology Working Group recommends that an evaluation of diastolic function begins with e' in patients with normal LV ejection fraction [1]. The E/e' ratio is thought to be a reflection of LVFP and can be used as a marker of LVDD. The correlation between E/e' and LVFP has been confirmed in patients with both HFrEF and HFpEF [63, 64]. To date, reduced e' and elevated E/e' are incorporated in guidelines as evidence of LVDD [44].

Although mitral annular velocities are less load dependent than conventional parameters of diastolic function, slowing of myocardial relaxation with increasing age can account for the decrease in both mitral E/A ratio and e' velocity. Moreover, several studies suggested that E/e' is not sensitive enough to detect HFpEF in an early stage of the disease, when alterations in diastolic processes are very subtle [65–67].

The recently updated recommendations for the evaluation of LV diastolic function by echocardiography proposed four variables to be evaluated when searching for the presence of LV DD in patients with normal LVEF. Three out of the four recommended variables are Doppler-derived indices: *annular e' velocity* (septal e' <7 cm/s, lateral e' <10 cm/s), *average E/e' ratio* >14 (E/e'lat > 13 or E/e'sep > 15), and *peak TR velocity* >2.8 m/s. Left atrial maximum volume index >34 mL/m^2 is the fourth parameter required for the diagnosis of LVDD [44].

More than half of the available parameters should meet these cutoff values to make the diagnosis of LVDD [1]. If more than two (or 50 %) of the available parameters do not satisfy these cutoff values, LV diastolic function will be considered normal. Between these two situations the study is considered inconclusive [44] (Fig. 3.2).

In patients with suspected HFpEF and inconclusive diastolic function parameters, evaluation of LV longitudinal systolic function may aid the diagnosis, providing evidence of myocardial dysfunction. Parameters such as mitral annular plane systolic excursion using M-mode (MAPSE), tissue Doppler–derived mitral annulus systolic velocity (S), and LV global longitudinal strain (GLS) by speckle-tracking may provide further insight when assessing LV diastolic function, since previous studies have demonstrated a close relationship between systole and diastole and a high prevalence of systolic longitudinal dysfunction in HFpEF population [68, 69].

Further diagnostic aid in patients with exertional dyspnea, preserved LVEF and inconclusive diastolic parameters at rest may be provided by **echocardiographic exercise testing** which has recently been added to the set of criteria that should be fulfilled for the diagnosis of HFpEF [3]. The recommendation is based on previous studies reporting a lack of diastolic reserve leading to increased LV filling pressure with exercise in patients with diastolic dysfunction compared to healthy subjects

Table 3.1 The interpretation of the diastolic stress test [1]

	Resting Septal e ’(cm/s)	Resting lateral e’(cm/s)	Exercise Average e/e’	Exercise Septal e/e’	Exercise Peak TR velocity (m/s)
Normal	<7	<10	<10	<10	<2.8
Definitely abnormal	<7	<10	>14	>15	>2.8

[39, 70–72]. The test may improve de specificity of diagnosing HFpEF in patients with no apparent signs of central fluid overload, grade 1 diastolic dysfunction, which indicates delayed myocardial relaxation and normal filling pressures at rest [44]. On the contrary, no valuable diagnostic input will be gained by extending the recommendation of a diastolic stress test to patients with normal heart and diastolic function at rest (it is unlikely that they will experience dyspnea due to diastolic dysfunction and elevated filling pressures with exercise), or to patients with abnormal findings at baseline consistent with elevated LV filling pressures (LVFP will further increase with exercise) [44].

A diastolic echocardiographic stress test can be performed using a semi-supine bicycle ergometer exercise protocol with the assessment of mitral inflow velocities, mitral annulus tissue Doppler velocities, and peak TR velocity by CW Doppler at baseline, during each stage including peak exercise, and in recovery (Table 3.1).

When the only abnormal finding of a diastolic stress test is an isolated increase in exercise peak TR velocity, available data should be analyzed with caution. Peak TR velocity may increase in healthy subjects due to increased pulmonary blood flow with exercise [44].

When resting echocardiography and diastolic stress test are inconclusive an invasive hemodynamic investigation may be performed in selected patients in order to explain their symptoms of heart failure or dyspnea, especially with exertion [44].

Echocardiographic Assessment of Left Ventricular Filling Pressures and Diastolic Dysfunction Grade

Evaluation of LV filling pressures and grading diastolic dysfunction with echocardiography are two essential components of LV diastolic function assessment in patients with HF irrespective of LVEF. The clinical purpose of LVDD grading is mainly the prognostic stratification of patients whereas the evaluation of LV filling pressures offers an estimate of invasively measured capillary wedge pressure, mean LA pressure, and LV end-diastolic pressure which is clinically relevant for diagnosis (particularly in HFpEF patients), monitoring and guiding therapy.

Different evidence emerged from validation studies in patients with preserved or reduced LVEF, and thus, two algorithms were used for several years for grading LVDD and estimating LVFP according to LVEF. Recently, the previously published decision trees merged into one single algorithm (Fig. 3.3). The principal variables

recommended for the assessment of LV diastolic function grade include mitral flow velocities, mitral annular e' velocity, E/e' ratio, peak velocity of TR jet, and LA maximum volume index [44].

Of note, the algorithm is based on expert consensus and has not been validated. It may be used in the absence of: atrial fibrillation, left bundle branch block, ventricular paced rhythm, at least moderate mitral annular calcification, more than moderate mitral regurgitation/stenosis, mitral valve repair or prosthetic mitral valve, LV assist devices [44].

In patients with HFrEF, since diastolic dysfunction is always present, transmitral inflow pattern is usually sufficient to predict LAP (Fig. 3.4). The restrictive filling pattern (RFP, E/A > 2) indicates grade III diastolic dysfunction, and it was associated with higher rates of adverse events than non-RFP patients. Moreover, the response of RFP to loading manipulation represents an even stronger predictive marker, since a significant rate of major events was reported in patients with irreversible RFP. The pseudonormal filling pattern has also been shown to predict poor outcomes in patients with HF, which was similar to that seen with restrictive LV filling in some studies. In patients with chronic heart failure, changes in transmitral flow patterns after chronic optimized therapy are correlated with changes in pulmonary wedge pressure, are accompanied by changes in functional capacity, and provide relevant independent prognostic information [73–76]. Deceleration time of mitral E velocity is usually short with RFP (<160 ms) and an important predictor of outcome in patients with reduced LVEF, symptomatic or asymptomatic [77].

With a "pseudonormal pattern" or when E/A ratio <0.8 with a peak E velocity of >50 cm/s, additional parameters are required to estimate LAP and conclude the grade of LVDD. Among these, average E/e'ratio >14 supports the presence of elevated LV filling pressure [44]. Several studies reported a high power of e' velocity and E/e' ratio to predict adverse events in patients after acute myocardial infarction, with and without heart failure [78, 79]. Increased LA volume index (<34 ml/m^2) and peak TR velocity (>2.8 m/s) are the other two recommended parameters supporting the presence of increased LVFP in this setting, both shown to be robust predictors of outcome in HFrEF patients [80–82]. If one of the three main parameters is not available, pulmonary venous flow S/D ratio <1 may is consistent with elevated LVFP [44].

The recommended approach for LV filling pressures assessment in patients with myocardial disease and preserved LVEF starts with a careful screening for cardiac structural and functional changes relevant in this setting: LA dilation, pathological LV hypertrophy, elevated PASP, provided that alternative explanations for these alterations have been excluded. The proposed algorithm is similar to that for patients with depressed LVEF. **Increased LA volume and LV hypertrophy** emerged as independently associated with an increased risk of morbidity and mortality in HFpEF patients in the I-PRESERVE study. Prognostic value was also reported for E/e" ratio, PASP, and pulmonary venous S/D ratio in HFpEF patients from different studies [48, 83].

The role of E/e' ratio as a predictor of LVFP has been debated in recent years. It was suggested the E/e' ratio lacks sensitivity to detect increased filling pressure since many patients with increased LVFP have an E/e' ratio lower than the recommended cutoff values, especially when ejection fraction is preserved [45]. Moreover,

in one study of decompensated patients with advanced systolic HF, the E/e' ratio showed a poor correlation with intracardiac filling pressures, particularly in those with larger LV volume, more impaired cardiac index, and in the presence of cardiac resynchronization therapy [84].

The perspective of using E/e' as a tool to monitor patient's evolution in time or their response to therapy was also hampered by the observation that as filling pressures are manipulated, the relationship between E/e' ratio and the pulmonary capillary wedge pressure is highly variable in healthy patients and patients with HFpEF [85].

Therefore, the current guidelines should not be read as a recommendation to resume the LV diastolic function evaluation to four key parameters, but to perform a complete echocardiographic exam and to integrate all the available parameters together with the clinical data in a pathophysiological scenario.

The evaluation of LV diastolic function in patients with specific cardiac or extracardiac conditions has features which have been detailed in the recently released document on recommendations for the evaluation of diastolic function [44].

Future Directions

Echocardiography provides essential information for diagnosis, prognosis and treatment in patients with HF. New echocardiographic technique for a detailed assessment of myocardial mechanics may provide more precise measurements to guide therapeutic decisions. The routine use of myocardial deformation parameters for the assessment of LV systolic function is likely to increase in the near future, as long as the limitations of this method will be overcome and clear cut-off values for practical use in different settings will be established. The evaluation of segmental myocardial deformation (amplitude and timing) can better detect and characterize dyssynchrony. Three-dimensional echocardiography may also provide a more accurate measurement of LVEF which may guide the more appropriate selection of patients for different therapies. These new techniques for characterization of myocardial mechanics and the development in 3DE hold great promise for improving the quality of care of the HF patients.

At the other end of the spectrum, the increasing use of hand-held ultrasound devices may greatly help in screening patients with acute dyspnea in settings where high-end echo systems are not available, for the proper diagnosis of HF, including the etiology.

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Chapter 4
The Imaging of Right Ventricular Dysfunction in Heart Failure

Elena Surkova, Denisa Muraru, and Luigi P. Badano

Abbreviations

CMR	Cardiac magnetic resonance
CT	Computed tomography
EDA	End-diastolic area
EDV	End-diastolic volume
EF	Ejection fraction
ESA	End-systolic area
ESV	End-systolic volume
ET	Ejection time
FAC	Fractional area change
IVCT	Isovolumic contraction time
IVRT	Isovolumic relaxation time
IVS	Interventricular septum
LV	Left ventricle
RIMP	Right ventricular myocardial performance index
RV	Right ventricle/ventricular
RVOT	Right ventricular outflow tract
S	Systolic velocity across lateral segment of tricuspid annulus by tissue Doppler imaging
SPECT	Single photon emission computed tomography

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M. Dorobanţu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_4

SSFP	Steady-state free precession sequence
TAPSE	Tricuspid annular plane systolic excursion
TDI	Tissue Doppler imaging
TEE	Transesophageal echocardiography
2D	Two-dimensional
2DE	Two-dimensional echocardiography
2DSTE	Two-dimensional speckle-tracking echocardiography
3D	Three-dimensional
3DE	Three-dimensional echocardiography

Introduction

Accurate assessment of the right ventricular (RV) function is important in the clinical management and prognostication of heart failure. Data accumulated over the last two decades demonstrated that RV performance is an important independent predictor of morbidity and mortality in patients with heart failure, pulmonary hypertension, coronary artery disease, left ventricular (LV) dysfunction, as well as in patients with implanted LV assist devices, congenital heart disease, dilated cardiomyopathy, heart transplant,and even in population free of cardiovascular diseases [1–3]. However, the precise evaluation of the RV functions and mechanics is challenging due to its unfavorable location within the thoracic cavity, complex three-dimensional (3D) geometry of this cardiac chamber, unique myocardial fiber architecture, limited number of well-defined anatomical landmarks, and significant dependence on pre- and afterload.

Being widely available, safe, fast and a relatively inexpensive modality suitable for various clinical settings, including acute conditions and intraoperative monitoring,echocardiography remains a cornerstone in RV assessment. Introduction of new echocardiographic techniques including two-dimensional speckle-tracking (2DSTE) and three-dimensional (3DE) echocardiography helped to achieve a level of accuracy in the functional assessment of the RV comparable to that obtained by cardiac magnetic resonance (CMR), which is considered the standard reference imaging modality for the evaluation of the RV [4]. Cardiac computed tomography (CT) provides an accurate and reproducible assessment of the RV ejection fraction and can be considered a reliable alternative for patients who are not suitable for either echocardiography or CMR.

The following chapter summarizes currently available data on the role of non-invasive imaging modalities in the assessment of RV function and mechanics in heart failure patients, their advantages, limitations and pitfalls, with an emphasis on the relative merits of newer imaging parameters and practical approach to data acquisition and analysis.

Echocardiography

Standard Echocardiographic Views of the RV

Figure 4.1 demonstrates the standardized two-dimensional echocardiographic (2DE) views,which should be obtained for a comprehensive assessment of the RV [5]. They allow to visualize different segments of the RV and tricuspid valve apparatus, to assess RV size, shape, wall motion and function with the RV–focused apical 4-chamber view (Fig.4.1b) being the most feasible and widely used.This view is also recommended for guiding 3DE full volume data acquisition and for the RV free-wall and global longitudinal strain analysis.

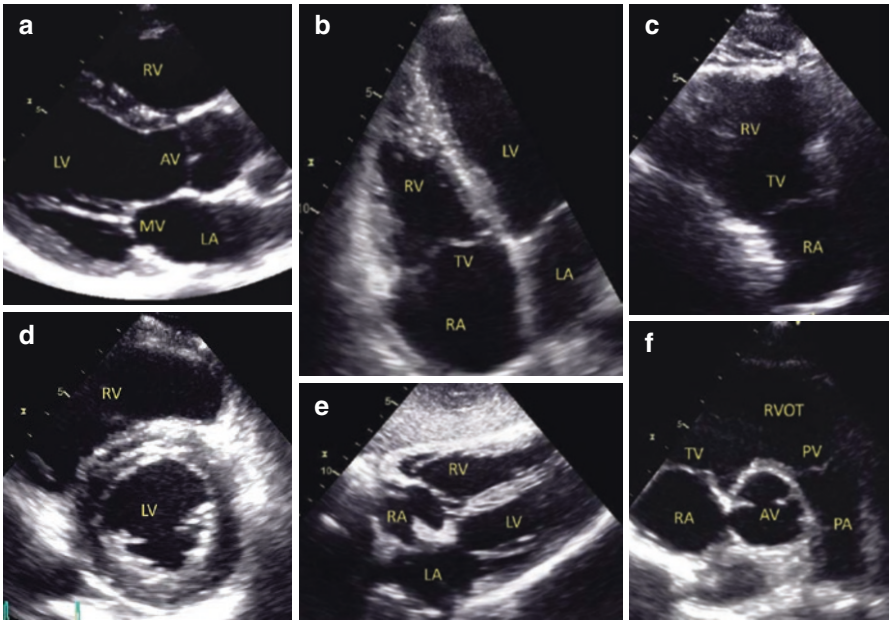

Fig. 4.1 Recommended echocardiographic views for assessment of the *RV*. (**a**) Parasternal long-axis view demonstrating the *RV* anterior wall and proximal part of the *RVOT*; (**b**) Right ventricle–focused apical 4-chamber view used to assess the inflow and apical part of the *RV*, *RV* lateral wall, interventricular septum, and tricuspid valve; (**c**) Parasternal long-axis view of *RV* inflow visualizing anterior and inferior walls of the *RV*, *RV* inflow tract, and two leaflets of the tricuspid valve; (**d**) Parasternal short-axis view at the level of papillary muscles used for the evaluation of the RV crescent shape, calculation of the eccentricity index and assessment of the interventricular septum motion; (**e**) Subcostal 4-chamber view visualizing the *RV* inferior wall; (**f**) Parasternal short-axis view of *RV* outflow tract and pulmonary artery showing basal part of *RV* anterior wall, *RVOT*, two leaflets of the *TV*, pulmonary valve, and pulmonary artery. *Abbreviations*: *AV*aortic valve, *LA*left atrium, *LV* left ventricle, *MV* mitral valve, *PA* pulmonary artery, *PV* pulmonary valve, *RA* right atrium, *RV* right ventricle, *RVOT* right ventricular outflow tract, *TV* tricuspid valve

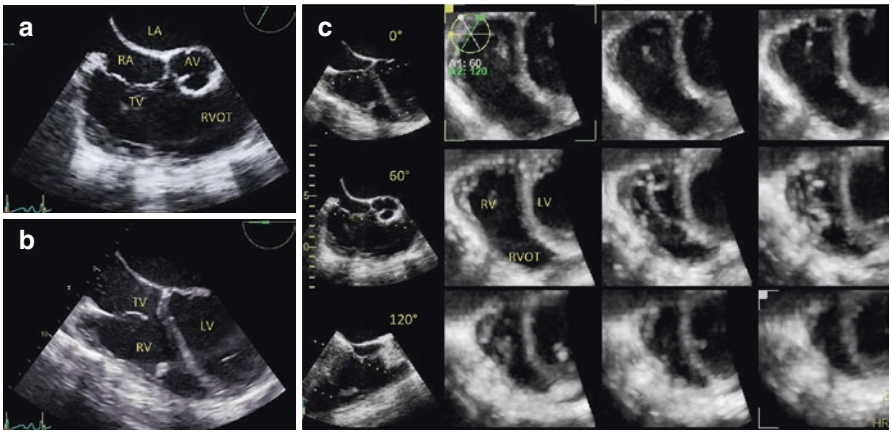

Fig. 4.2 Transesophageal echocardiographic assessment of the *RV*. (**a**) 2D echocardiographic mid-esophageal*RV* inflow-outflow view (60°) and (**b**) midesophageal four-chamber view (0°) allow to assess RV diameters, areas and wall motion. (**c**) 3D data set of the *RV* obtained from the same trans-esophageal view using full-volume multi-beat acquisition. In addition to *RV* volumetric measurements, multi (twelve)- slice mode including 3 longitudinal (0°, 60° and 120°), and 9 transversal equidistant tomographic views between the apex and the base allows for a detailed analysis of regional wall motion to be performed. *Abbreviations*: *AV* aortic valve, *LA*left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle, *RVOT* right ventricular outflow tract, *TV* – tricuspid valve

Given the complex 3D shape of the RV, some segments, such as the outflow tract (contributing up to 25–30 % of the RV volume) could be overlooked when using standard two-dimensional (2D) transthoracic echocardiography. Transesophageal echocardiography (TEE) with the midesophageal inflow-outflow view can evaluate RV outflow tract (RVOT) with a higher precision [5](Fig.4.2). TEE is essential in the peri- and intraoperative settings and allows a continuous monitoring of right heart function during non-cardiac surgery [6].The current guidelines for the 28-view comprehensive TEE examination incorporate several RV views in order to optimize its visualization depending on the clinical situation and diagnostic task [7].In case of discrepancies among the parameters of RV structure and function obtained from the different views, the interpreting physician should consider and integrate all the information contained within the echocardiographic study in order to perform a global assessment of the RV.

3DE is free from 2DE limitations and allows to assess all three structural components of the RV (inflow, outflow, and apex) in a single data set providing information on the RV geometry, volumes and function without using geometrical assumptions about RV cavity shape.

Right Ventricular Global Systolic Function

The RV ejection fraction (EF) is an independent predictor of cardiovascular morbidity and mortality in heart failure[3, 8, 9]. However, the assessment of RV EF using 2DE is no longer recommended due to its inaccuracy [5, 10]. In the absence of a

Table 4.1 Normal values for conventional echocardiographic parameters in assessing systolic function of the RV [10]

Parameter	Normal values(mean ±SD)	Abnormality threshold	Load dependence
FAC (%)	49 ± 7	<35	+++
TAPSE (mm)	24 ± 3.5	<17	+++
Pulsed Doppler RIMP	0.26 ± 0.085	>0.43	++
Tissue Doppler RIMP	0.38 ± 0.08	>0.54	++
Pulsed Tissue Doppler S′ wave (cm/sec)	14.1 ± 2.3	<9.5	+++
Color Tissue Doppler S wave (cm/sec)	9.7 ± 1.85	<6.0	+++
dP/dT (mmHg/s)	–	<400	+++

FAC fractional area change, *RIMP* right ventricular index of myocardial performance, *SD* standard deviation, *TAPSE* tricuspid annulus peak systolic velocity

single reliable measure of the RV systolic function using conventional echocardiography, a number of surrogate echocardiographic parameters have been proposed for clinical use (Table 4.1). Importantly, all echocardiographic measures of RV function are load dependent; therefore, the same measurements taken in different loading conditions can be significantly different.

Conventional 2DE Parameters

1. *RV fractional area change (FAC)*(Fig.4.3) includes both longitudinal and radial components of the RV contraction and may be considered an indirect method of estimating the RV global systolic function. It correlates well with CMR-derived RV EF [11, 12] and it is superior to other 2DE parameters [13]. Its usefulness to predict heart failure was demonstrated in patients with myocardial infarction and pulmonary hypertension [14, 15]. FAC is calculated using the following formula:

   $$RV\ FAC = (RV\ EDA - RV\ ESA)/RV\ EDA,$$

   where EDA and ESA are the RV areas obtained at end diastole and end systole in RV focused 4-chamber view.

   Both areas measurements are significantly affected by the position of the imaging planes, image quality and tracing pitfalls. Care should be taken to obtain the recommended echocardiographic view, adjust depth and gain settings. RV FAC does not take into account the RV rotation during systole that can produce both under- and over-estimation of RV pump function.
2. *Tricuspid annular plane systolic excursion (TAPSE)*(Fig.4.4) is another easily obtained parameter of RV function, and its prognostic value was shown in heart failure, myocardial infarction, pulmonary embolism, and critically ill patients [16].Data on the correlation between TAPSE and CMR-derived EF has been conflicting so far [11, 13, 17]. It is measured from the apical 4-chamber view by positioning the M-mode cursor at the lateral part of tricuspid annulus and

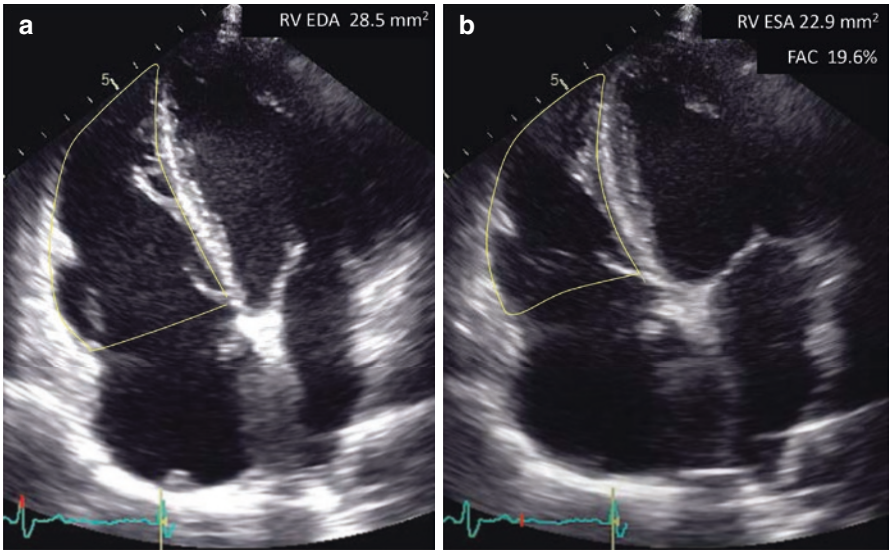

Fig. 4.3 Estimation of the RV fractional area change in a patient with RV myocardial infarction. The endocardial border is traced from the tricuspid annulus along the free wall to the apex and then back to the annulus along the interventricular septum at end-diastole (**a**) and end-systole (**b**). Trabeculation, tricuspid leaflets, and chords should be included into the cavity. Figure demonstrated dilated RV with hyperechogenic free wall and decreased systolic function. *Abbreviations*: *EDA* end-diastolic area, *ESA* end-systolic area, *FAC* fractional area change, *RV* right ventricular

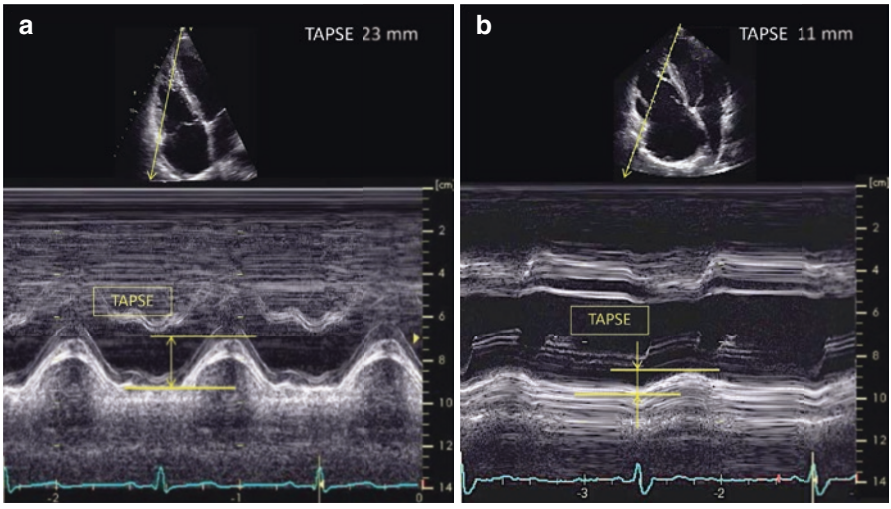

Fig. 4.4 Estimation of tricuspid annular plane systolic excursion (*TAPSE*). Panel A shows measurement of TAPSE in a patient with preserved RV systolic function, while Panel B demonstrates significantly decreased TAPSE in a patient with RVmyocardial infarction and RV failure. *Abbreviations*: *TAPSE* tricuspid annular plane systolic excursion

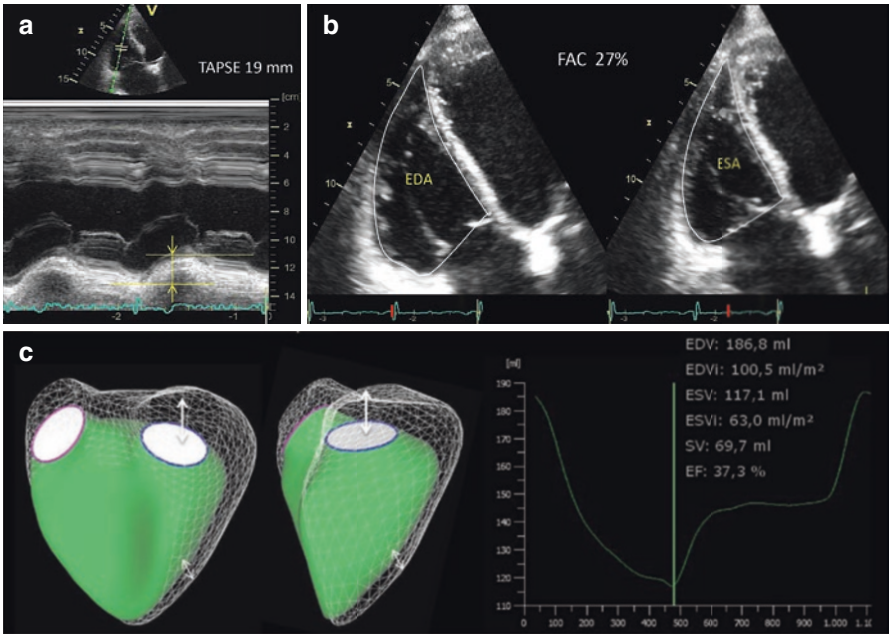

Fig. 4.5 Evaluation of RV systolic function in a patient with severe pulmonary hypertension by different echocardiographic techniques. Panel (**a**) shows normal TAPSE, while panel (**b**) shows decreased FAC, and panel (**c**) – decreased ejection fraction assessed by 3D echocardiography. Figure illustrates the possible misinterpretation of RV global systolic function if its assessment is based on a single conventional parameter. 3D reconstruction of the RV (*green models* with *white cage* representing the end-diastolic phase in panel (**c**) provides clear information that despite preserved longitudinal contraction of the basal part of RV (as demonstrated by TAPSE), other mechanisms contributing to RV pump function (displacement of the RV free wall, IVS and the RVOT) are impaired resulting in decreased global RV systolic function. *Abbreviations*: *EDA* end-diastolic area, *EDV* end-diastolic volume, *EF* ejection fraction, *ESA* end-systolic area, *ESV* end-systolic volume, *FAC* fractional area change, *SV* stroke volume, *TAPSE* tricuspid annular plane systolic excursion

measuring the distance between the lowest and highest points of the excursion curve on the M-mode tracing. Despite TAPSE is less dependent on image quality than FAC, it however requires perfect alignment of the scan line along the direction of the tricuspid lateral annulus displacement. Importantly, TAPSE represents only longitudinal function of the basal part of RV free wall and its extrapolation to the global RV function leads to disregarding the contribution of the interventricular septum, transversal displacement of the RV free wall and the RVOT(Fig.4.5). Since TAPSE is measured by M-mode using an external reference point, it is not recommended to be used for RV function assessment in longitudinal studies of patients undergoing procedures that affect the overall heart motion, such as cardiac surgery [18].

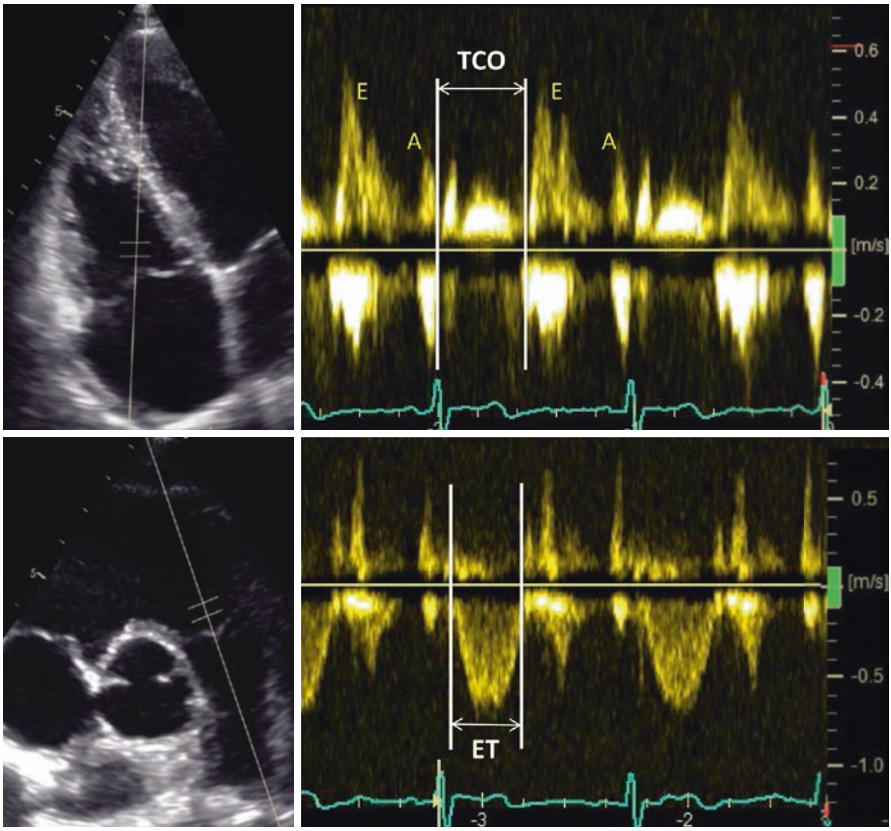

Fig. 4.6 Calculation of right ventricular myocardial performance index by pulsed wave Doppler. The tricuspid closure opening time (*TCO*) is the time interval between tricuspid valve closure and opening measured by pulsed wave Doppler of RV inflow. It encompasses isovolumic contraction time, ejection time (measured by pulsed wave Doppler of RV outflow), and isovolumic relaxation time. *Abbreviations*: *ET* ejection time, *TCO* tricuspid closure opening time

3. *RV myocardial performance index (RIMP, Tei index)* is a Doppler-derived non-geometric index of global RV function. It mainly reflects physiological rather than structural features, and correlates well with radionuclide- [19] and CMR-derived RVEF [17, 20]. RIMP is calculated as the ratio between the total RV isovolumic time (isovolumic contraction + isovolumic relaxation) and the RV ejection time using the following formula:

$$RIMP = (TCO - ET)/ET,$$

where TCO is the time interval between TV closure and opening time and ET is transpulmonary ejection time (Fig.4.6).

As these time intervals cannot be measured from the same cardiac cycle, it is important to ensure that the nonconsecutive beats have similar RR intervals (e.g. it is not feasible in patients with atrial fibrillation or with frequent ectopic beats). It also requires high quality pulsed wave Doppler tracing recorded at a sweep speed of 100 mm/s to increase the accuracy of time interval measurements. The

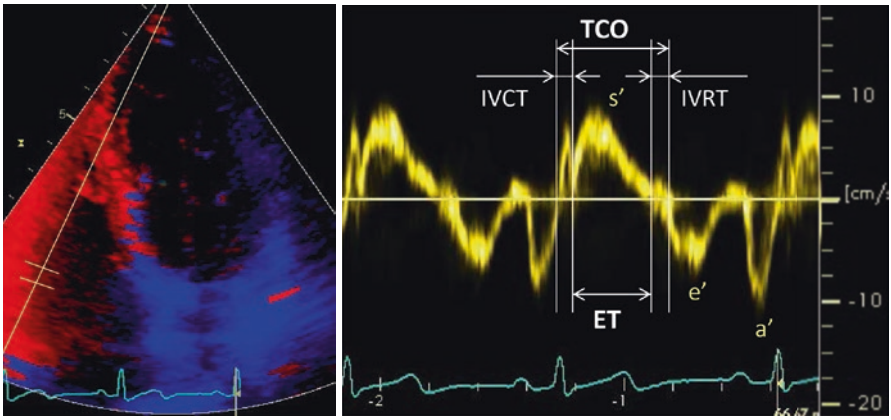

Fig. 4.7 Calculation of right ventricular myocardial performance index using tissue Doppler. It allows to measure all time intervals in the same cardiac cycle from tissue Doppler-derived myocardial velocities of the lateral tricuspid annulus. Peak systolic velocity of the lateral tricuspid annulus by tissue Doppler (s') represents additional index of RV systolic function. *Abbreviations*: *ET* ejection time, *IVCT* isovolumic contraction time, *IVRT* isovolumic relaxation time, *TCO* tricuspid closure opening time

loading dependence of the RIMP is still unclear. Moreover, RIMP is adversely affected by high heart rate and conduction disorders and, under conditions associated with elevated right atrial (RA) pressures, values obtained using this method may be false. All these limitations explain why its clinical significance is not widely recognized.The TDI-derived RIMP allows to measure isovolumic and ejection time intervals in the same cardiac cycle from tissue Doppler-derived myocardial velocities of the lateral tricuspid annulus using the following formula:

$$RIMP = (IVRT + IVCT)/ET,$$

where IVRT is isovolumic relaxation time, IVCT is isovolumic contraction time, and ET is ejection time (Fig.4.7).

TDI-derived RIMP is less dependent on cardiac rhythm and heart rate [21]. High correlation was reported between the TDI-derived and conventional Doppler RIMPs [22], however the data about the correlation of TDI-derived RIMP with CMR-derived RV EF has been controversial so far [23, 24].

4. *Peak S-wave velocity of the lateral tricuspid annulus by tissue Doppler imaging* (TDI) is another index of RV longitudinal function shown to predict global RV dysfunction [25] and closely correlated with CMR-derived RV EF [11, 17, 23]. Being TDI a Doppler method, s'-wave velocity is influenced by the angle between the ultrasonic beam and the direction of RV free wall basal segment excursion and cannot distinguish between actual myocardial velocity and heart translational motion. Peak systolic velocities obtained with pulsed TDI (s') (Fig.4.7) and color TDI (s) (Fig.4.8) are not identical. The former reflects peak myocardial velocities, whereas the latter represents mean myocardial velocities, which are usually lower.

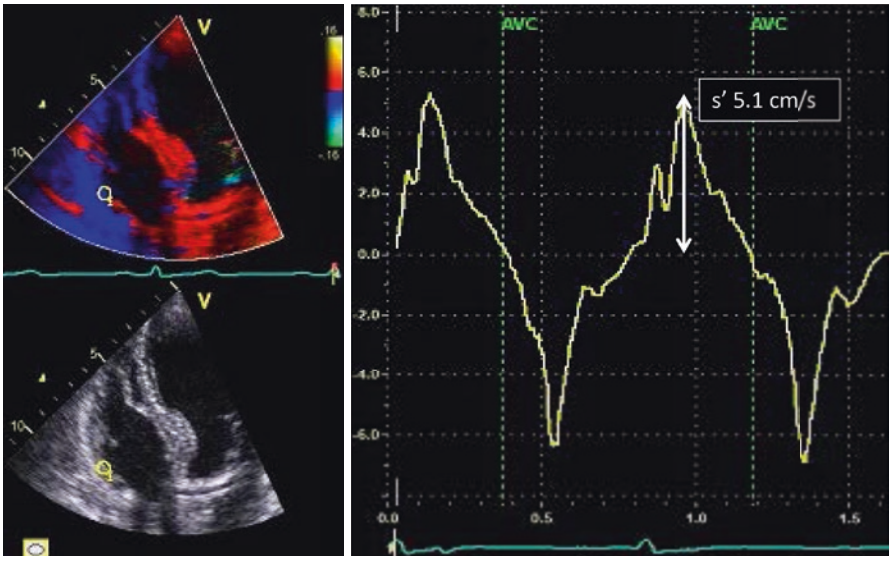

Fig. 4.8 Color-coded offline analysis of tissue Doppler imaging of the tricuspid annulus in a patient with impaired right ventricular systolic function

5. *RV dP/dt* (Fig.4.9) is a parameter of RV contractility, which expresses the rate of pressure rise in the RV. It can be estimated from the ascending slope of the tricuspid regurgitation continuous-wave Doppler tracing by measuring the time interval required for the tricuspid regurgitation jet to increase the velocity from 1 to 2 m/s (which is equal to a 12 mm Hg increase in pressure according to the simplified Bernoulli equation). The dP/dt is calculated as 12 mm Hg divided by this time interval (in seconds). However due to important limitations (load dependence, suboptimal accuracy in severe TR and non-applicability in patients with no/trace TR, lack of normative data) this method cannot be recommended for routine use [5].

3DE Assessment of the RV Systolic Function

It's worth stressing out that 3DE remains the only echocardiographic technique capable of a reliable calculation of RV EF from end-diastolic (EDV) and end-systolic volume (ESV) measurements. Unlike 2DE, 3DE allows to obtain multi-plane imaging and volumetric datasets derived from either a single beat capture or consecutive multibeat narrow angle volumes stitched together with higher temporal and spatial resolution. The 3DE dataset can be analyzed using dedicated software packages to obtain the mapping of the RV endocardial surface and measure the RV volumes (Fig.4.10). 3DE measurements of the RV EF were proved to be accurate, reproducible and correlated well with CMR both in adults and children [26–29]. In the most recent meta-analysis aimed to explore the accuracy of different imaging

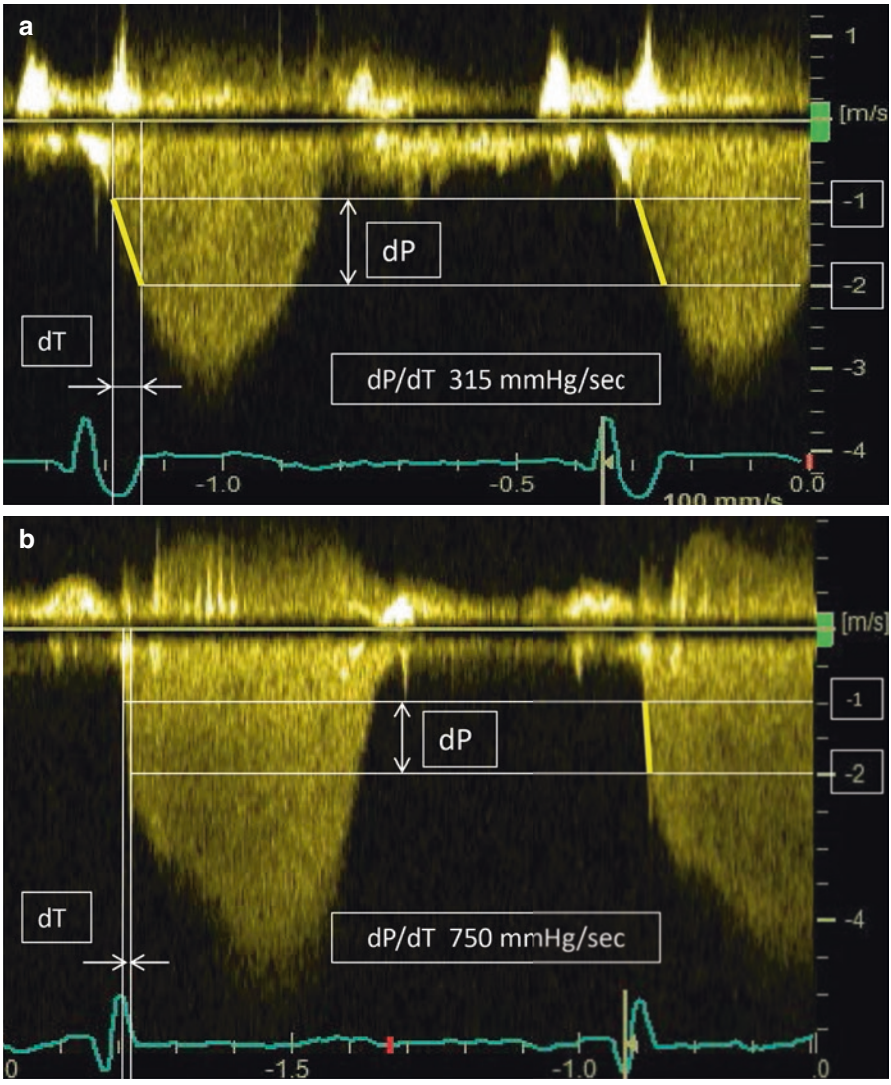

Fig. 4.9 Calculation of dP/dT in a patient with normal RV systolic function (**a**) and a patient with pulmonary hypertension and systolic dysfunction of the RV (**b**). Yellow line represents the time required for the tricuspid regurgitant jet to increase from 1 to 2 m/s. It is gently sloping in normal RV function and almost vertical in failing RV

modalities (2DE, 3DE, radionuclide ventriculography, CT, gated single-photon emission CT, and invasive cardiac cineventriculography) for RV EF using CMR as reference method, 3DE has proven to be the most reliable technique, overestimating the RV EF only by 1.16 % with the lowest limits of agreement (form −0.59 to 2.92 %) [30]. Importantly, due to the architecture of the RV, RV EF is particularly sensitive to RV loading conditions and cannot be considered a reliable parameter of

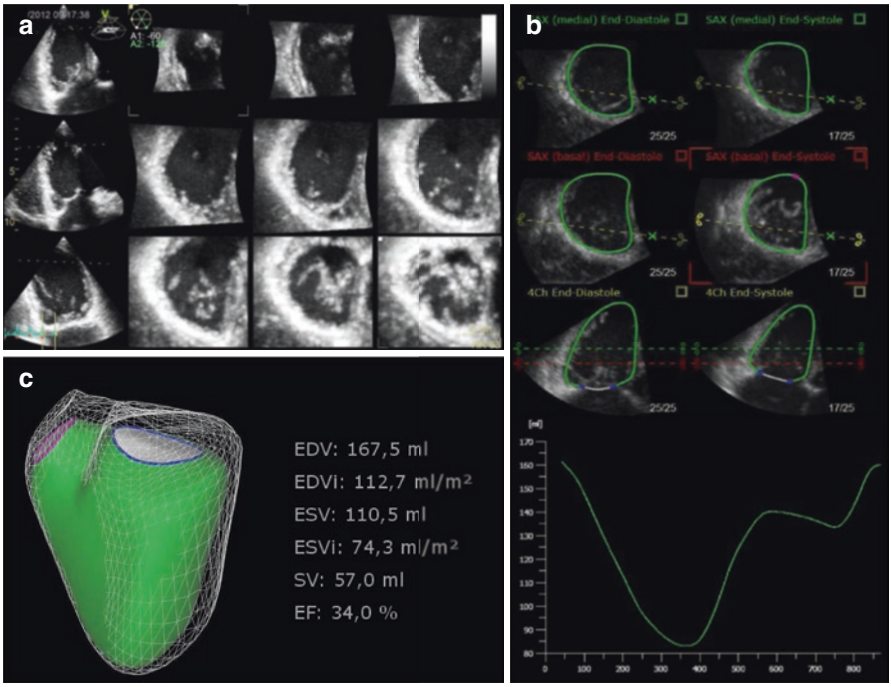

Fig. 4.10 Display modes of a 3D data set of the right ventricular obtained from the RV-focused apical 4-chamber view using full-volume multi-beat acquisition (four to six consecutive beats). (**a**) Multi (twelve)- slice mode including 3 longitudinal (0°, 60° and 120°), and 9 transversal equidistant tomographic views between the apex and the base of the RV; (**b**) Semiautomatic identification of the RV endocardial surface in the right ventricular short-axis and four-chamber views at end-diastole and end-systole; (**c**) Surface rendered three-dimensional model of the right ventricle (*green model*) combining the wire-frame (*white cage*) display of the end-diastolic volume. Surface rendered dynamic model changes its size and shape throughout the cardiac cycle enabling the visual assessment of the RV dynamics and quantitation of RV volumes and ejection fraction. *Abbreviations*: *EDV* end-diastolic volume, *EF* ejection fraction, *ESV* end-systolic volume, *SV* stroke volume

RV myocardial contractility in patients with significant RV volume- or pressure overload.

Normative data for 3DE RV volumes and EF including age-, body size-, and sex-specific reference values based on large cohort studies of healthy volunteers has recently become available (Table 4.2) [31, 32]. Although 3DE quantification of the RV volumes and EF requires certain level of expertize, in laboratories with appropriate 3D platforms and experience 3DE-derived RV volumes and EF should be considered a method of choice for quantifying RV systolic function, with the EF abnormality threshold <45 % [10].

3DE, however, has specific limitations. 3D volumetric analysis of the RV is highly dependent on image quality especially at the step of identification of the endocardial surface in coronal view required by existing software packages. An

Table 4.2 Principal studies of 3DE reference values for the RV volumes and EF in adult healthy volunteers

	Maffessanti (2013) [32]		Tamborini (2010) [31]	
Population size	507 (247 male)		245 (119 male)	
Population type	Healthy adult volunteers		Healthy adult volunteers	
Age	45 ± 16		48 ± 17	
	Male	Female	Male	Female
EDV (ml)	107 (74, 163)	81 (58, 120)	99 ± 14	74 ± 14
EDVi (ml/m^2)			52 ± 8	46 ± 8
ESV (ml)	44 (22, 80)	30 (15, 52)	35 ± 7	23 ± 7
ESVi (ml/m^2)			18 ± 4	14 ± 4
EF (%)	60 (45, 75)	63 (49, 79)	64 ± 8	69 ± 8
Studies' limitations	• No comparison between RV parameters obtained by 3DE and CMR.			
	• The RV values in patients ≥70 years (males in particular) should be interpreted with caution, given the small size of this age group.			

Data are expressed as mean± SD or median (5th, 95th percentile)
3DE three-dimensional echocardiography, *CMR* cardiac magnetic resonance, *EDV* end-diastolic volume, *EDVi* index of end-diastolic volume, *EF* ejection fraction, *ESV* end-systolic volume, *ESVi* index of end-systolic volume, *RV* right ventricle

advanced software for RV volumes analysis, eliminating the need for extraction of coronal views from 3D data set, was recently implemented [33]. It proved to be fast and highly reproducible on a large cohort of patients with different RV size and function, and its results correlate well with the CMR [34, 35].

Other important limitations of 3DE are the possible dropout of the RV anterior wall, incomplete inclusion of the whole RV in the pyramidal data set in case of severe dilation, need for a regular heart rate and patients' cooperation. Nevertheless, specific advantages of 3DE over other modern imaging modalities including its portability, absence of ionizing radiation, and the ability to examine patients with pacemakers and defibrillators make the technique one of the most versatile and important modality to assess the RV.

Right Ventricular Regional Systolic Function

Evaluation of the RV walls' structure and motion is clinically important since some pathological conditions are characterized by specific patterns of RV regional contraction. Localized RV dyskinesia or aneurysm is an important diagnostic criterion for arrythmogenic RV cardiomyopathy (Fig.4.11) [35]. Hypokinesia of the RV free wall combined with the normal contraction of the RV apex (McConnell sign) in the presence of RV pressure overload is a typical finding in patients with acute pulmonary embolism [36]. RV wall motion abnormalities could be also seen in patients with RV myocardial infarction, chronic pulmonary hypertension, sarcoidosis and congenital heart disease. Although clinically important, imaging the RV wall

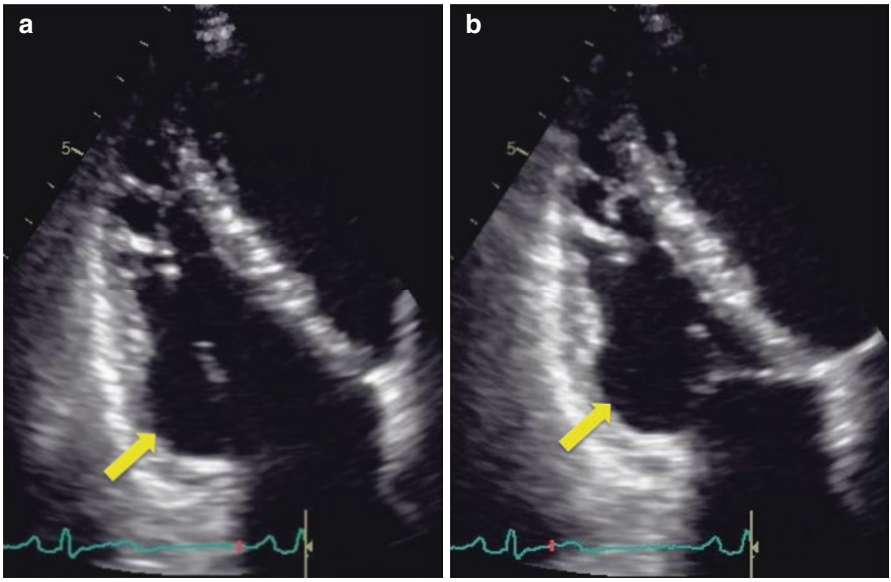

Fig. 4.11 Localized deformation of the basal segment of the RV lateral wall (*arrow*) seen in the apical RV-focused 4-chamber view both in diastole (**a**) and systole (**b**) due to RV aneurysm in a patient with arrhythmogenic RV cardiomyopathy

motion remains challenging because of its myocardial fiber orientation, complex anatomy that prevents the visualization of the same segments from orthogonal views, thin myocardial wall and peculiar myocardial mechanics. RV wall motion and shape sometimes is interpreted in a way similar to LV counterpart, which may be misleading: while the LV is symmetric and ellipsoidal, the geometry of the RV is complex; tethering of the freewall by the moderator band and a nonlinear shape of the RV significantly contribute to a lack of understanding of the normal and pathological RV wall motion patterns [37]. Furthermore, identification of wall motion abnormalities only on the basis of visual echocardiographic assessment may be inaccurate [4].

RV Diastolic Function

During acute RV pressure overload, RV diastolic function is not affected.Conversely, chronic RV pressure overload impacts RV diastolic dysfunction, resulting in prolonged diastolic relaxation time and increased RV diastolic stiffness [38]. The assessment of RV diastolic function includes the evaluation of the RV inflow by pulsed wave Doppler sampling at the tips of the tricuspid valve leaflets; measuring the TDI velocities of the tricuspid annulus at RV free wall; evaluation of right atrial, inferior vena cava and hepatic vein size and function (Fig.4.12). Although preload-dependent, the tricuspid E/e' ratio is a good marker of RV diastolic dysfunction in

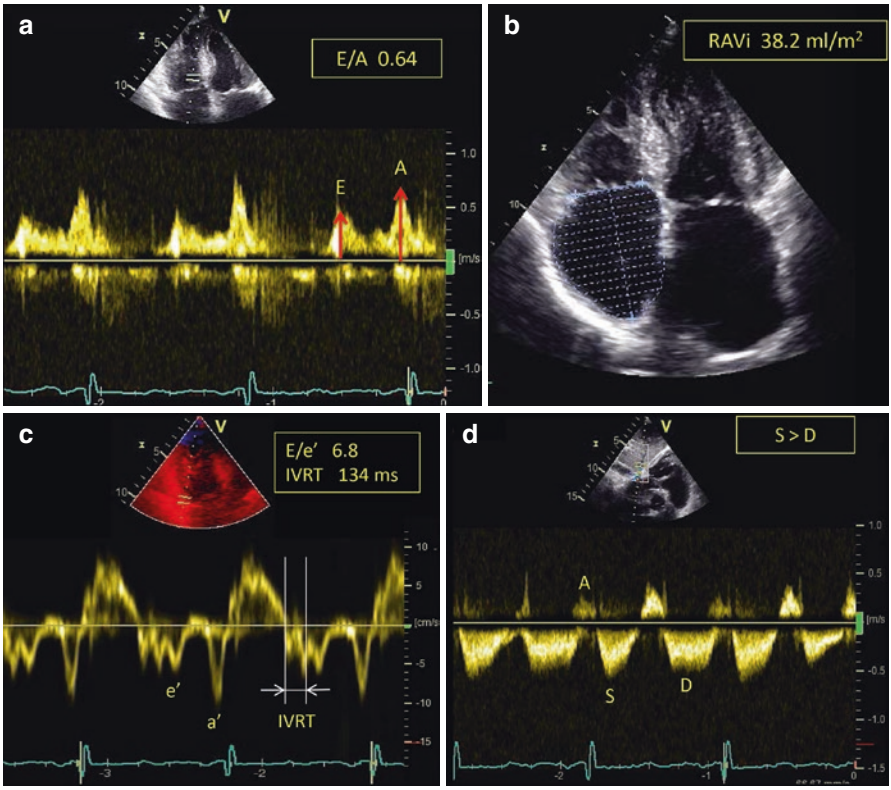

Fig. 4.12 Assessment of RV diastolic function in a patient with secondary pulmonary hypertension. Panel (**a**) shows measurement of tricuspid E/A in apical 4-chamber view. Doppler beam-should be aligned parallel to the RV inflow with the sample volume placed at the tips of the tricuspid valve leaflets. Acquisition should be performed at end-expiration. Panel (**b**) shows dilatation of the RA as assessed by single-plane area-length technique in apical four-chamber view. Tracing is performed from the plane of the tricuspid annulus, along the interatrial septum, superior and anterolateral walls of the RA. Panel (**c**) demonstrates tissue pulsed wave Doppler of the tricuspid annulus and calculation of E/e' ratio. Panel (**d**) shows assessment of hepatic vein flow pattern. Tricuspid E/A<0.8, E/e'>6, dilated RA, IVRV >75 ms and normal systolic flow predominance in the hepatic veins suggests impaired relaxation. *Abbreviations*: *IVRT* isovolumic relaxation time, *RAVi* index of right ventricular volume

pulmonary hypertension and an indicator of RV filling pressure; E/e' values >6 have a sensitivity of 79 % and a specificity of 73 % for the detection of right atrial pressure >10 mmHg.The following grading of RV diastolic dysfunction had been suggested: tricuspid E/A <0.8 suggests impaired relaxation, a tricuspid E/A of 0.8–2.1 with an E/e' >6 or diastolic flow predominance in the hepatic veins suggests pseudonormal filling, and a tricuspid E/A >2.1 with a deceleration time <120 ms suggests restrictive filling [5]. RV isovolumic relaxation time>75 ms can be used as additional sign of the RV diastolic dysfunction[39](Fig.4.12c). It has been shown to correlate well with pulmonary arterial systolic pressure [25] and may be particularly important if the tricuspid inflow Doppler signal is poor.

The data about the impact of RV diastolic dysfunction on patient's outcome are scarce. It was demonstrated that patients with left-sided heart failure and RV diastolic dysfunction defined by abnormal filling profiles have an increased risk of unstable angina and hospital readmissions due to heart failure deterioration [40].

Right Ventricular Mechanics

Being extremely load dependent, RV EF is a partial indicator of the RV systolic dysfunction. Myocardial deformation imaging is a relatively novel echocardiographic technique that allows the evaluation of RV myocardial mechanics. The clinical and prognostic value of the RV strain was demonstrated in patients with heart failure, LV assist devices, pulmonary hypertension, congenital heart diseases, storage diseases, and cardiomyopathies with high risk of malignant ventricular arrhythmias [41–45]. Echocardiographic assessment of RV myocardial deformation can be performed using either TDI or 2DSTE techniques (Fig.4.13). The correlation between TDI and 2DSTE-derived RV longitudinal strain appears to be moderate, however both techniques are considered feasible and accurate enough to differentiate between physiological and pathological conditions [46].

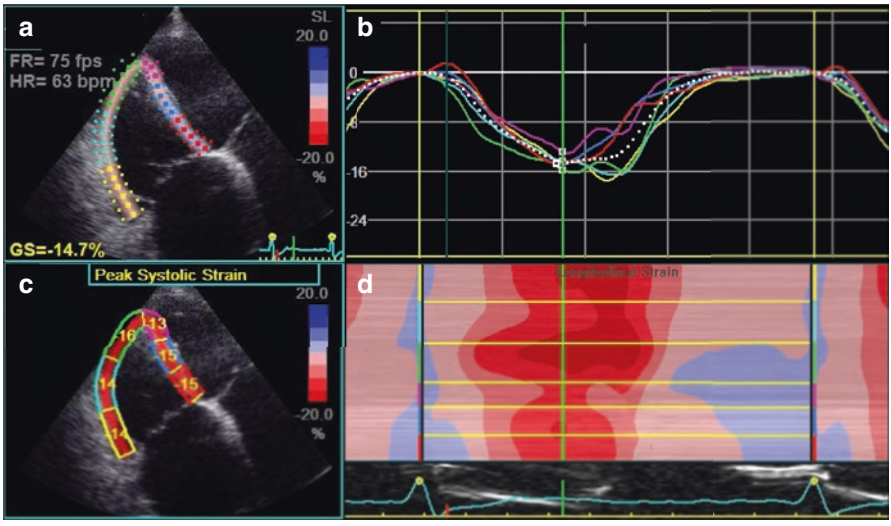

Fig. 4.13 Peak systolic longitudinal strain of the RV free wall and interventricular septum obtained with two-dimensional speckle tracking analysis. Panel (**a**) shows parametric color-coded display of end-systolic strain. Panel (**b**) demonstrates regional end-systolic strain. Panel (**c**) shows strain-time curves. Colored curves show the segmental strain change during the cardiac cycle, and white dotted line shows the global RV strain changes during the cardiac cycle. Panel (**d**) represents the anatomical M-mode color-coded display of segmental strain variations during the cardiac cycle. Figure illustrates decreased RV global longitudinal strain in a patient with pulmonary hypertension and RV failure. *Abbreviations*: *FR* frame rate, *HR* heart rate, *LS* longitudinal strain

Although TDI strain does not rely on specific geometrical assumptions, several technical issues, including angle-dependence of the Doppler technique, thin myocardial wall with large systolic longitudinal and transversal excursion, high frame rate and drifting of the strain curve, as well as influence of age and heart rate significantly affect the accuracy and reproducibility of strain and strain rate measurements with TDI. Conversely, 2DSTE is a relatively angle-independent technique. However, it relies on the image quality more than TDI. Both techniques are mostly limited to the apical 4-chamber view and evaluate only RV longitudinal myocardial deformation.

The normative data for the RV strain were mostly obtained from small cohorts of adults representing the control groups in pathologic studies [5]. In the most up-to-date version of the chamber quantification guidelines an abnormality threshold for the RV free-wall longitudinal strain was set at −20 % [10]. In the prospective study performed on 116 subjects free from cardiopulmonary disease and/or risk factors mean free wall longitudinal systolic RV strain value was −26 ± 4 %, which is in agreement with the value of −27 ± 2 % obtained in meta-analysis of 10 studies involving 486 healthy individuals [47]. The most recent prospective study of 276 healthy volunteers provided sex- and method-specific reference values for RV longitudinal strain, demonstrating that free wall RV strain was 5 ± 2 % larger in magnitude than 6-segment RV strain, and 2 ± 4 % larger in women than in men [48]. 2DSTE parameters were also studied in healthy children [49] and athletes [50].

There is a need in normative values of longitudinal strain for separate segments of the RV, as the information on regional strain impairment may play an important role in diagnosis of specific RV pathology, such as arrhytomogenic RV cardiomyopathy. In addition to the lack of reference values, the major limitations of 2DSTE longitudinal strain of the RV include the loss of speckles due to excessive motion of RV lateral wall, intervendor variability, and the lack of standardization in the measurement and reporting of strain parameters [47, 51].

Although "global" RV longitudinal strain is supposed to represent the longitudinal deformation of the whole RV, none of 2DE algorithms is capable of providing such information. The term "global" RV longitudinal strain is commonly used for an average values calculated from 3 segments of the RV free wall and 3 segments of the interventricular septum (IVS) from apical 4-chamber view. It is worth noting that in fact it describes only the deformation pattern of the RV lateral wall and IVS regardless of the contribution of other walls and RVOT. Lack of agreement on defining the target point where the RV longitudinal strain should be measured (the mean strain measured on the average strain curve of all segments or the peak systolic strain calculated by averaging the peak segmental values) constitute another important technical issue which may affect the results of RV strain calculation. In a recent study of healthy individuals authors recommend to use a 6-segment approach on the apical 4-chamber RV-focused view as a more robust analysis method, and to compute the RV free wall longitudinal strain by averaging the peak segmental values displayed by the software [48]. Reference values for RV strain with and without including the IVS are listed in Table 4.3.

Table 4.3 Reference values of the RV longitudinal strain in the overall study population and separated by gender [48]

Strain parameters		Overall	Men	Women	p-value[a]
Global6-seg RVLS	Average (%)	−25.7 [−23.5; −28.1]	−24.5 [−22.6; −26.3]	−26.6 [−24.5; −28.5]	<0.001
Free wall3-seg RVLS	Average (%)	−30.6 [−27.7; −33.0]	−29.3 [−27.0; −31.9]	−31.8 [−29.3; −33.9]	<0.001
	Basal (%)	−30.0 [−26.0; −35.0][b]	−28.0 [−25.0; −33.0][b]	−31.0 [−27.0; −37.0][b]	0.002
	Mid (%)	−34.0 [−30.0; −37.8]	−32.0 [−29.0; −35.0]	−35.0 [−32.0; −40.0]	0.001
	Apex (%)	−28.5 [−25.0; −32.0][b]	−27.0 [−25.0; −30.0][b]	−30.0 [−26.0; −33.0][b]	<0.001
Septal3-seg RVLS	Average (%)	−20.0 [−18.0, −22.0]	−19.0 [−17.3; −21.7]	−20.3 [−18.9; −22.4]	0.012
	Basal (%)	−20.0 [−18.0; −22.0][b]	−19.0 [−17.0; −22.0][b]	−20.0 [−18.0; −23.0][b]	0.002
	Mid (%)	−20.0 [−19.0; −22.0]	−20.0 [−18.0; −22.0]	−21.0 [−19.0; −23.0]	0.001
	Apex (%)	−20.0 [−17.00; −23.0][b]	−19.0 [−15.0; −23.0][b]	−20.0 [−17.0; −24.0][b]	0.017

Data represent median [I, III quartile]
RVLS right ventricular longitudinal strain,*seg* segments
[a]Men vs. women
[b]$p < 0.05$ for mid vs basal or mid vs apex

The determination of circumferential shortening requires short-axis views of RV, which are hardly obtainable by 2DE, and data on its potential role in clinical management is limited. The possibility of obtaining the RV free wall circumferential strain from the subcostal LV short-axis view was demonstrated in a group of children with RV pressure overload. It provided better information about RV function, and significantly higher correlated with RV EF and RV systolic pressure, obtained by cardiac catheterization, than global RV longitudinal strain [52].

The development of 3DE enabled the echocardiographic assessment of RV mechanics in various directions (i.e. longitudinal, circumferential and area strain, a combination of longitudinal and circumferential shortening), similar to CMR, however the data on inter- and intra-observer reproducibility has been conflicting so far [53, 54], and even if good reproducibility for all the dimensions of 3D strains was demonstrated (correlation coefficients 0.7–0.9), the absolute error widely varied depending on the examined RV wall (from 12 to 44 %) [54]. In pulmonary hypertension patients significant correlation with RV EF was demonstrated for 3D global longitudinal strain of whole RV and of the RV free wall only [55], and for area strain [56]; importantly, the latter was a strong independent predictor of death, suggesting the superiority of 3DE–derived area strain over the other deformation parameters [56]. Whether 3DE-derived strain has an added value in routine assessment of RV remains unclear, given the fact that only small populations have been investigated to date and normal values are yet to be established.

RV Dyssynchrony

In addition to quantification of regional RV systolic function and myocardial mechanics, strain and strain-rate can be used for the assessment of RV dyssynchrony, a new promising approach to evaluation of the RV dysfunction in patients with different cardiac conditions. Interventricular and RV intraventricular dyssynchrony have been described in pulmonary artery hypertension showing strong correlation of RV dyssynchrony indexes with the extent of RV dysfunction, pulmonary artery pressure and adverse RV remodeling [57, 58]. Due to the RV complex geometry the assessment of its dyssynchrony is only feasible by measuring IVS –RV free wall delay obtained by TDI or 2DSTE algorithms (Fig.4.14). The cut-off values to identify RV intraventricular dyssynchrony were described in a small cohort of healthy individuals representing the control group [59] and calculated as the standard deviation of the time to peak-systolic strain for the mid and basal RV segments corrected to the R-R interval. Using the upper 95 % limit of normal range a cutoff value of 18 ms was introduced as a criterion for RV dyssynchrony [59]. RV dyssynchrony was also demonstrated being an independent predictor of unfavorable prognosis in patients with pulmonary hypertension. Moreover, RV dyssynchrony might regress as a result of effective therapy. For better understanding of the role of RV dyssynchrony as a biomarker of treatment success and predictor of survival these findings should be confirmed in larger studies.

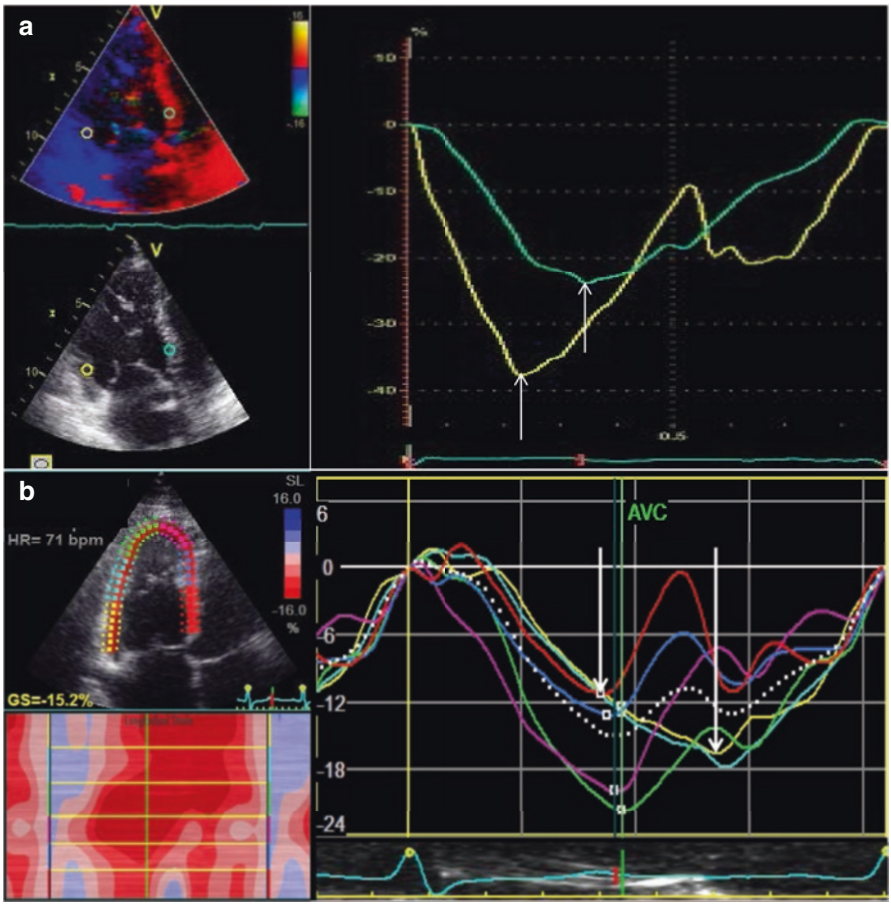

Fig. 4.14 Measurement of the right ventricular dyssynchrony. (**a**) Tissue Doppler pulsed wave Doppler algorithm for assessment of RV dyssynchrony based on the difference between time-to-peak strain of the basal segments of IVS and free wall of the RV in apical 4-chamber view (*arrows* indicate peak systolic strain). (**b**) Peak systolic longitudinal strain of the RV free wall and IVS obtained with 2DSTE. The colored lines represent the time-interval between QRS onset and peak systolic strain for each RV segment for dyssynchrony measurement. *Arrows* indicate the peak systolic strain of basal lateral (*yellow curve*) and basal septal (*red curve*) segments

Cardiac Magnetic Resonance

RV Global Systolic Function

Before the introduction of 3DE, CMR and CT have been the only imaging modalities capable of providing accurate morphological and functional evaluation of the RV. Notably, CMR does not provide real 3D full-volume images, and the demarcation of the RVOT for this modality depends only on a single coronal view.

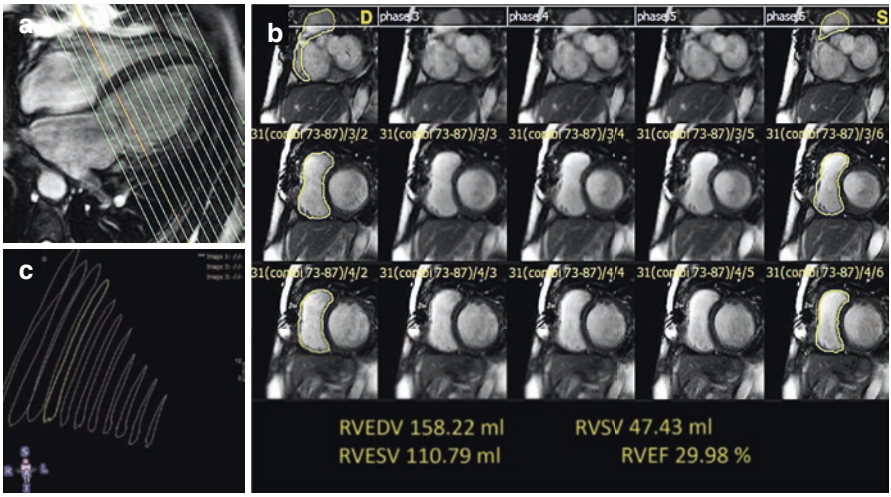

Fig. 4.15 Assessment of the RV volumes and ejection fraction in a patient with secondary RV dysfunction using steady-state free precession sequence. (**a**) Acquisition of a set of 12 adjacent slices on a vertical long-axis four-chamber view. (**b**) Tracing of endocardial contour (*yellow line*) of the RV in the end-systole and end-diastole. (**c**) Three-dimensional reconstruction of the RV shape using disc summation method (Courtesy of Dr. Chiara Bucciarelli-Ducci). *Abbreviations*: *RVEDV* right ventricular end-diastolic volume, *RVEF* right ventricular ejection fraction, *RVESV* right ventricular end-systolic volume, *RVSV* right ventricular stroke volume

However, due to its unlimited imaging planes and superior spatial resolution, CMR is currently considered the "gold standard" for RV morphological and quantitative assessment [4].

Evaluation of the RV is usually performed with T1-weighted black-blood turbo spin-echo sequence or with the steady-state free precession sequence (SSFP). Detailed description of the intra- and extracardiac anatomy can be achieved by 3D rendering techniques Short-axis or axial SSFP images and the discs summation method are used for calculation of RV volumes and EF (Fig.4.15). Normal age- and gender-specific values for RV volumes and EF are available for both the adult and the pediatric population (Table 4.4) [60–63]. Provided adequate standardization, CMR measurements show high reproducibility with interobserver variability <7 % for the EDV, <14 % for the ESV, and <7 % for the RVEF [4, 61].

Identification of the RV boundaries near the RVOT and correct position of the basal tomographic plane are the main issues with the accurate quantification of RV volumes by CMR [27].

RV Regional Systolic Function

CMR provides a more accurate evaluation of RV segmental function than visual echocardiographic assessment. In addition to better qualitative characterization due to its high spatial resolution, regional dysfunction can be assessed quantitatively by

Table 4.4 Principal studies of CMR and CT reference values for the RV volumes and EF in individuals with no history of cardiovascular diseases

Imaging modality	CMR						CT
Study	Sarikouch (2010) [62]		Buechel (2009) [61]		Maceira (2006) [60]		Lin (2008) [77]
Population size	114 (55 male)		50 (23 male)		120 (60 male)		103 (59 male)
Population type	Healthy children and adult volunteers (not older than 20 years)		Children with orthopedic disorders and no history of cardiovascular diseases		Healthy adult volunteers		Normotensive adults with no history of cardiovascular diseases
Age	12.4 ± 4.1		11 (0.7–18)[a]		20–79[c]		51 ± 14
	Male	Female	Male	Female	Male	Female	All
EDV (ml)			83.8 ± 0.0499[b]	72.7 ± 0.0499[b]	163 ± 25	126 ± 21	174.9 ± 48.0
EDVi(ml/m^2)	84.5 ± 12.7	76.9 ± 12.7			83 ± 12	73 ± 9	93.3 ± 20.3
ESV (ml)			35.3 ± 0.0737[b]	30.2 ± 0.0737[b]	57 ± 15	43 ± 13	82.1 ± 29.2
ESVi (ml/m^2)	32.5 ± 6.4	28.6 ± 5.4			29 ± 7	25 ± 7	
EF (%)	61.6 ± 4.5	62.8 ± 4.3			66 ± 6	66 ± 6	57.9 ± 8.0
Study limitations	Small cohort size		Small cohort size 14 children were examined under sedation and the images were acquired while freely breathing, that compromised the image quality		N/A		No comparison between RV parameters obtained by CT and CMR

Data are expressed as mean± SD or median (5th, 95th percentile) unless stated otherwise

CMR cardiac magnetic resonance, *CT* computed tomography, *EDV* end-diastolic volume, *EDVi* index of end-diastolic volume, *EF* ejection fraction, *ESV* end-systolic volume, *ESVi* index of end-systolic volume, *RV* right ventricle

[a]Median (range)

[b]Logarifmic SD

[c]Range

using myocardial tagging or strain encoding CMR; both methods have been shown to correlate well with echocardiographic data [64, 65]. However, feasibility of these techniques is limited due to the thin wall of the RV and need of extensive image postprocessing [66]. Furthermore, unlike LV, the normal CMR pattern of RV wall motion remains to be fully documented [67]. A recent study involving 65 healthy individuals demonstrated the presence of regional hypokinesia, dyskinesia in the apicolateral and mediolateral segments of RV detected by CMR in 92 % of the study subjects and the involvement of two or more segments in 60 % of them [37]. These findings should be taken into account since RV dyskinesia or aneurysm are major diagnostic criterion for arrhythmogenic right ventricular cardiomyopathy, which can be mimicked by either common diseases or even normal variants in healthy individuals [37]. The clinical consequences of misinterpretation of the RV wall motion abnormalities by CMR have been documented [68].

RV Myocardial Mechanics

CMR was the first method to provide a multidirectional RV strain assessment, including area strain. The reduction of the CMR-derived RV longitudinal strain at the basal, mid, and apical levels, and radial deformation at the midventricular level was demonstrated in patients with pulmonary hypertension [69]. In patients with arrhythmogenicRV cardiomyopathy, CMR-derived strain analysis has been reported to be an objective and reproducible parameter to quantitate wall motion abnormalities, and it allowed to differentiate between manifest or borderline disease and healthy individuals, despite a normal RV EF [70]. Khalaf et al. demonstrated that RV circumferential strain obtained by CMR can be a parameter of interventricular interactions showing a good agreement with LV EF and segmental deformation in patients with repaired tetralogy of Fallot [71]. However, the main problems of this method lie in large intervendor variability, and lack of reference values.

Computed Tomography

Multidetector cardiac CT provides an accurate and reproducible assessment of the RV volumes and EF demonstrating good agreement with CMR [72] and nuclear techniques [73]. It can be considered a reliable alternative for patients with limited acoustic window and who are not suitable for CMR (such as patients with pacemaker, incompatible prosthetic material and claustrophobia) (Fig.4.16). Recent meta-analysis showed that CT was the second most accurate imaging modality, after 3DE, to assess RVEF with a slight overestimation of CMR measurements by 4.67 %, with 95 % limits of agreement ranging from −3.71 to 5.62 % [30].

This modality, however, cannot be used for the routine assessment of the RV due to the significant radiation exposure and the use of potentially nephrotoxic contrast

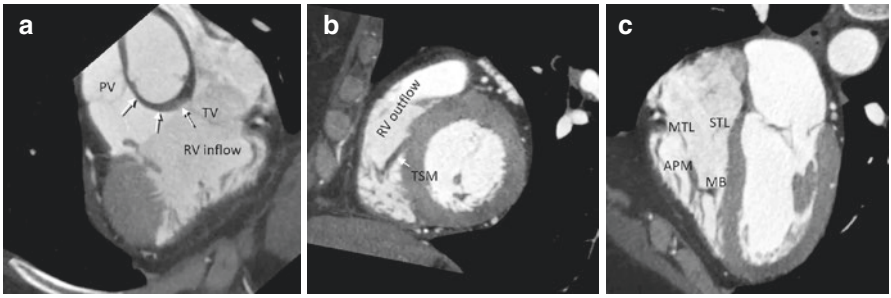

Fig. 4.16 Detailed assessment of the RV morphology using multidetector computed tomography. (**a**) RV inflow tract and the ventriculo-infundibular fold (*arrows*) which separates the pulmonary valve from the tricuspid valve; (**b**) RV outflow tract and the trabecula septomarginalis; (**c**) a four-chamber view with septal tricuspid leaflet, mural tricuspid leaflet and moderator band connected with the anterior papillary muscle(Courtesy of Dr. Francesco Faletra). Abbreviations: *APM* anterior papillary muscle, *MB* moderator band, *PA* pulmonary artery, *PV* pulmonary valve, *RV* right ventricle, *TSM* trabecula septomarginalis, *TV* tricuspid valve

agents [74]. CT also has a limited use in heart failure patients with tachycardia, as beta-blockers need to be administered for optimizing image acquisition (Table 4.1) [75].

Besides RV volumes and EF standard morphological evaluation of the RV by CT includes RV free wall thickness, as well as the diameters of the systemic veins and pulmonary arteries, and it is usually indicated when concomitant pulmonary circulation disorders, such as pulmonary embolism, are suspected [4, 74–76]. Accordingly, the RV parameters obtained by CT have mainly been validated in patients with pulmonary hypertension [76].

Normal values for RV volumes and EF estimated by CT are available (Table 4.4) [77]. In spite of a good correlation between RV volumes obtained using CT and CMR, CT has lower temporal resolution compared to CMR and tends to overestimate RV volumes [12, 72]. In addition, observed variations in RV volumes may be partially explained by the different respiratory phase at which data acquisition is performed (end-inspiration for CT and end-expiration for CMR). Since the venous return to the RV increases during inspiration, both EDV and ESV enlarge, while the EF remains unchanged [74]. This fact necessitates the need in technique-specific reference values (Table 4.4).

Nuclear Imaging

Radionuclide techniques have been the first imaging modality used for assessing RV volumes and global systolic function. However, earlier radionuclide modalities such as first-pass radionuclide ventriculography had severe limitations for RV

size assessment and they have been largely replaced by safer and more feasible CMR and echocardiography. Gated blood-pool single photon emission computed tomography (SPECT), being a 3D technique, may be able to provide a reliable RV volumetric and functional data but the evidence has been so far controversial [78, 79]. In one small study, a significant correlation between RV volumes assessed by gated blood-pool SPECT and CMR ($r = 0.82$ for both EDV and ESV; $p < 0.001$) with large limits of agreement (−44 to 22 ml for EDV, −25 to 21 ml for ESV, and −15 to 8 % for EF) was demonstrated [78]. Another study showed a significant RV volume underestimation and RV EF overestimation as the biventricular volumetric ratio decreased ($r = 0.61$ for RV EDV, 0.68 for RV ESV, and −0.55 for EF; $p < 0.001$) [79]. Accordingly, and in the absence of larger validation studies, gated SPECT derived RV volumes and EF should be interpreted with caution.

Metabolic imaging and tracing of RV myocardial oxygen consumption may help in understanding the mechanisms and extent of the pathological processes affecting RV myocardium. There are only limited and fairly controversial data on the utility of SPECT to measure myocardial fatty acid uptake [80], positron emission tomography with different isotopes for detecting myocardial glucose metabolism [81] and myocardial oxygen demand [82] in patients with pulmonary hypertension. Further investigations are needed to establish the pathophysiological pathways of myocardial diseases, enable its longitudinal monitoring and potentially identify new therapeutic tools [83].

Conclusions

RV function and mechanics have proven to be important indicators of overall cardiac function in heart failure patients and strong predictors of cardiovascular morbidity and mortality. Recent developments in the imaging techniques, including 3DE and 2DSTE opened new exciting opportunities in RV imaging. 3DE has proven accurate in measuring RV volumes and EF when compared with CMR, which is still considered the "gold standard" for RV assessment, while 2DSTE plays a critical role in measuring RV myocardial deformation, which is a powerful predictor of patients' functional capacity and survival. Cardiac computed tomography provides an accurate and reproducible assessment of the RV volumes and can be considered a reliable alternative for patients who are not suitable for echocardiography or CMR. Combined results and collective evidence generated using different imaging techniques will provide deeper insight into the pathology of the RV, translating into more accurate reproducible and safe assessment of the RV performance and better clinical management of heart failure patients.

Future Directions

Specific anatomical and functional features of the RV present challenges for modern imaging modalities and therefore a concept of multimodality assessment of RV compensating the limitations of individual techniques is currently seen as an optimal choice in a wide range of clinical settings. Technical advances combined with the further development of data capturing and its analysis may transform a current concept into utilizing a fusion imaging technique for a comprehensive evaluation of RV in a variety of clinical settings and conditions which will be an exciting step forward in the clinical management of cardiac patients.

At some point the use of multimodality imaging may compensate the limitations of different technics, but it still includes several unsolved issues. In particular, further investigations will be needed to establish correct ways of the RV global systolic function assessment. Being load dependent, the RVEF cannot be considered ideal parameter of systolic function in patients with different loading conditions (significant tricuspid regurgitation, pulmonary embolism etc). Certain widely used surrogate parameters of the RV systolic function are limited to specific cohorts of patients and cannot correctly assess it in conditions affecting the whole heart motion (e.g. after cardiac surgery or heart transplantation).

The normal pattern of the RV contraction is not fully understood. Due to a variety of mechanisms contributing to RV pump function and varying degree of their involvement in (patho-) physiological conditions, a future imaging modality should be capable of assessing the relative contributions of these three mechanisms.

The ideal parameters of RV diastolic function are also yet to be defined. Reference values obtained on large cohorts of healthy volunteers will be crucial for a correct interpretation of an integral modality data.

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Chapter 5
The Role of Atrial Functional Assessment in Heart Failure

Matteo Cameli and Francesca Maria Righini

Abbreviations

AF	Atrial fibrillation
CT	Computed tomography
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
LA	Left atrium/left atrial
LAEF	Left atrial emptying fraction
LV	Left ventricle/left ventricular
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
PALS	Peak atrial longitudinal strain
RV	Right ventricle/right ventricular
STE	Speckle tracking echocardiography
TDI	Tissue Doppler imaging

Left Atrial Function

The left atrium (LA) is far from being a simple passive transport chamber. The LA serves multiple functions, acting as a reservoir during left ventricular systole, a conduit for blood transiting from pulmonary veins to the left ventricle (LV) during

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M. Dorobanţu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_5

early diastole, an active contractile chamber that augments LV filling in late diastole and a suction source that refills itself in early systole. Through these varying mechanical functions, the LA modulates LV filling [1, 2].

In addition, LA also acts as volume sensor with the atrial wall releasing natriuretic peptides in response to stretch, generating natriuresis, vasodilatation and inhibition of the sympathetic nervous system and renin-angiotensin-aldosterone system. Contributing up to 30 % of total LV stroke volume in normal individuals, this atrial contribution is of particular importance in the setting of LV dysfunction to maintain adequate LV stroke volume; the loss of this atrial contribution to LV filling and stroke volume with atrial fibrillation can often lead to symptomatic deterioration [3].

LA reservoir function is influenced by LA compliance as well as LV contraction via descent of the LV base during systole, and RV systolic pressure transmitted via the pulmonary circulation. LA conduit function is inversely related to reservoir function and strongly modulated by LV relaxation and compliance. LA pump function reflects LA contractility and is also dependent on both LA preload (venous return) and LA afterload (LV end-diastolic pressure). Of note, the Frank–Starling mechanism applies to LA mechanics (as with LV mechanics), wherein LA ejection volume increases as LA filling volume increases, but reaches a tipping point in severe LA dilation where LA contractility drops. Thus the assessment of LA function provides important information beyond LA volume alone [4].

Echocardiographic Assessment of Left Atrial Function

Left atrial function can be assessed non-invasively by echocardiography, cardiac computed tomography (CT), and cardiac magnetic resonance imaging (MRI). Echocardiography is most often used clinically because of its widespread availability, safety, convenience, low cost, ability to image in real time, and technical advancements which have enabled imaging with high temporal and spatial resolution as well as quantification of LA longitudinal deformation throughout the cardiac cycle.

LA mechanical function can be evaluated by two- and three-dimensional echocardiography, Doppler analysis of trans-mitral and pulmonary vein flow, Tissue Doppler assessment of LA myocardial velocities and, recently, by the measurement of LA strain by speckle tracking echocardiography.

LA phasic function, calculated by volumetric assessment of LA size at different time points of the cardiac cycle, is more accurate than linear measurement and it has been well validated [5, 6, 7, 8].

Real-time 3-dimensional echocardiography allows to assess the physiologic volume changes of the left atrium during cardiac cycle and to quantify the contribution of LA contraction to LV filling, through the measurement of LA emptying fraction (LAEF) [9].

Pathological LA enlargement can be viewed as an adaptive response with an initial increase of LA volume and serves to maintain LV stroke volume and cardiac output. However, continued LA enlargement may ultimately exceed its optimal Frank-Starling relationship, resulting in decrease LA compliance, reduced reservoir and contractile pump functions, and eventually increased incidence of atrial arrhythmias [10].

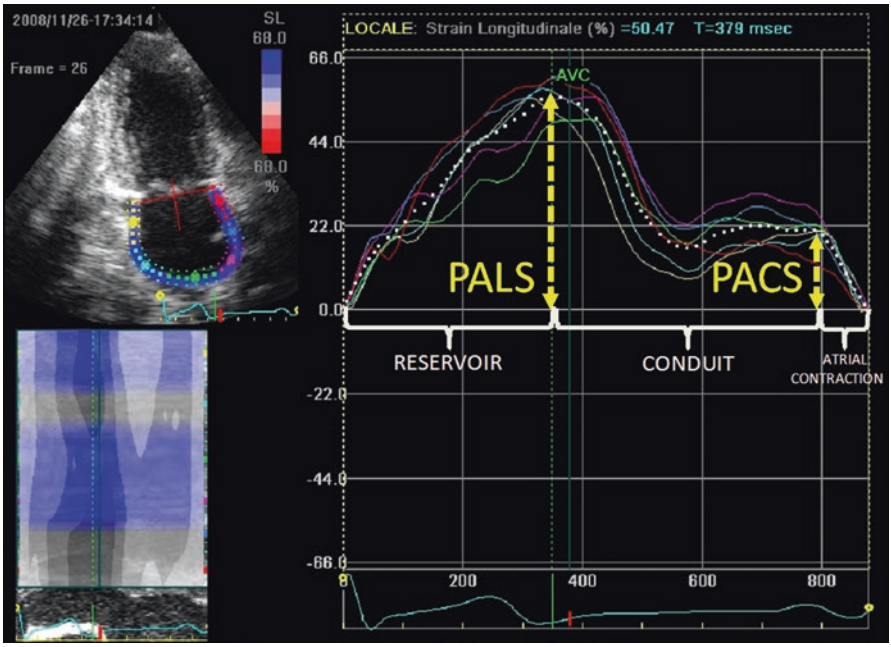

Fig. 5.1 Composite figure showing the measurement of Peak Atrial Longitudinal Strain (PALS) using the speckle tracking echocardiography (STE) from an apical two-chamber view, in a representative subject. The dashed curve represents the average atrial longitudinal strain along the cardiac cycle (AVC aortic valve closure)

Functional assessment of the LA also includes Doppler echocardiography evaluation of the pulmonary vein, transmitral flow pattern and also tissue Doppler imaging (TDI) of the mitral annulus, used all to describe LV diastolic function which was shown to greatly influence LA size and function [1]. The E wave of the transmitral flow is exponential for the conduit function, while the positive A wave provides information about the booster pump function [11]. Moreover, in the presence of reduced LV compliance and elevated filling pressures, atrial contraction results in significant flow reversal into the pulmonary veins [1, 12, 13].

Regarding TDI analysis, an excellent correlation between mitral annulus A′ and atrial function has been demonstrated in a large number of studies [1]. In the setting of heart failure (HF), peak A′ correlates well with maximum exercise capacity. Both LV systolic and diastolic functions affect LA contractile function. A higher LV ejection fraction is associated with higher A′, and restrictive LV diastolic filling is associated with lower A′ [14].

However, all these techniques are affected by several disadvantages, especially the effects of angle dependency that remain a technical challenge of Doppler echocardiography.

Recently, these limitations can be overcome thanks to the measurements of atrial longitudinal strain, a parameter obtained from the application of the analysis of myocardial deformation using speckle tracking echocardiography (STE) at atrial chambers (Fig. 5.1). First described in 2009 [15], there has been increasing evi-

dence suggesting that this imaging modality is highly promising for LA function assessment, providing a comprehensive regional function assessment of all LA walls [16].

Atrial strain results the first parameter useful for functional analysis of the LA and, as shown by recent studies, it presents considerable feasibility and reproducibility [16, 17, 18, 19, 20].

Several studies have shown that strain imaging can detect LA dysfunction before the manifestation of LA structural changes. The decrease of LA reservoir and the increase of LA pump functions are the first manifestations of the burden of diastolic dysfunction, appearing before the LA structural changes [21].

Left Atrial Function and Heart Failure

The understanding of heart failure (HF) haemodynamics has traditionally focused on left ventricular (LV) structure and function, with the left atrium being viewed simply as a passive transport chamber that empties into the left ventricle. Over the last decade, there has been increasing recognition of the importance of left atrial (LA) structure and function in the pathophysiology of HF. LA volume was first to be established as a biomarker integrating the magnitude and duration of LV diastolic function, and a predictor of cardiovascular outcomes in HF. More recently, LA function has emerged as a novel determinant of clinical status and outcomes in HF, and perhaps an even more robust prognostic marker than LA volume [4].

Heart failure is now recognized as a progressive disorder in which asymptomatic risk factors (Stage A) progresses to a pre-clinical stage of LV dysfunction (Stage B) and finally to the clinically manifest stage of symptomatic HF (Stages C and D). While the role of LV functional changes in the staged progression of HF has been well described, the role of LA dysfunction has received relatively little attention. Increases in LA preload initially enhance LA contractility by the Frank–Starling mechanism; thus the relative contribution of LA pump function increases, whereas conduit function decreases, in the presence of abnormal LV relaxation such as in Stage B patients. As LV filling pressures further increase in Stage C HF, LA enlargement reaches the limits of LA preload reserve, and LA conduit function becomes predominant, as shown in the study by Pellicori et al [22].

Growing evidence suggests that LA dysfunction is an active contributor to symptoms [23, 24, 25, 26] and to disease progression [16, 27]. HF-related LA remodelling is poorly understood, and it is not known whether there are fundamental differences between HF patients with preserved (HFpEF) or reduced LV ejection fraction (HFrEF), though prior studies suggest greater adverse effects from loss of LA function in HFpEF compared with HFrEF [28].

Although advanced age, hypertension, diabetes, coronary heart disease and female gender identify patients at high risk of diastolic HF, the underlying

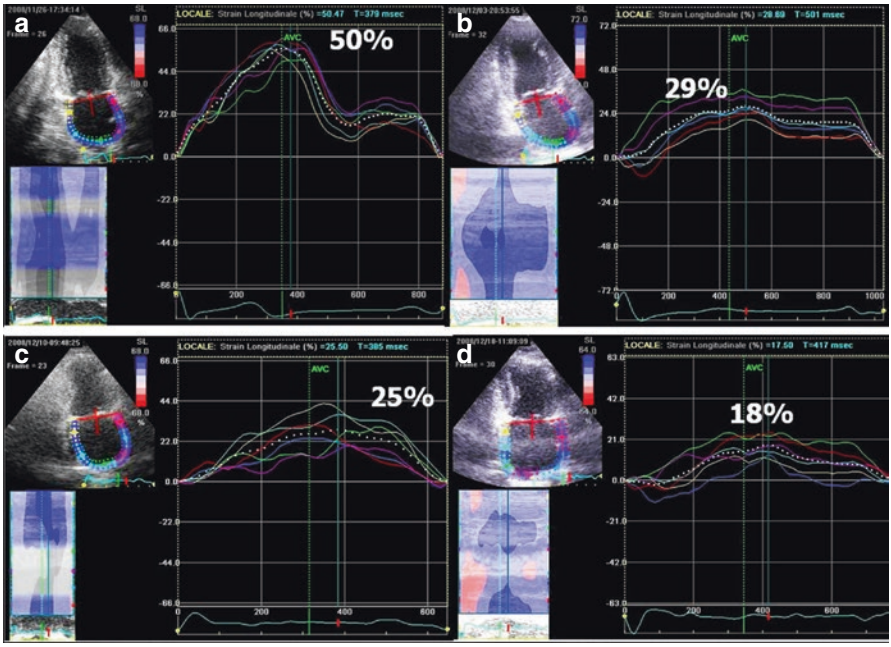

Fig. 5.2 Peak atrial longitudinal strain measurements in a healthy subject (**a**) and in a hypertensive (**b**), diabetic (**c**) and hypertensive-diabetic (**d**) patients. Atrial strain appeared reduced in hypertensive and in diabetics. In the case of association of the two diseases the reduction is even more evident

pathophysiological mechanisms for the transition from an asymptomatic state to a state of symptomatic heart failure are not well defined [33, 34].

The relationship of LA function with HF symptoms has received attention from clinicians. Although LA enlargement increases with the severity of diastolic dysfunction, the ability of LA volume measurements to discriminate asymptomatic LV diastolic dysfunction from early diastolic HF has not been possible.

Kurt et al. [8] sought to advance our knowledge of diastolic HF with a particular focus on LA diastolic function and stiffness; their main finding was that although asymptomatic hypertensive patients with LV hypertrophy and patients with normal LV ejection fraction (LVEF) and diastolic HF had no difference in LV mass, LA volumes or LA contractile function, LA strain during atrial systole was significantly reduced in diastolic HF patients secondary to LA stiffness.

Moreover, using STE, it has been demonstrated in hypertensive patients, diabetic and hypertensive-diabetic patients with ejection fraction and LA volumes preserved, that the atrial strain occurs progressively reduced, demonstrating the ability of this new method in identifying the premature atrial dysfunction before the appearance

of LA structural changes, identified also by standard methods (atrial dilatation) (Fig. 5.2) [29].

Moreover, LA functional assessment permits an accurate estimation of LV filling pressure that represents the afterload of LA chamber.

In fact, LA function is dependent not only on LA intrinsic contractile properties but it is also strongly influenced by LV function in term of LV end-diastolic pressure that is the afterload that LA have to face.

Previous studies have investigated the effect of LV end-diastolic pressure on LA wall tension during systole, demonstrating that elevated LV end-diastolic pressure is associated with a decrease of peak LA wall strain in the longitudinal direction during LV systole. Greater LV filling pressure is associated to a reduced LA deformation; in fact atrial longitudinal strain has demonstrated a good correlation and diagnostic performance in an accurate estimation of high pulmonary capillary wedge pressure (>18 mmHg) [30, 31, 32].

Thus, LA functional dynamics are determined by integration of LA relaxation but also LV systolic and diastolic functions.

The analysis of atrial function has resulted very useful also in the clinical settings of end-stage HF. In these patients it is essential the management of the precarious hemodynamic balance and the accurate estimation of left ventricular filling pressure is very useful to assure proper management. The ratio E/E', the main parameter for echocardiographic estimation of ventricular filling pressures, was recently proved inadequate for this purpose [33].

In a population of patients with advanced systolic heart failure LA longitudinal deformation analysis correlated well with pulmonary wedge pressure, providing a better estimation of LV filling pressures. In this study [33], the global PALS, parameter for the functional evaluation of the atrial reservoir phase, resulted progressively decreased with the augmentation of LV filling pressures which represent the afterload of LA chamber, following finally by remodelling with LA chamber dilatation (Fig. 5.3) [34].

In all stages of HF, a reduction in LA function has been identified to be an independent predictor of adverse events, including death and congestive HF [4].

Several recent studies raise the possibility that LA function may be a better prognostic marker than LA structure in HF [35].

A previous study has demonstrated as mitral annular A' velocity is the most powerful predictor of cardiac death or HF hospitalization among clinical, haemodynamic, and echocardiographic variables in chronic HFrEF.

More recently, Pellicori et al. [23] demonstrated that LAEF by MRI, but not LA volume, is associated with HF hospitalization, cardiovascular and all-cause mortality, and AF, independent of clinical predictors and NT-proBNP level in stable HF regardless of ejection fraction.

Given that the risk associated with impaired LA function has been shown in several studies to be independent of, or incremental to, LV diastolic function or LA volume, it is likely that mechanisms beyond increased LA afterload (impaired LV diastolic function) or increased LA preload (LA dilatation) are involved [4].

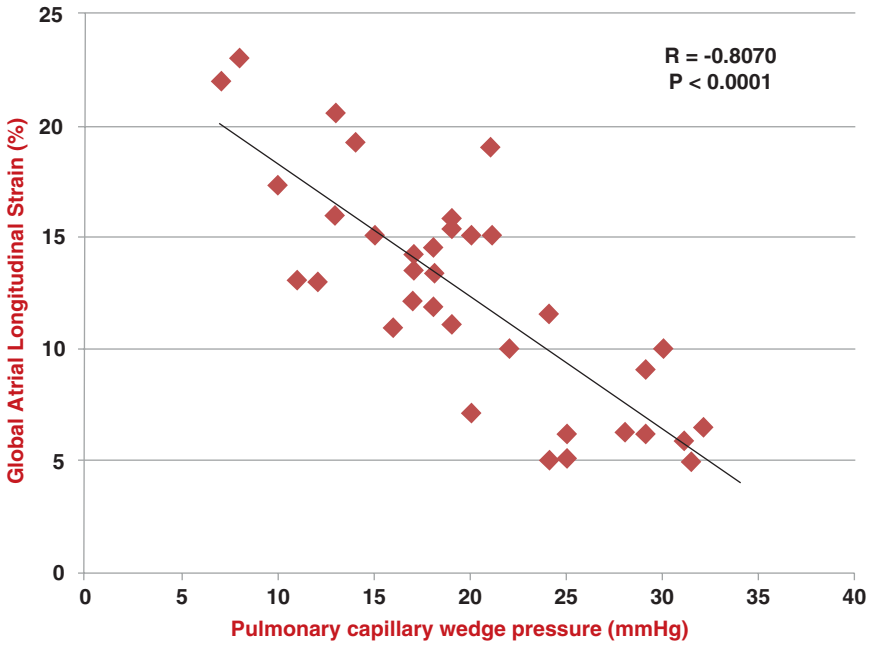

Fig. 5.3 Correlation between global peak atrial longitudinal strain (PALS) and pulmonary capillary wedge pressure. $R = -0.8070$; $p < 0.0001$. (PALS, peak atrial longitudinal strain)

Conclusion

Our understanding of LA function is rapidly evolving, and data are accumulating to suggest that this is a powerful biomarker for HF.

There have been tremendous advances in terms of our ability to characterize and quantitate LA function using non-invasive imaging. Regional assessment of LA function by STE provides more detailed information about LA mechanics and may prove to have a very important clinical impact.

Future Directions

Despite considerable data demonstrating the utility of LA function in predicting incrementally cardiovascular events, risk stratification strategies incorporating these parameters are not currently exploited in clinical practice.

Robust outcome data from large prospective clinical trials are needed to confirm the incremental predictive utility of LA function compared with other measures.

Thus, whether LA function will surpass form as a prognostic biomarker and surrogate endpoint in HF is yet to be seen.

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Chapter 6
Assessment of Secondary Mitral Regurgitation

Raluca Dulgheru, Pierluigi Incarnate, and Patrizio Lancellotti

Introduction

Secondary mitral regurgitation (SMR) is a common finding in symptomatic patients with systolic heart failure of ischaemic or non-ischaemic aetiology. When present, any degree of SMR seems to be associated with increased risk of mortality [1]. Echocardiography, both transthoracic (TTE) and transoesophageal (TOE), plays a central role in the evaluation of patients with SMR. It is the first choice non-invasive technique to diagnose the disease, quantify its severity, assess its dynamic component, and evaluate mitral valve morphology, which is of outmost importance for planning intervention. Moreover, TOE plays an active role in the interventional treatment aiming to correct SMR in heart failure patients, by assisting and guiding transcatheter procedures in high-risk patients. This chapter will cover the role of 2D and 3D TTE and/or TOE and the role of stress echocardiography in the assessment of patients with systolic heart failure and SMR.

Electronic supplementary material The online version of this chapter (doi:10.1007/978-3-319-45237-1_6) contains supplementary material, which is available to authorized users.

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M. Dorobanţu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_6

Definition, Mechanisms, and Physiopathology

While in primary mitral regurgitation (MR) it is the valve lesion that leads to left ventricular (LV) dilatation and dysfunction and, ultimately to heart failure, in chronic SMR, it is the LV dilatation and/or dysfunction that generates the valve incompetence through distortion of the valve geometry. Hence, the MR is only "secondary" to the LV disease, in the absence of any detectable lesion of the valvular tissue. Therefore, in these patients, treatment strategies first address the LV disease (heart failure treatment, complete revascularization, cardiac resynchronization therapy) with the aim to indirectly correct SMR once LV pathology regresses.

The proposed mechanism of chronic SMR is the loss of balance between the closing forces and the tethering forces that act on the mitral valve (MV) with each systole in a dysfunctional and/or remodeled LV. Apical and outward papillary muscle displacement secondary to LV dilatation/deformation, annular dilatation/deformation and the increase in left atrial (LA) pressure, all have a tethering effect on the mitral leaflets, precluding adequate sealing of the atrioventricular orifice in systole, and leading to SMR. Little force is needed to seal the MV in systole in a LV with normal geometry and function. However, in the presence of leaflet tethering, any decrease in myocardial contractility, any degree of LV/papillary muscle dyssynchrony, and any decrease in the mitral annulus sphincteric function (i.e. any decrease in closing forces) may be sufficient to promote SMR. In the absence of tethering in patients with isolated LV systolic dysfunction, significant SMR does not occur [2]. Therefore, LV dilatation and deformation are requirements for the development of significant SMR. Not surprisingly, SMR has a high prevalence in patients with systolic heart failure. Recently, several studies have suggested that mitral valve leaflet may enlarge as a response to chronic tethering and have the potential to compensate for annular enlargement and leaflet tethering, contributing, thus, to the reduction of SMR in some patients [3, 4].

SMR is dynamic by nature, since its development is triggered by the loss of the equilibrium between tethering and closing forces. During each systole, the equilibrium is continuously changing, and the resulting dynamic change is translated into a decrease in SMR severity in mid-systole, when the closing forces are at their highest [5]. The loss of equilibrium may be sometimes only transient, depending on loading conditions. The classic examples are the disappearance of SMR during anesthesia or dobutamine infusion, once preload and afterload are reduced, and the increase in SMR with exercise in patients presenting with recurrent acute pulmonary oedema [6]. This dynamicity of SMR is very important to keep in mind at the first echocardiographic evaluation of a patient with systolic heart failure and SMR to ensure correct management. If an intervention aiming to correct SMR is contemplated, reassessment of the SMR severity should always be performed after appropriate treatment of the acute episode of heart failure.

It was hypothesized that SMR imposes a chronic increase in volume overload on a LV less able to cope with this supplementary volume load (with preceding LV systolic dysfunction/remodeling). A vicious circle is established: in the presence of significant SMR, LV may continue to dilate and remodel, leading to a progressive

increase in MV leaflet tethering and aggravating the SMR, and so on. Interestingly, in a recent randomized trial comparing coronary artery bypass grafting (CABG) alone to CABG with MV repair in patients with moderate ischemic SMR, no differences in LV end-systolic volume index (ESVI) or survival at 2 years, were found [7]. However, the results after a longer follow up period of this study are expected in order to draw a solid conclusion, since echocardiographic methods to detect LV remodeling, such as assessment of end-systolic volume index (ESVI), may have a low accuracy to detect subtle short term changes in LV volumes in patients with chronic SMR.

Apart from the downstream consequences on the LV, SMR may lead to LA enlargement and progressive increase of pulmonary venous pressure. In most patients with chronic SMR, LA enlarges gradually, and the increase in pulmonary venous pressure occurs in the late stages of the disease. Once pulmonary venous pressure has increased, signs and symptoms of pulmonary congestion usually develop. Moreover, another vicious circle is closed, as the increase in LA pressure will, a component of the tethering forces, contribute to the worsening of chronic SMR and to further increase in pulmonary venous pressure.

Echocardiographic Assessment of SMR

Diagnosis and Mechanism of SMR

Valve Morphology: Overall Assessment

In patients with systolic heart failure**,** 2D TTE should systematically assess: (1) the presence/absence of SMR (even a mild SMR has been associated with poor outcome in heart failure patients) [1, 8]; (2) SMR severity (graded relationship between effective regurgitant orifice area (EROA) and reduced event free survival) [1, 9]; and (3) carefully assess MV geometry, whenever SMR severity is more than mild.

Systolic apical displacement of mitral leaflets coaptation line from the annular plane is the key conformational change of the MV apparatus in patients with SMR (Fig. 6.1. Movie 6.1) [10, 11]. However, this conformational change has to be identified in the context of LV regional and/or global remodeling, since LV remodeling is a prerequisite for SMR [2, 12].

LV dilatation and/or regional remodeling may displace the papillary muscles outward and apically. This conformational change is transmitted, through the inextensible MV chordae, to the MV leaflets leading to leaflet tethering, apical displacement of the coaptation line, reduced systolic motion of the leaflets with reduction of the coaptation surface (Fig. 6.2). Traction of MV leaflets and the apical displacement of the coaptation line from the annular plane results in a conformational change of leaflet geometry, which is known as “tenting” of the mitral leaflets. Mitral tenting is a major determinant of SMR, and is directly related to local remodeling [13]. Continuous traction of the leaflets during systole leads to restrictive systolic

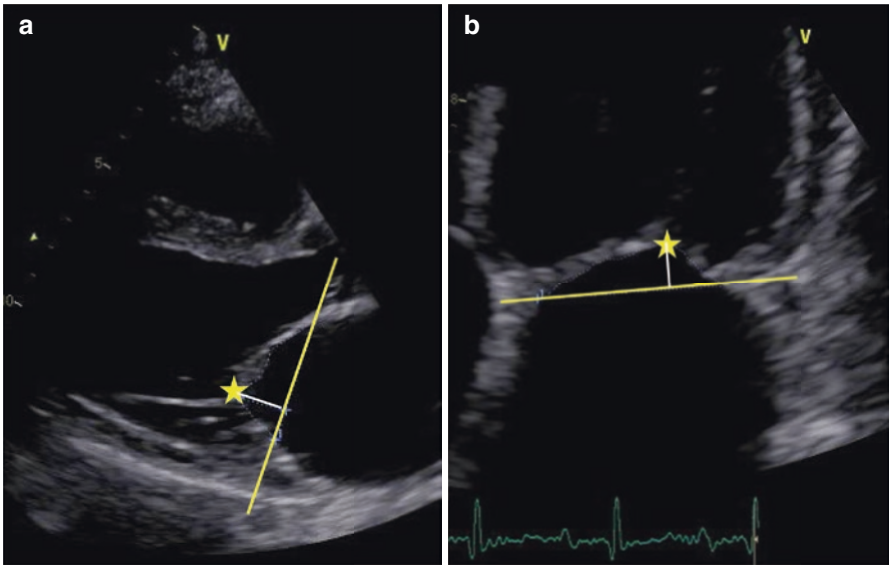

Fig. 6.1 Apical displacement of the coaptation point of the mitral valve leaflets (as seen from the parasternal long axis view – panel (**a**) and from the apical 4-chamber view – panel (**b**)) in a patient with secondary mitral regurgitation and systolic heart failure. The yellow line indicates the mitral annular plane, the yellow star indicates the coaptation point of the mitral leaflets, the white line is the distance between the mitral annular plane and the coaptation point of the leaflets, known as the "***coaptation height***"

motion of the leaflets which classifies this type of SMR as a type IIIb, according to the Carpentier classification.

After a myocardial infarction involving the papillary muscles and leading to papillary muscles elongation, the mechanism of chronic ischaemic SMR may be different than a Carpentier IIIb type. In this case, through elongation of one of the papillary muscles, the free edge of one of the mitral leaflets, usually the anterior leaflet, can show an excessive mobility, and climbs higher than normally inside the LA cavity in systole, leading to a decrease leaflet coaptation and to SMR (Fig. 6.3, Movie 6.2). This rare type of ischaemic SMR designates a type II Carpentier SMR, with excessive leaflet motion. In patients with "the right amount" of papillary muscle contractile dysfunction/elongation, ischaemic SMR may be reduced because papillary muscle contractile dysfunction/elongation may reduce leaflet tethering [14, 15].

With Carpentier IIIb SMR, two patterns of leaflet tethering have been classically described: symmetric and asymmetric (Fig. 6.4) [16]. If both papillary muscles are displaced apically and outward, both MV leaflets are equally tethered (i.e symmetric tethering) and a typically central MR jet (with respect to LA walls) can be seen (Fig. 6.4, Panel a and b). Whenever only one of the two papillary muscles is displaced, tethering is predominant on one of the leaflets, usually the posterior leaflet. This leads to asymmetric apposition of the two leaflets over the length of a segment of the coaptation surface and to an eccentric SMR jet. Commonly, the

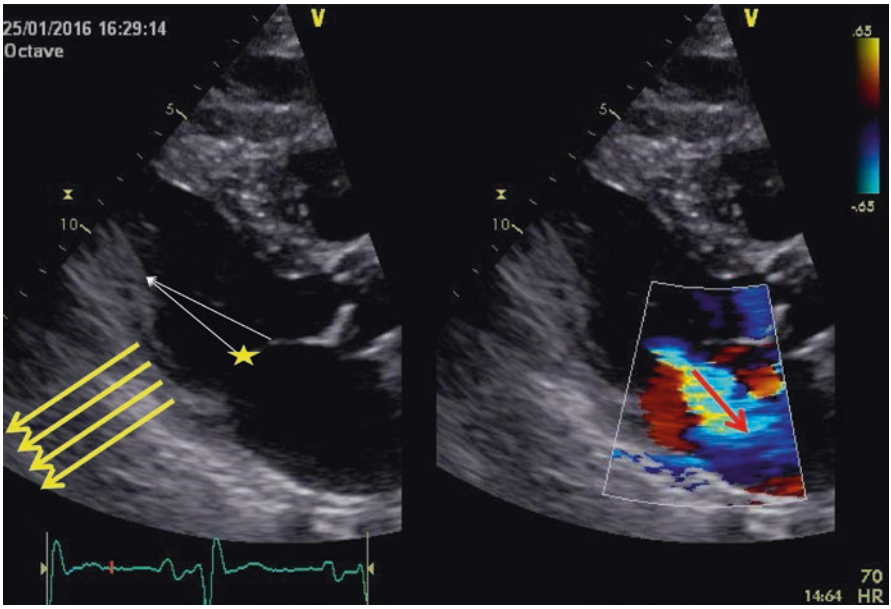

Fig. 6.2 Schematic representation of the mechanism of secondary mitral regurgitation: regional remodeling of the left ventricle leads to outward displacement of the posteromedial papillary muscle (*yellow arrows*); leaflet tethering ensues through the inextensible mitral chordae (*white arrows*); the coaptation line of the mitral leaflets is displaced apically (*yellow star*), the coaptation surface decreases and secondary mitral regurgitation appears (*red arrow*)

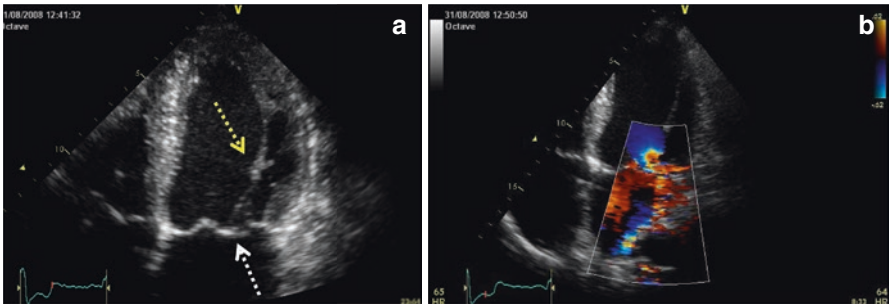

Fig. 6.3 Secondary mitral regurgitation related to papillary muscle elongation. The yellow arrow indicates the elongation of the papillary muscle after a myocardial infarction, while the white arrow indicates the "pseudo-prolapse" of the anterior leaflet related to the elongation of the papillary muscle (panel **a**). In consequence, secondary mitral regurgitation ensued, with a jet direction oriented posterior and lateral (panel **b**)

postero-medial papillary muscle displacement, as in inferior and inferolateral wall myocardial infarction, will create an asymmetric tethering pattern with severe tethering on the posterior-medial scallop of the posterior leaflet (P3), asymmetric apposition of the leaflets at the level of this scallop, and an eccentric, posterior oriented

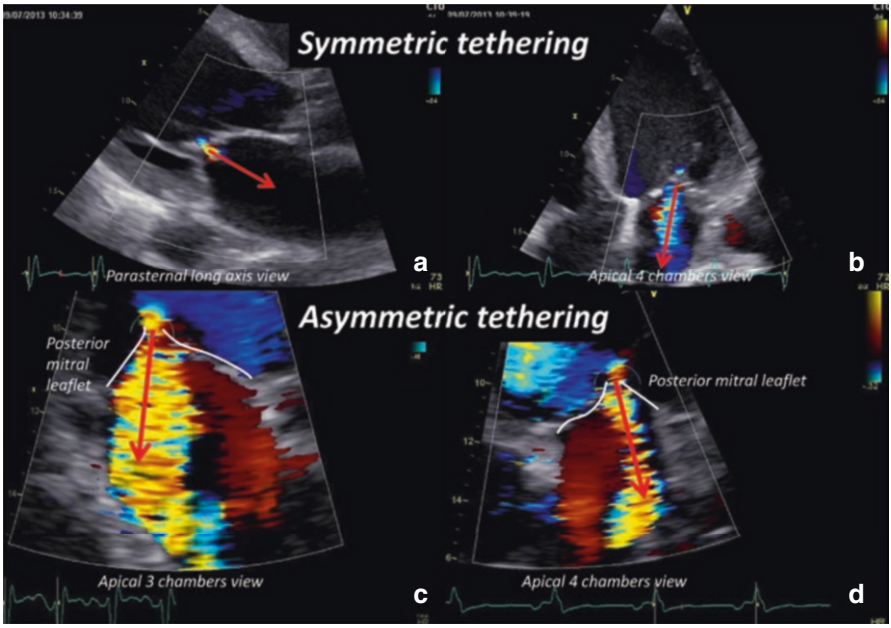

Fig. 6.4 Examples of the two patterns of leaflet tethering (symmetric tethering- panel **a**, **b**; asymmetric tethering- panel **c**, **d**) in patients with secondary mitral regurgitation. Analysis of the jet direction by colour flow Doppler is the key to identify the type of leaflet tethering pattern. The red arrows indicate jet direction inside the left atrial cavity.

MR jet (Fig. 6.4, Panel c and d). To note, with Carpentier type II SMR, the jet is also oriented posteriorly. Therefore, jet direction analysis with colour flow Doppler in patients with chronic SMR can give useful hints about the type of tethering.

3D echocardiography, through the **"en face"** view (i.e. from LA perspective) allows direct examination of the atrial surface of both MV leaflets, coaptation line and of the two commissures. With 3D echocardiography, due to leaflets tethering, when examined from the LA, the MV has a funnel shape, with the lowest points of the funnel at the level of the coaptation line (Fig. 6.5). However, the mechanism of SMR is best identified with 2D echocardiography by analyzing the relationship of the coaptation point to the mitral annular plane, the coaptation surface (edge-to-edge vs. edge-to-body) and the direction of the regurgitant jet.

Valve Morphology: Quantitative Analysis of Mitral Valve Deformation

In patients with SMR, the following parameters can be measured to assess the degree of deformity of the mitral valve apparatus: annular dimensions, MV tenting area (area of the region enclosed between the annular plane and the mitral leaflets), coaptation distance (longest distance between the mitral annulus plane and the leaflet coaptation point), coaptation surface length (a measure of coaptation reserve),

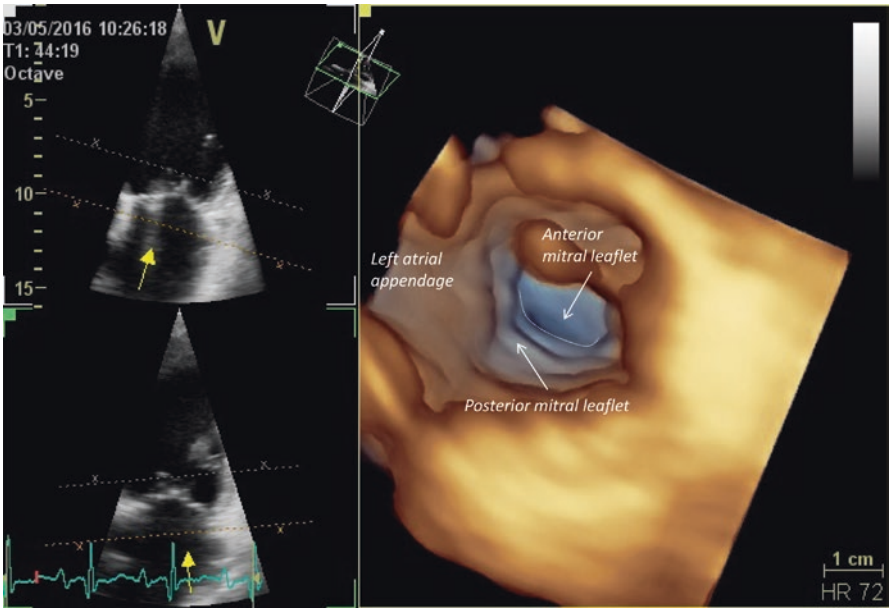

Fig. 6.5 "En face" view of the mitral valve leaflets, from the left atrial perspective in a patient with secondary mitral regurgitation as obtained with 3D transthoracic echocardiography. Note the "funnel shape" of the mitral valve geometry and the coaptation line, which dives deep into the left ventricle as a result of leaflet tethering in systole. The white dashed line represents the coaptation line

anterior and posterior leaflets angle and bending distances (Fig. 6.6) [17, 18]. Frequently used in clinical practice and with prognostic implications are: tenting area, coaptation distance, posterior leaflet angle and mitral annulus diameter. Tenting area is a major determinant of SMR and was the best predictor of SMR severity in terms of effective orifice regurgitant area (EROA) in one study [19]. A MV tenting area ≥2.5 cm² or ≥1.6 cm², a coaptation distance ≥1 cm, a posterior leaflet angle ≥45 and an annulus diameter ≥37 mm predict persistence of MR after restrictive annuloplasty [20, 21]. In SMR, echocardiographic parameters that quantify mitral valve apparatus deformation, such as posterior leaflet angle (PLA), can predict late SMR recurrence after myocardial infarction [22]. These measurements are usually performed in apical 4-chamber view in mid systole with the exception of mitral annulus diameter in which the cut-off value was obtained from TOE in diastole.

3D echocardiography, and especially 3D TOE, has the potential advantage to provide all the above mentioned measurements with better accuracy, because this technique lowers the risk of measurements performed in off-axis planes (Fig. 6.6, panel h). The major limitation is the dependency on image quality and a relatively low spatial resolution with 3D TTE. However, this is less of an issue with 3D TOE, which offers a good spatial resolution and excellent quality images.

The tenting volume (the volume enclosed between the surface of the mitral leaflets and the annular plane), can be computed from the 3D datasets through off line analysis with dedicated software. Tenting volume correlated better with EROA in patients with SMR and proved to be a reliable marker of leaflets tethering severity [23] Leaflet surface area, leaflet area/closure area and leaflet area/annular area ratios are best assessed with 3D TOE. Leaflet surface area proved to increase by at least 35 % on average in patients with SMR [3], while leaflet area/closure area and leaflet area/annular area ratios are lower in patients with significant SMR [24]. Leaflet enlargement in response to chronic tethering as a compensatory mechanism aiming to reduce SMR severity has first been demonstrated with 3D echocardiographic studies on animal models [3]. This has been recently confirmed in humans [4].

Mitral annular geometry and dynamics are best assessed by 3D TOE [25]. Mitral annular reconstruction is available using commercial software by offline analysis (Fig. 6.7) Annulus reconstruction from 3D datasets, can accurately evalu-

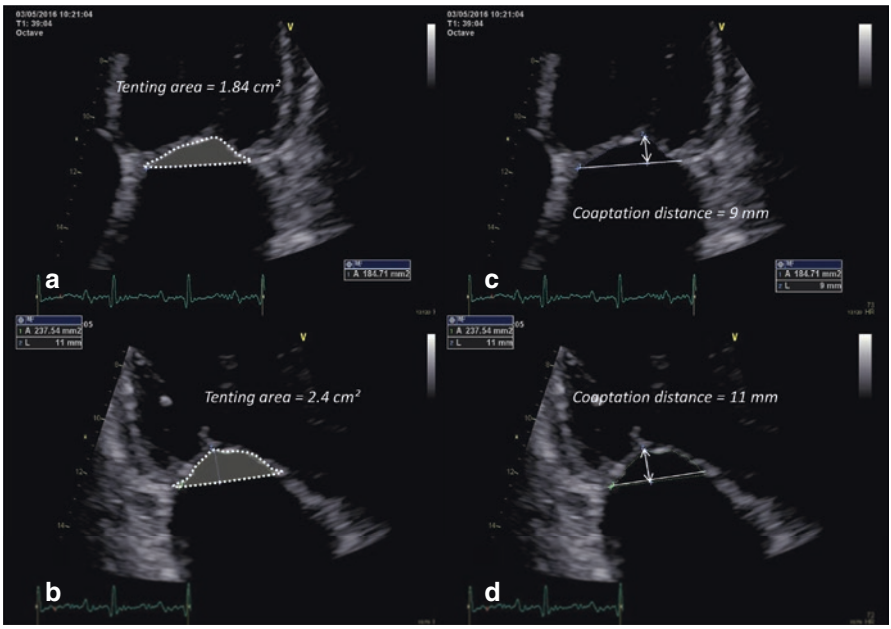

Fig. 6.6 Assessment of mitral valve deformation with 2D and 3D transthoracic echocardiography in a patient with secondary mitral regurgitation. Measurement of tenting area from apical 4-chamber view (panel **a**) and parasternal long-axis view (panel **b**). Measurement of the coaptation distance from apical 4-chamber view (panel **c**) and long-axis view (panel **d**). Assessment of coaptation surface length (panel **e**). Assessment of posterior leaflet angle using the formula of $\sin^{-1}$ (coaptation distance/posterior leaflet length) (panel **f**). Assessment of anterior leaflet angle using the formula of $\sin^{-1}$ (bending distance/anterior leaflet bending distance) (panel **g**). Measurements are performed in mid-systole, in zoomed mode with 2D transthoracic echocardiography. (Panel **h**) Assessment of tenting area and coaptation distance after cropping of a 3D transthoracic data set from the same patient. Note that the results are not the same, and that 3D echocardiography has the potential of providing more accurate values

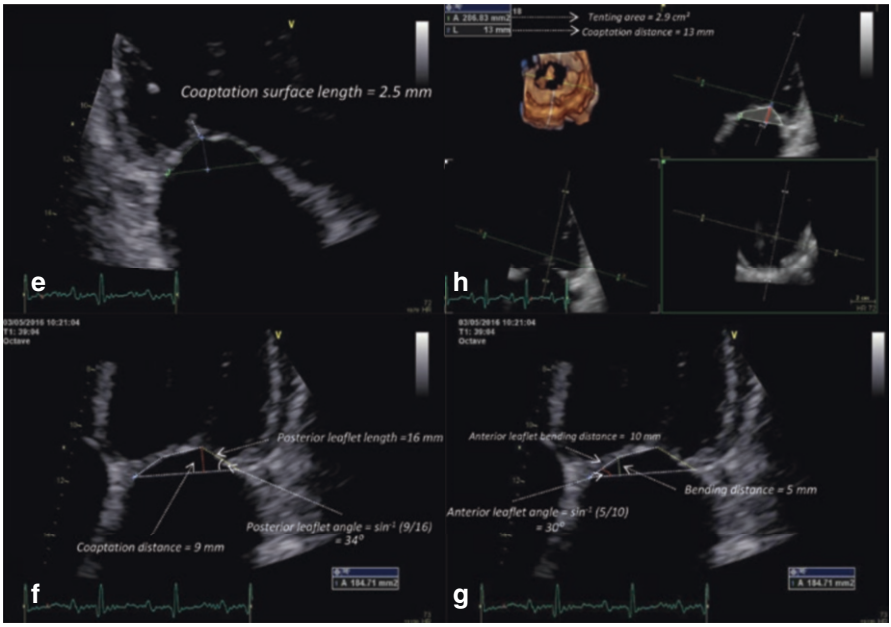

Fig. 6.6 (continued)

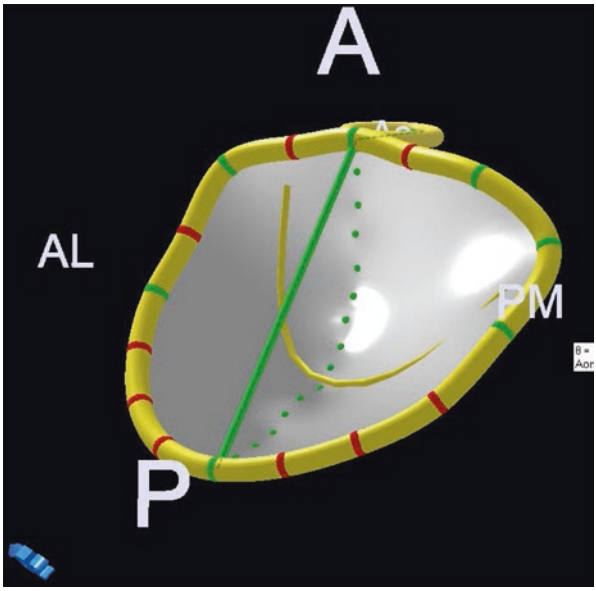

Fig. 6.7 Mitral annulus reconstruction using a 3D transoesophageal data set and a dedicated software (Xcelera by Philips Medical Systems) in a patient with secondary mitral regurgitation

ate the antero-posterior diameter, the inter-commissural diameter, the sphericity index of the mitral annulus, the perimeter of the mitral annulus without geometric assumptions, and length of each annular segment (anterior annulus length vs.

posterior annulus length). The height of the annulus, i.e. the distance between the highest and the lowest points on the annulus, can also be measured, giving information on its degree of deformation. In SMR, annular diameter and area are increased, the annulus is less elliptical and more flattened, and there is a decrease in annular "sphincteric" function (the capacity to reduce its surface during systole) as compared to normal subjects [25–28]. Mitral annulus dilation by itself does not lead to significant SMR, but in the presence of leaflet tethering, mitral annular dilation worsens SMR severity by increasing leaflet tethering [26]. Flattening of the mitral annulus, which has a saddle shape in normal individuals [29], leads to an increase in the systolic stress exerted on the MV leaflets, contributing to SMR [28]. In normal subjects, there is systolic caudal displacement of the mitral annulus and this phenomenon is more accentuated in the posterior region of the annulus. Oppositely, in patients with SMR, systolic annular displacement is reduced, most notably in the posterior region [27]. Moreover, that the degree of mitral annular deformation in ischemic SMR is more pronounced following anterior MI than inferior MI [30].

3D echocardiography allows also a comprehensive evaluation of the MV subvalvular apparatus and its position relative to the mitral annular plane. The tethering distance is one of the most relevant parameters that can be measured with 3D echocardiography. It is measured between the medial trigone (medial junction of aortic and mitral annuli) and the head of the postero-medial papillary muscle. This parameter proved to be a reliable indicator of the severity of distortion on MV apparatus and a strong predictor of SMR after MI [2]. The advantage of 3D echocardiography over 2D echocardiography is that it can accurately identify papillary muscle tips closest to the base of the heart, making the measurement more reliable.

LV Remodeling Assessment

LV volumes, LV ejection fraction, wall motion abnormalities, LV systolic sphericity index (LV short axis-to-long axis diameter ratio measured at end-systole), the inter-papillary muscle distance (the length between the papillary muscles in short axis view at end-systole) and the tethering distance (the distance between the intervalvular fibrosa and the head of the posteromedial papillary muscle (at mid-systole) are indicators of LV remodeling and should be assessed in patients with SMR whenever corrective surgery of SMR is contemplated (Fig. 6.8). A LV end-systolic volume $\geq$145 mL, a systolic sphericity index $\geq$0.7 [31, 32] and an inter-papillary muscle distance >20 mm measured at end systole using 2D echocardiography perform well in predicting recurrent MR after undersized annulopasty for chronic ischemic MR [33]. Careful analysis of regional and or global LV remodeling and careful assessment of LV systolic function should be performed in patients with chronic ischemic SMR since infero-basal aneurism or dyskinesis, significant LV dilation and severely depressed LV ejection fraction are all predisposing factors for SMR recurrence after surgical MV repair [34, 35].

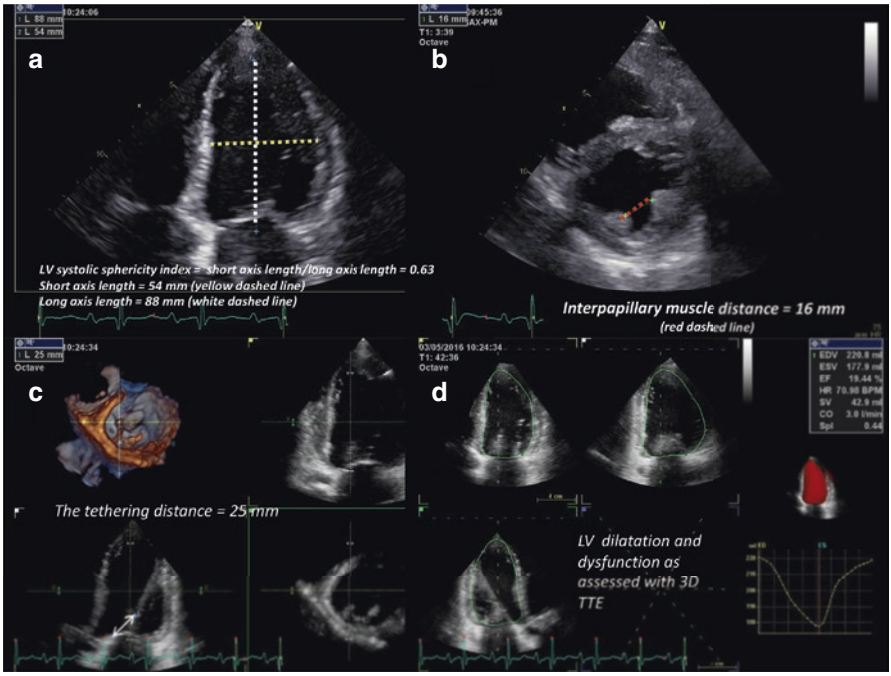

Fig. 6.8 Assessment of left ventricle (*LV*) remodeling using 2D and 3D transthoracic echocardiography (*TTE*): LV systolic sphericity index assessment (panel **a**), interpapillary muscle distance (panel **b**), tethering distance (panel **c**) and assessment of LV end-diastolic (*EDV*), end-systolic volume (*ESV*) and ejection fraction (*EF*) with 3D TTE (panel **d**)

Quantification of SMR Severity

2D Echocardiography

Quantification of chronic SMR severity by echocardiography is necessary, since a graded relationship between ischaemic MR severity and reduced survival has been described [1, 9]. Quantitative and semi-quantitative methods can be used, and the guidelines recommend an integrative approach [36]. Semi-quantitative methods such as vena contracta (VC) width and regurgitant jet area have lower accuracy in eccentric jets and poorer reproducibility [37]. Quantitative methods, such as the Doppler volumetric method and the proximal isovelocity surface area (PISA) method are considered accurate for MR severity grading and encouraged by the current recommendations [37–39]. The Doppler volumetric method allows the calculation of regurgitant volume (RV) as the difference between mitral and aortic stroke volumes. Whenever more than 50 % of the LV total stroke volume regurgitates, the SMR is considered as severe [38]. However, the Doppler volumetric method is rarely used in the clinical setting because it is time consuming, needs several measurements on different cardiac cycles, because small errors may

lead to significant inaccuracies, and no outcome studies using this method to derive cut-off values for SMR are available. The PISA method allows the quantification of both RV and EROA [39]. Based on outcome studies and applying the PISA method, SMR is considered severe when EROA is >20 mm² or/and RV is >30 mL [9, 40] In SMR quantification, the PISA method has several limitations [41]. First, the PISA radius often changes during systole, being larger in early and late systole and smaller in mid-systole [42]. Performing only one measurement in mid-systole systematically underestimates EROA and RV. Optimally, PISA radius should be averaged throughout systole, but software capable of performing an automated PISA measurement throughout systole is no yet available. Second, the PISA method assumes that the flow convergence area is hemispherical. In practice, flow convergence area is frequently hemielliptic, especially in chronic ischemic MR, and applying PISA method may lead to underestimation of EROA and RV [43, 44]. Real-time 3D echocardiography emerged as a solution to this problem, but large outcome studies and validated cut-off values for severity are still missing.

With 2D echocardiography, acquisition of VC width from a plane perpendicular to the direction of the regurgitant jet, especially in eccentric jets, may be sometimes challenging. Moreover, VC of the regurgitant jet is not always circular and, in the more frequent cases of SMR with elliptical VC, its width might be underestimated or overestimated (Fig. 6.9 pitfalls in assessment of SMR severity, Movie 6.3).

3D Echocardiography

3D echocardiography can overcome some of these limitations by allowing direct planimetry of VC area with no geometric assumptions. VC area is measured from the 3D dataset by cropping and tracing of the colour flow Doppler contour in the plane perpendicular to the direction of the regurgitant jet. (Fig. 6.10) 3D derived VC area has been shown to correlate more closely with Doppler-derived EROA than 2D VC width [45] A 3D derived VCA of ≥0.41 cm² seems to indicate severe SMR. Further validation studies of this cut-off value are needed before entering clinical arena [46]. 3D colour flow Doppler derived PISA method (3D PISA) is a new technique allowing quantification of EROA and RV without geometric assumptions (Fig. 6.11). It allows computation of a peak 3D effective regurgitant orifice area (3D-EROA) from the peak regurgitant jet velocity (as assessed by CW Doppler) and the direct 3D based measurement (without any geometrical assumption) of the PISA [47]. However, as for VC area, validation and outcome studies are still needed. 2D derived EROA and RV using the PISA or the Doppler volumetric method are still the recommended methods to quantify chronic SMR in every-day clinical practice [37]. Decision making is still based on these 2D echocardiography derived cut-off values. Severe ischaemic MR is defined as ERO area >20 mm² and RV >30 mL [9, 37]. An average value of VC width (average of VC width in 4-chamber and 2-chamber view) >8 mm has been reported to define severe MR, irrespective of aetiology (primary or SMR) [45, 48].

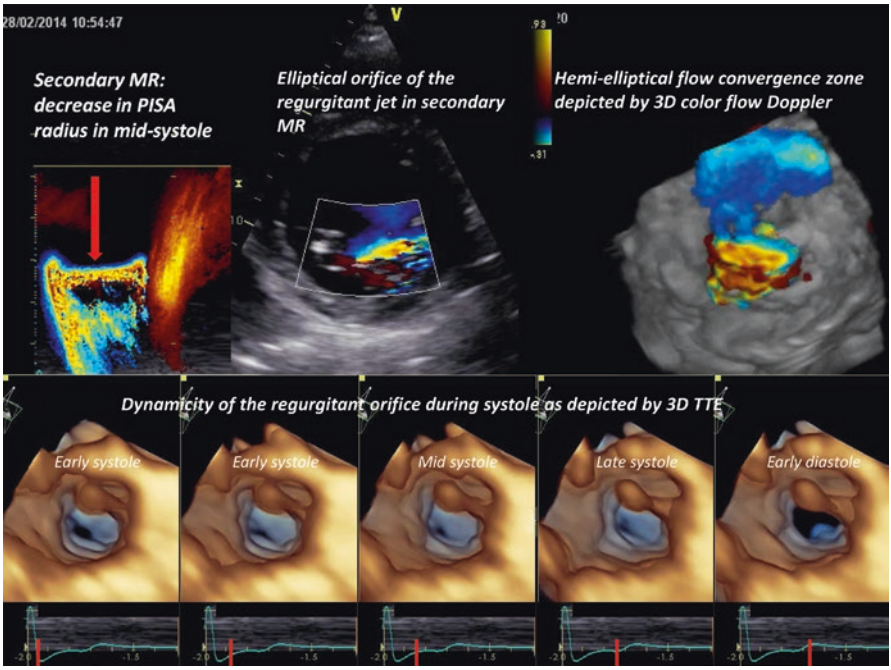

Fig. 6.9 Some of the pitfalls in assessment of secondary mitral regurgitation severity are summarized in this figure. Upper panel depicts the limitations of proximal isovelocity surface area method that tend to underestimate the secondary mitral regurgitation severity (decrease in PISA radius at mid-systole as shown by the colour flow Doppler M-mode assessment and the fact that the flow convergence has an elliptical shape, not hemispherical as assumed by the PISA method). Lower panel shows, with the help of 3D echocardiography, the fact that the regurgitant orifice is dynamic during systole with the smallest regurgitant orifice in mid-systole and the largest at early and late-systole. This phenomenon leads to a systematic underestimation of secondary mitral regurgitation

The Dynamic Nature of Chronic Ischaemic MR: Role of Stress Echocardiography

Chronic SMR has a dynamic nature [49]. Its severity varies throughout systole, with a decrease of severity in mid-systole that parallels the increase in LV closing forces [42]. The change in SMR severity with different loading conditions is another facet of the dynamic character of SMR. The classical example of preload and afterload dependency of SMR was highlighted by Levine et al. who described the vanishing of MR intraoperatively (preload and afterload reduction concomitant with increase in contractility due to inotropic agents) in patients with ischaemic SMR undergoing CABG [49]. In our experience, exercise stress echocardiography (ESE) is one of the best methods to explore the dynamic behavior of chronic SMR. Exercise modifies preload, afterload and contractility of the LV, leading to a shift in the balance

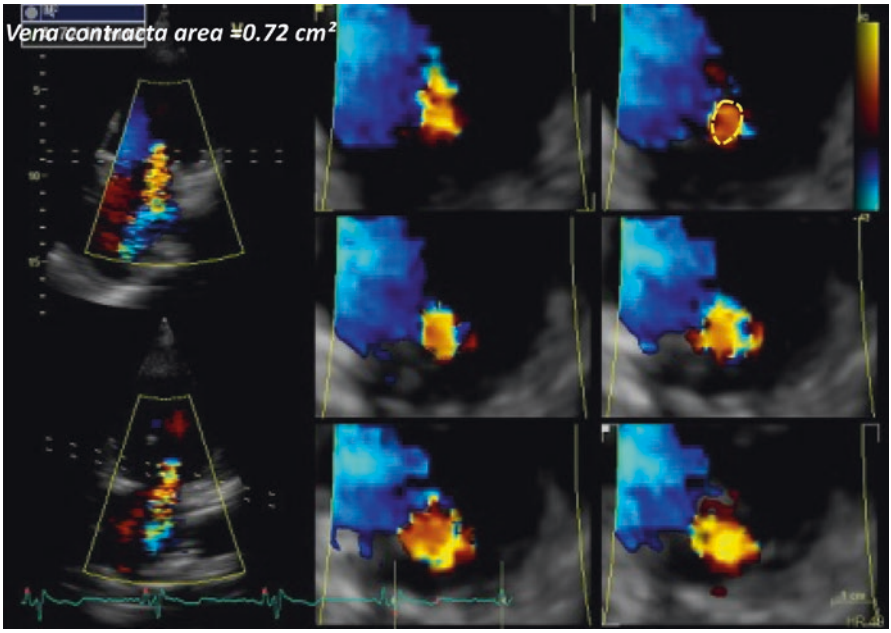

Fig. 6.10 Assessment of vena contracta area with 3D colour flow Doppler transthoracic echocardiography after cropping of the 3D data set. The smallest area of the regurgitant orifice measured by direct planimetry in a plane perpendicular to the jet direction allows estimation of the vena contracta area (*yellow dashed line*)

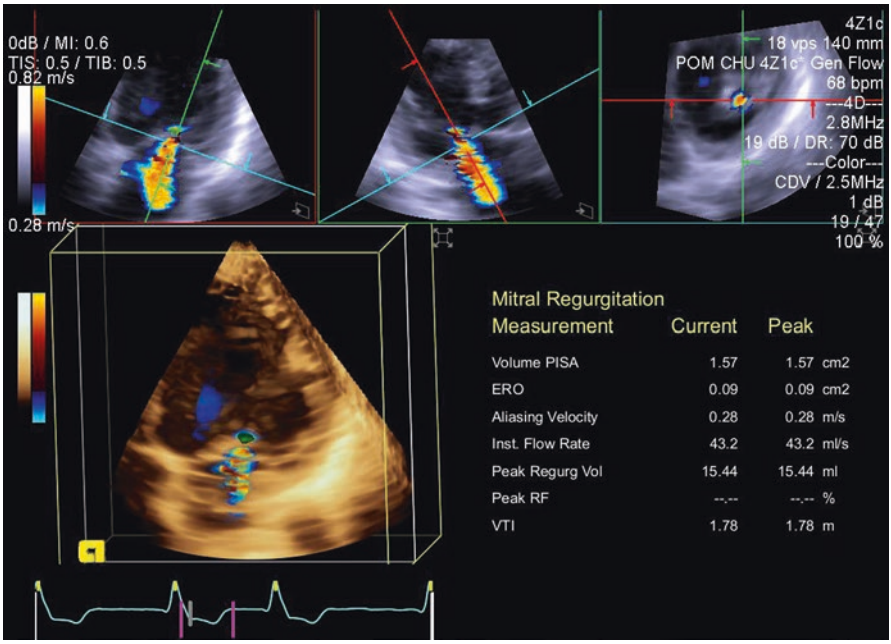

Fig. 6.11 3D Color flow Doppler assessment of PISA radius (3D PISA) with eSiePISA Volume Analysis

between the closing and tethering forces acting on the MV, and exerting an unpredictable effect on SMR severity in each individual patient [6]. If an exercise test is performed parallel to imaging of the LV and Doppler interrogation of the MV, the mechanisms involved in the dynamic behavior of chronic ischaemic MR can be revealed. ESE is able to provide prognostic information, over resting echocardiography, by unmasking patients at high risk for poor outcome [6, 50], and allows matching of MR severity with symptoms development [6]. An exercise induced increase in EROA by ≥13 mm² proved to be a predictor of mortality and of hospital admission for heart failure in patients with SMR [50].

Several methods can be used to quantify the severity of SMR at rest and during exercise (i.e. Doppler volumetric method and PISA method) [37]. However, during exercise, the most robust are the Doppler volumetric method and the PISA method [51]. EROA estimation using the PISA method during ESE was validated against Doppler volumetric method [51] and is quick to perform in experienced hands. It has also the most robust body of evidence in the quantification of SMR at rest. Consequently, we recommend quantification of SMR severity during ESE by EROA estimation with the PISA method.

The most recent guidelines of the European Society of Cardiology on the management of valvular heart disease emphasize that the dynamic component of SMR can be assessed and quantified by ESE. In patients capable of exercising, ESE should thus be considered whenever possible when surgical revascularization is contemplated [36].

Based on our experience, ESE may be of interest in the following categories of patients: (1) in patients with LV dysfunction who present exertional dyspnea out of proportion to the severity of resting LV dysfunction or MR severity; (2) in patients in whom acute pulmonary oedema occurs without any obvious causes; (3) to unmask patients at high risk of mortality and heart failure; (4) before surgical revascularization in patients with moderate ischaemic MR; and (5) following surgery, to identify persistence of pulmonary hypertension and explain the absence of functional class improvement.

ESE requires a dedicated tilting table, continuous electrocardiographic monitoring, advanced life support facilities, and medical personnel with adequate expertise in the field. A symptom limited and graded exercise test (workload increase by 25 watts each 2 min) is recommended. In the absence of symptoms, the test should be continued until 85 % of the age predicted heart rate is reached. The test should not be performed in NYHA class IV patients, in patients with uncontrolled blood pressure values at rest (systolic arterial pressure >200 mmHg or diastolic arterial pressure >110 mmHg), in symptomatic patients or patients with uncontrolled arrhythmias or unable or unwilling to perform such a test.

A complete resting echocardiography is performed at rest, prior to exercise. Image acquisition both at rest and during exercise is done with the patient on a tilting table located on the left side of the sonographer. The following imaging sequence is recommended to be recorded during the test: continuous-wave Doppler imaging of the tricuspid valve for assessment of peak systolic trans-tricuspid gradient, pulsed-wave Doppler at the level of the mitral leaflet tips for the LV inflow profile (only at low level exercise, before fusion of the early and late trans mitral diastolic velocity), at the level of the mitral annulus and of the LVOT for stroke volume cal-

culation, colour Doppler imaging of the mitral valve for the PISA radius measurement, continuous-wave Doppler imaging of the MR jet, and gray scale loops focused on the LV in apical 4-, 2- and 3-chamber views.

ESE enables continuous observation of all mechanisms involved in SMR genesis during each step of the exercise: changes in MV geometry during exercise (such as tenting area, coaptation distance), changes in global and regional LV systolic function (viable or ischemic myocardium), detection of LV dyssynchrony, and most importantly, accurate and reproducible quantification of SMR through the measurement of EROA and RV by the PISA method or the Doppler volumetric method. Additionally, it enables assessment of the upstream consequences of SMR, with estimation of pulmonary artery systolic pressure during each step of the exercise.

After ESE and with careful off-line analysis of the acquired images, the following questions should find an answer: (1) what happens with the MR: does it increase/decrease or remains unchanged?; (2) does the tethering on MV increase/decrease or remain unchanged?; (3) are there new wall motion abnormalities or is there a recruitment of the hibernating myocardium?; (4) is there a significant and rapid increase in systolic pulmonary artery pressure with exercise?; (5) what is the mechanism of MR behavior during exercise: a decrease in closing forces or an increase in tethering of the MV?

Dobutamine stress echocardiography (DSE) is essentially used to assess the presence of myocardial viability in patients with SMR. Identification of viable myocardium predicts the likelihood of functional recovery and positive reverse remodeling after revascularization [52], beta-blocker treatment [53] or cardiac resynchronization therapy [54]. Dobutamine is known to decrease preload and afterload and increase LV contractility, creating thus haemodynamic conditions that are “artificial” as opposed to the haemodynamic load imposed on the LV during every-day life activities. Overall, dobutamine induces haemodynamic changes that usually lead to a decrease in SMR severity, with some notable exceptions. In the rare patients with inducible ischaemia in the anterolateral, inferior and inferolateral LV wall, SMR severity may increase. In such patients, the transient regional LV systolic dysfunction that leads to leaflet tethering and the concomitant decrease in closing forces may be responsible for the increase in SMR severity. In these patients, revascularization of the coronary artery responsible for myocardial ischaemia abolishes this type of SMR. In other patients, the increase in contractility of non-ischaemic myocardial segments may not be enough to properly close the MV in systole. The increase in intracavitary systolic pressure determined by the increase in contractility of the unaffected myocardial segments may lead to expansion of scarred inferior, posterior or lateral walls that will increase the tethering forces and lead to an increase in SMR severity. Hence, decrease in SMR severity is not the rule with DSE.

Role of 3D During MitraClip Therapy

SMR is at present the most common indication for MitraClip use in Europe. Echocardiography, especially TOE, plays an important role in patient selection for MitraClip procedures and in guiding the intervention. The first step of the echocardiographic approach in patients planned for a MitraClip therapy is to confirm that SMR remains severe, despite optimal medical therapy, revascularization or cardiac synchronization therapy (with TTE). The second step is the evaluation of the extent of MV morphological changes that could influence the device implantation (with TOE).

MV morphology assessment According to EVEREST criteria, the suitability of MitraClip therapy can be established by analyzing the leaflet apposition-coaptation shape [55, 56]. The ideal valve lesion correctable with the percutaneous Mitraclip approach consists of a symmetrical mal-apposition of structurally normal leaflets, ideally at the A2-P2 level, and without a complete coaptation gap between the leaflets (at least 2 mm of coaptation length present) [55–57]. The coaptation height of the two leaflets has to be strictly smaller than 11 mm to make sure no technical difficulties will be encountered during the procedure (leaflets too low to grasp). Leaflet fibrotic retraction (usually leading to a Carpentier IIIa type of MR), calcifications of the free-edges of the leaflets at the site of grasping, significant difference between the leaflets thickness at the site of grasping, are all considered to be unfavorable morphologic modifications of the MV that preclude edge-to-edge transcutaneous approach to resolve SMR. The mitral valve area in diastole has to be superior to 4.0 cm^2 to make sure that no significant iatrogenic mitral stenosis develops after the procedure. Measurement of the length of the mobile part of the posterior leaflet (from edge to leaflet base >10 mm) is important before procedure planning to make sure enough leaflet tissue will be available for correct grasping. All these measurements are usually performed with 2D TOE and 3D TOE, when available, may be useful.

Monitoring during implantation 2D TOE is essential to monitor the MitraClip procedure, including trans-septal puncture site, guidance of the delivery system towards the MV, detection of the "landing site", adjustment of opened clip perpendicular to coaptation line, grasping and leaflet insertion, effectiveness on MR downgrading and assessment of residual mitral valve area after clip implantation [57]. Real-time 3D TOE is complementary to 2D TOE during the procedure, and may facilitate appropriate MitraClip orientation and a more rapid detection of the 'lading site' and of its surroundings. A successful MitraClip procedure reduces significantly or ideally abolishes SMR without creating an iatrogenic mitral stenosis. Transmitral diastolic pressure gradient and the smallest valve area are important parameters to assess before the final clip deployment.

Future Direction
Despite the dire prognosis it brings with it when present, it is not yet fully accepted that systematic correction of SMR improves the outcome of these patients. Hence, better understanding of the origin and evolution of SMR is necessary to enable building more effective therapeutic strategies of this complex valvular disease. Detailed mapping of the geometric substrates promoting SMR will likely allow developing tailor-made innovative technical approaches, targeted towards specific mechanisms. Advances in diagnostic imaging techniques will continue to play a major role in the assessment of SMR.

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Chapter 7
Left Ventricular Contactile Reserve

Serban Mihaileanu

Introduction

Investigation of left ventricle contractile reserve (CR), in heart failure, is an enthusiastic way to approach a very complex situation. In clinical terms, CR is a virtual ability of the LV to augment its performance, accordingly to inotropic stimulation. There are several ways, through different mechanisms, to demonstrate the inotropic response. Choosing the most appropriate method is the beginning of a good interpretation.

The aim of this chapter is to try to familiarize clinical cardiologists with the fundamental relationship between left ventricular contraction and afterload, which is a governing principle in heart failure. J. Ross brought to light the concept of afterload mismatch, considered by some physiologists as important as the Frank-Starling law. It is difficult to conceive the ventricular contraction, as well as the contractile reserve, isolated from the ventriculo-arterial coupling. Is contraction more important than arterial elastance? Contractile reserve is a virtual situation: the way to demonstrate it needs to go through fundamentals.

Several important cardiac properties and physio-pathological situations related to this subject will briefly be enumerated.

The Force-Frequency Relation (FFR) or the Bowditch treppe effect or the staircase effect Consists in increasing contractility along with the increased heart frequency. Increasing contraction force when heart frequency increase, is one of the main investigative way for contractile reserve. This property of cardiac muscle is amplified by β-adrenergic stimulation, and, in a coordinated way, the neurohumoral

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M. Dorobanțu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_7

state alters both frequency (acting on the sinoatrial node) as well as force generation (modifying ventricular myocytes). This synchronized tuning is needed to meet new metabolic demands [1]. In failing hearts the FFR may have a negative treppe at HR >100/min, suggesting that a correlation between myocardial disease and optimal contraction frequency may exists. The negative treppe can be shifted even much lower in advanced heart failure [2]. Many studies on contractility reserve are based on the FFR effect: increasing frequency – increases contractility. However, an expected positive effect may be negative from the beginning of the study.

Afterload mismatch John Ross defined this historical concept: "Afterload mismatch may be simply described as the inability of the left ventricle, operating in any stable level of inotropic state, to maintain a normal stroke volume against the prevailing systolic load on the ventricle, and it generally occurs in the setting of limited preload reserve" [3]. Limited or exhausted preload reserve means the situation where LV cannot more benefit from the length-tension relationship, no more inotropy being added if preload increases. Ross defined also the concept of afterload sensitivity, in conditions of altered contractility and preload reserve fully utilized. In such situations, an afterload mismatch may occur at different levels of systolic pressure and stroke volume. In simple words, when preload and contractile reserves are exhausted, the LV function is mostly governed by the afterload status. The afterload mismatch is a core situation in heart failure, well defined by the ventriculo-arterial coupling. In case of afterload mismatch, contractility reserve measured by volumetric tests (stroke volume, ejection fraction) cannot be highlighted by those clinical stress tests that may significantly augment the afterload.

The Metaboreflex During physical exercise, the muscle metaboreflex is a cardiovascular reflex capable to provoke marked increases in sympathetic activity during exercise. The efferent response to metaboreflex activation is an increase in sympathetic nerve activity that constricts the systemic vasculature and also stimulates parallel inotropic and chronotropic effects on the heart as to increase cardiac output [4]. Metaboreflex activation in patients with congestive heart failure will raise the blood pressure, mostly due to an exaggerated increase of the systemic vascular resistances but not by the stroke volume. Blood pressure increase, in those patients is achieved by shifting from an output-increase to a vasoconstriction mediated mechanism. This shift may contribute to the early fatigue experienced by CHF patients [5]. In heart failure patients, this shift might be due to an abnormal response to high sympathetic activity, determining coronary constriction and leading to impaired cardiac function and limited cardiac output [6]. Exercise testing in heart failure patients has to take into account that an existing contractile reserve may by blunted by abnormal high systemic resistances and/or effort induced myocardial ischemia.

The Gregg Effect Increased coronary perfusion determines increased contractility. Increased perfusion pressure increases microvascular volume, thereby opening stretch-activated ion channels, resulting in an increased intracellular Ca_2+ transient, which is followed by an increase in Ca_2+ sensitivity and higher muscle contractility [7].

Pharmacological tests used for LV contractile reserve investigation The most widespread pharmacological test uses Dobutamine, which is a potent inotrope, with weaker chronotropic activity, often producing mild vasodilation at lower doses (≤5 μg/kg/min). Doses up to 15 μg/kg/min increases cardiac contractility without greatly affecting peripheral resistance; vasoconstriction progressively dominates at higher infusion rates [8]. For this property, the low doses Dobutamine infusion protocol is widely used for CR. At higher doses tachycardia, hypertension and maybe myocardial ischemia may blunt the result, diminishing the contractile response.

Based on the Gregg effect, Dipyridamole, as a potent coronary vasodilator, was used to investigate contractile reserve [9].

Exercise testing No standard protocol exists; upright, supine or semi-supine exercise is mostly used in Europe, while treadmill exercise is more popular in North America. Normally exercise hemodynamic should be investigated in upright position but echo-Doppler imaging during upright treadmill exercise is quite inaccessible. Semi-supine exercise offers a good compromise, permitting imaging during exercise. An exercise protocol for HFpEF is proposed by Erdei et al. [10].

Contractility Indices

Contractility, except in vitro studies, doesn't function in a stand-alone mode. A comprehensive approach has to integrate the results into the ventriculo-arterial coupling (VAC) concept, which is determined by the relation between arterial effective elastance (Ea) and ventricular end-systolic elastance (Ees).

Left ventricular Elastance (Ees) and Pressure-Volume Loops Elastance is the opposite term of compliance or distensibility, referring to elasticity. Both elastance and compliance are measured in pressure and volume units: Elastance in mmHg/ml and inversely, compliance in ml/mmHg. Pioneers in the research on contractility, Suga and Sagawa [11] demonstrated that the momentum corresponding to the end of contraction (maximal pressure), at the minimal LV volume (end-systolic), the end-systolic pressure to volume ratio (LVESP/LVESV = ESPVR) is rather insensitive to loading conditions but sensitive to inotropic interventions (Fig. 7.1).

Several pressure-volumes curves can be obtained relative to a variable, like contractility, afterload or preload. Connecting the points from each curve, corresponding to the upper left corner, the end-systolic pressure-volume ratio, will draw a linear relationship of the different ESPVR points, which is characterized by the elastance slope (Ees). The point where this slope intercepts the zero pressure line is the "zero volume (Vo)" which means the theoretical LV volume at zero pressure. The elastance formula is based on Ees = LVESP/(LVESV − Vo) or LVESP/(LVEDV-SV-V0) where LVESV is the end-systolic volume, SV is the Stroke Volume, Vo the theoretical volume when no pressure is generated and LVESP the end systolic pressure. The V0 is a point above the 0 line but it can also be negative [12]. Within physiological

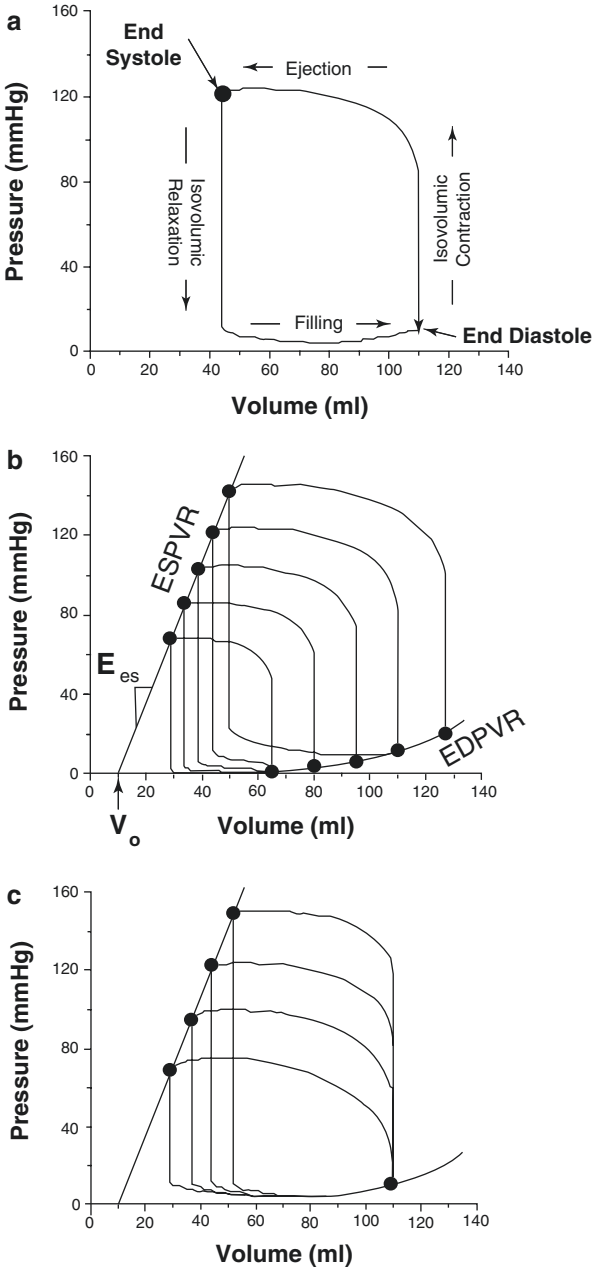

Fig. 7.1 (**a**) The four phases of the cardiac cycle are readily displayed on the pressure-volume loop, which is constructed by plotting instantaneous pressure vs. volume. This loop repeats with each cardiac cycle and shows how the heart transitions from its end-diastolic state to the end-systolic state and back. (**b**) With a constant contractile state and afterload resistance, a progressive reduction in ventricular filling pressure causes the loops to shift toward lower volumes at both end

limits, elastance is a load-independent measure of left ventricular contraction (chamber stiffness at end systole). An increase in contractility is depicted by an increase in the slope and a shift in the end-systolic pressure–volume relationship to the left, which means more force of contraction increasing the pressure against the same volume [13] (Fig. 7.2a). A depressed contractility will shift the slope to the right. However, Ees is also determined by structural myocardial modifications, like myocardial stiffness or compliance of the myocytes or fibrosis. A concentric remodeling, a stiffer LV will need higher Ees as to eject into a stiffer aorta. E_{es} should, therefore, be considered an integrated measure of left ventricular chamber performance that can be related to an integrated measure of arterial load (i.e., E_a). In their editorial Chantler and Lakatta [13] stressed out, that because Vo and Ees are measured on a linear segment of a non-linear function, the values of these parameters will covary when inotropic or loading conditions are modified. Burkhoff et al. [12] combining Ees and V0 possible variations during an intervention that increase contractility, obtained four possible situations: an increase in Ees with no change in V0, a decrease in V0 with little change in E_{es}, a decrease in both E_{es} and V_o, or an increase in both Ees and V0. An example of V0 variation is given in Fig. 7.2b. However, when a serial measurement is done on the same subject, LV structure being unchanged, a shift of the ESPVR unambiguously signifies change in intrinsic myocardial contractility, underlining the appropriateness of acute studies. What are we measuring and what should we measure for assessing CR, ESPVR or Ees? Considering that V0 is minimal and can be neglected, the simple ESPVR approach ignores V0, therefore the simple relation between LVESP/LVESV (ESPVR) will be related to Ees. Every new stage of an inotropic intervention will create another point, drawing a line well correlated to Ees. As to offer a wider clinical application for non-invasive studies, Chen et al., calculated a "single-beat Ees" estimation [14] based on: systolic and diastolic pressure, SV, LVEF, pre-ejection time and total ejection time:

Ees = (DBP − (End(est) × SBP × 0.9))/End(est) × SV (DBP: diastolic blood pressure cuff estimation; SBP: systolic arterial pressure by cuff estimation; End(est): estimated normalized ventricular elastance at the onset of ejection; SV: Doppler-derived stroke volume).

End(est) = 0.0275 − 0.165 × LVEF + 0.3656 × (DBP/SBP × 0.9) + 0.515 × End(avg).

systole and end diastole. When the resulting end-systolic pressure-volume points are connected, a reasonably linear end-systolic pressure-volume relationship (ESPVR) is obtained. The linear ESPVR is characterized by a slope (E_{es}) and a volume axis intercept (V_o). In contrast, the diastolic pressure-volume points define a nonlinear end-diastolic pressure-volume relationship (EDPVR). (**c**) When afterload resistance is increased at a constant preload pressure, the loops get narrower and longer and, under idealized conditions, the end-systolic pressure-volume points fall on the same ESPVR as obtained with preload reduction (Daniel Burkhoff et al. [12]) (Reproduced with permission, from the American Physiological Society; Copyright © 2005 by the American Physiological Society)

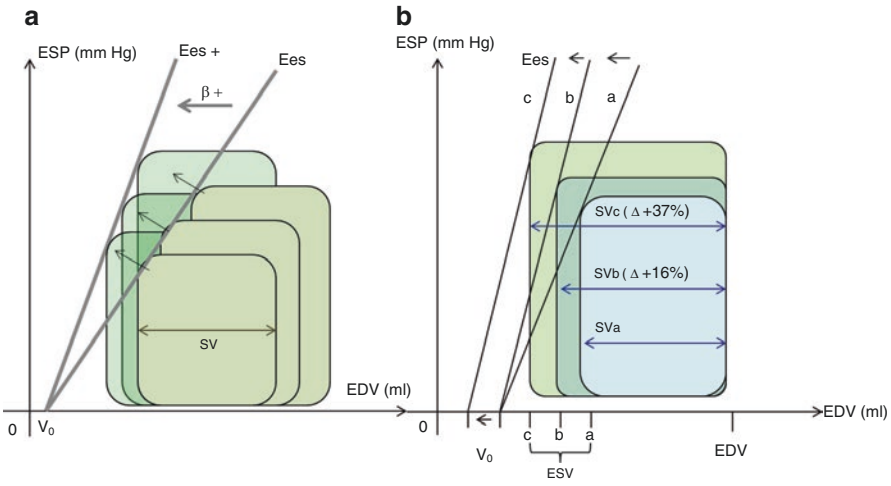

Fig. 7.2 (**a**) Influence of inotropic stimulation on pressure-volume loops, leading to higher end-systolic pressure-volume ratio (ESPVR). Several ESPVR points willdraw the line of end-systolic elastance (Ees). Ees is shifted to left by inotropic stimulation. (**b**) Sketch of stroke volume variation (Flow reserve) under low doses Dobutamine echocardiography, in a failing dilated LV. EDV was considered constant. *ESP*: end-systolic pressure, *EDV*: end-diastolic volume, Δ*SV*: variation of the stroke volume; *a*: basal Ees; *b*: stimulated Ees by 10 μg/kg/min; *c*: stimulated Ees by 20 μg/kg/min. $E_{es}= \frac{ESP}{ESV - V0}$. *a*➔*b*: A moderate increase in +ΔSV but less than 20 %, produced by a shift to the left (*arrow*) of the Ees and a steeper angle related to increased contractility. *b*➔*c* variation depicts the possible diminution of V0, obtaining a shift to the left of the Ees, a more important +ΔSV but due to a lower V0 volume and not by a further increase in contractility – note that Ees (*b*) is parallel to Ees (*c*) without notable angle modification.

End(avg) = 0.35695 − 7.2266 × tNd + 74.249 × tNd^2−307.39 × tNd^3 + 684.54 × tNd^4 – 856.92 × tNd^5+ 571.95 × tNd^6 − 159.1 × tNd^7 (tNd is the ratio of pre-ejection time to total systolic time) [15] where $E_{Nd(est)}$ is group-averaged value adjusted for individual contractile/loading effects, needing computation facilities. This formula is highly sensitive to systolic time intervals, "tNd" being used from 1 to its 7th order! A 5 ms variation for the isovolumic contraction time can lead up to 9 % variation of the calculated Es. Systolic time intervals can be measured by spectral pulsed Doppler or tissue Doppler (Fig. 7.3) at a high scrolling speed, at least 100 mm/s. LVESP is approximated from the brachial artery systolic pressure (greatest obtained value) where LVESP = 0.9 *SBP (brachial artery) [16]. Compared to the ESPVR, this formula is better correlated to Ees, while ESPVR overestimates Ees, especially for greater values. Another way to calculate the "single beat Ees" was published by Shishido et al. [17] requiring invasive measurement of the LVEDP.

$E_{es(SB)} = [P_{ad} + (P_{ad} - P_{ed})/PEP \times ET \times \alpha\text{-}P_{es}]/SV$, ($E_{es(SB)}$: single-beat estimation of Ees, P_{ad}: pressure at the end of isovolumic contraction, P_{ed}: end-diastolic pressure, P_{es}: end-systolic pressure, SV: stroke volume) α = −0.21 + 1.348 × LVEF + 0.682 × ICT/(ICT + ET) (ICT: iso-volumic contraction time: ET: ejection time).

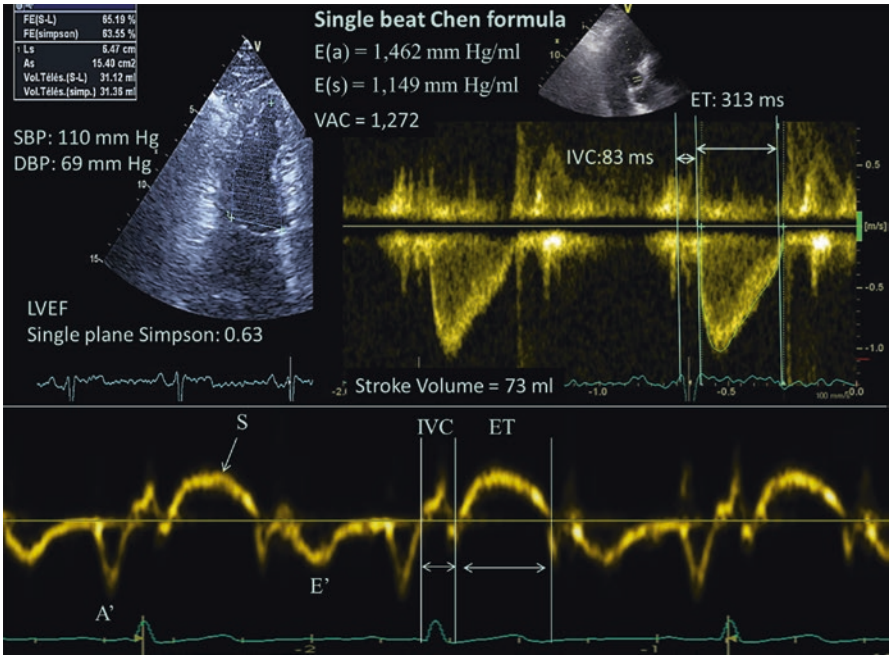

Fig. 7.3 Single-beat Chen formula calculation. Systolic time intervals calculation by spectral Doppler or tissue Doppler

Non-invasive estimation of the LVESP is feasible. A Dobutamine echo study (5 and 10 μg/kg/min) on control subjects vs dilated cardiomyopathy with low LVEF [18] compared Chen's to Shishido's formulas. LVEDP was derived from the Doppler pulmonary venous diastolic deceleration time, LV volumes were computed by 3D echocardiography and LVSP was appreciated by carotid tonometry. In normal subjects mean Es values were 1.8 mmHg/ml (1.7–1.9) using Chen's formula and 2.18 mmHg/ml by Shishido's formula. Chen's formula produced a considerable overlap between the two groups, while Shishido's formula had no overlap and a better reproducibility.

Attention must be payed to systolic time intervals measurements and accuracy of biplane Simpson derived LVEF. High quality brachial blood pressure measurements have to be concomitant to image acquisition. Any kind of arrhythmia can heavily impact the results.

Easier to calculate in non-invasive studies, ESPVR is well correlated to contractility being highly sensitive to contractility reserve. On this basis, Bombardini et al. [19] studied the FFR based indexed Δ ESPVR (variation of the end-systolic pressure-volume ratio: ESPVR mmHg/mL/m^2) in 400 in patients with left ventricular dysfunction (LVEF: 30 ± 9 %) and negative stress echocardiography results. The event-free survival was higher ($p < 0.001$) in patients with ΔESPVR ≥0.4 mmHg/mL/m^2. Same authors, in 10 echo studies on a total number of 1502 patients,

calculated the predictive value for cardiac death (10/10 studies), heart failure or heart failure aggravation (6/10 studies). The positive predictive value was variable, sometimes rather weak (24 % up to 77 %) meantime the negative predictive value was very strong (84 % up to 98 %).

Ees reserve ($\Delta ESPVR \geq 0.4$ mmHg/mL/m^2) was studied for its prognostic value of stress-induced in 891 patients with negative stress echocardiography (exercise, Dobutamine or Dipyridamole). Predictability of the Ees reserve was tested for death and heart failure hospitalization. Best results were found for exercise (AUC = 0.871) and dobutamine (AUC = 0.848) and in lesser degree the VAC reserve (AUC = 0.696) for dipyridamole [20].

Clinical outcome after resynchronsation therapy (CRT) is contractility dependent. Echo derived Δ ESPVR under Dobutamine infusion was used to predict improvement after CRT [21]. The cut-off value for Δ ESPVR was set this time at > 0.72 mmHg/ml/m^2. For the follow-up, responder criteria were: clinical improvement and LVESV decrease > 15 %. Patients with higher ESPVR had better clinical improvement (86 % vs 46 % P < .001) and were better echocardiographic responders to CRT (79 % vs 40 %, P = .002).

Arterial Effective Elastance (Ea) LV doesn't eject in a void space, its function being a part of a more complex system function described as the ventriculo-arterial coupling (VAC). Borlaug and Kass defines this relation as the optimal transfer of blood from heart to periphery without excessive changes in blood pressure or, a way to provide optimal cardiovascular flow reserve without compromising arterial pressure [22]. The LV is coupled to an arterial load composed by: the peripheral vascular resistance (determined, in large part, by the small arteries), total arterial compliance (determined, in large part, by the central elastic arteries), characteristic impedance, and systolic and diastolic time intervals [13]. Sunagawa et al. [23] grouped all the components of the arterial load in an all-in-one single entity named effective arterial elastance (Ea), measured in the same units as the Ees (mmHg/ml) as to can compare LV contraction stiffness to the total arterial load. Ea = LVESP/SV, where LVESP may be estimated as 0.9 × Systolic brachial pressure. Segers et al. [24] based on a mathematical model, concluded that Ea has a linear relation with R/T (R: peripheral vascular resistance; T: cycle length) and 1/C (C: compliance) giving the formula: $Ea = -0.13 + 1.02R/T + 0.31/C$. This formula indicates that R/T contributes about three times more to Ea than arterial stiffness (1/C). This relationship indicates that tachycardia by shortening the cardiac cycle length, sometimes associated to insufficient arterial dilation at exercise, may play a major role in Ea increase. On the other hand, age induced artery stiffening [25] by decreasing the compliance (C), will produce a progressive and irreversible Ea augmentation.

Ventriculo-Arterial Coupling (VAC) Ventriculo-arterial coupling (VAC = Ea/Ees) express the permanent instantaneous interplay between Es and Ea, as to obtain the best possible relation between LV stroke work and systemic circulation and provide an optimal cardiac output at optimal pressure for tissular perfusion. As it was mentioned before, the Ea/Es ratio is related to many variables: LV end-diastolic volume, V0, LV end-systolic volume, systolic time intervals, systolic and diastolic

blood pressure, arterial stiffness and total arterial resistances – integrating therefore the cardio-vascular function. VAC is not a "per se" value. Knowing the VAC ratio value is of equal importance as determining by what modifications, of the numerator and/or denominator, the result was obtained. Abnormal VAC is a key understanding of heart failure with reduced or preserved LVEF. In normal subjects the optimal range of Ea/Ees to cardiac efficiency and stroke work is generally ranging from 0.7 to 1.0 [13, 25–27] or 0.6 to 1.2 [22]. In healthy young subjects, during exercise, increased LV ejection force will act against a compliant aorta and arterial tree as to conduct higher blood volumes. As an approximation, in healthy young subjects, VAC value can be considered around 1. For maintaining the VAC within the optimal limits Ea should diminish or remain stable or, at least, have a minimal augmentation compared to Es.

Heart failure with reduced ejection fraction (HFrEF) VAC reserve was studied by low doses Dobutamine echocardiography, in patients with dilated cardiomyopathy. VAC, had much higher values in patients with DCM compared with controls (Ea/Ees: 2.49 ± 1.02 vs. 1.04 ± 0.21). The coupling reserve cut-off was defined as a >0.29 Ea/Ees decrease, at 20 μg/kg/min Dobutamine infusion. Patients with good VA coupling reserve showed significantly favorable event-free survival compared those with poor VA coupling reserve ($P < 0.001$) [28]. Patients in HFrEF have an increased VAC ratio by a concomitant decrease of the contractility (Ees) and parallel increase of the Ea. Ky et al. [29] in a non-invasive study (single-beat Ees estimation) on 466 patients with HFrEF found that VAC had elevated values at 1.92 (median values; 25th, 75th percentile) by depressed Es (0.89) and elevated Ea (1.66). A very important finding published by the same authors has to be developed: this group of 466 patients with chronic systolic heart failure (low LVEF) was investigated for the combined endpoint of death, cardiac transplantation, or ventricular assist device placement; and 2) cardiac hospitalization. While Es was not found predictable, VA coupling (calculated by $Ea/E_{s\ single\ beat}$), V0 (derived from single-beat Chen formula) and ventricular size were associated to prognosis. In other words, they found that the most prognostic factors were the LV remodeling (V0) and the LV mismatching to the afterload (Ees/Ea =VAC) but not the contractility by itself (Ees). There are several possible developments: in a most important position appears the principle of the VAC, which demonstrates that the afterload sensitivity and mismatch is the great ruler in HF progress. Not the contractility (Ees) by itself, but its relationship to afterload (Ea) results as a governing principle. In the same study V0 was more predictable than Ees. V0 reflects the LV remodeling: dilatation, geometry modifications, wall thickness /cavity relation and indirectly (in some cases) fibrosis. Of course, mirroring such important structural modifications, V0 is naturally a strong predictor.

VA coupling is an independent echocardiographic correlate of BNP levels in patients with previous myocardial infarctions and has a significant role in predicting long-term cardiovascular mortality in this setting [30].

Contractile reserve, in HFrEF, is a virtual situation being subordinated to the VAC status. CR may be "hidden" by an afterload mismatch, with a null result at exercise despite some inotropy reserve.

Heart failure with preserved ejection fraction (HFpEF) HFpEF patients have a lower VAC than normal values. Kawaguchi et al. [31] in a historic study, compared HFpEF patients to normotensive and to hypertensive subjects. End-systolic elastance was higher in patients with HFpEF (4.7 ± 1.5 mm Hg/mL) than in controls (2.1 ± 0.9 mm Hg/mL for normotensives and 3.3 ± 1.0 mm Hg/mL for hypertensives). Effective arterial elastance was also higher (2.6 ± 0.5 versus 1.9 ± 0.5 mm Hg/mL). Both Ees and Ea were significantly higher than controls. Despite that, both numerator and denominator being elevated, the ratio Ea/Ees was much lower in HHpEF than in normal subjects: Ea/Ees = 0.55 vs 0.90 respectively. Very demonstratively, at handgrip exercise (Fig. 7.4) an exaggerated hypertensive response was observed accompanied by an elevation of the LV end-diastolic pressure. It can be summarized that during handgrip was observed a brutal increase of the LV end-systolic pressure, a much higher LV end-diastolic pressure and a lower stroke volume – despite an important raise in ESPVR. Contractile reserve, measured by the Ees variation, when high rest values exists, is somehow exhausted, leaving to further inotropic stimulation to few reserve as to increase SV against a very elevated afterload. The same study considers that energy cost is predicted to be >50 % higher HFpEF versus controls and might limit reserve in those with concomitant heart or coronary artery disease. Borlaug and Kass made an important statement: "Perhaps more important than the coupling ratio of ventricular and vascular stiffness are their absolute values" [22] which seems to be the core situation in the HFpEF. Further studies for cardiac reserve in HFpEF patients demonstrated the inability to increase cardiac output with exercise. During upright cycle ergometry at maximal effort, HFpEF patients have a threefold smaller increase in Ees and a reduced ability to lower their peripheral resistance and increase their heart rate during exercise compared with hypertensive controls with left ventricular hypertrophy [22]. Higher will be Ea and Ees values at rest, more important will be the LV diastolic filling pressure elevation induced by exercise.

Exercise reserve is severely compromised in HFrEF and HFpEF patients, characterized by high VAC due to elevated Ea and lower than normal Ees in HFrEF and in an opposite situation, HFrEF being dominated by high Ees, high Ea, and low VAC ratio – leaving a low or absent reserve of SV and LVEF (Fig. 7.5).

Ventricular and arterial elastance alone or integrated into the ventriculo-arterial coupling, permits today by non-invasive approach a better understanding of the pathology and a better choice of the method to use for investigation. Simplified formulas made them affordable in clinical research and practice, but don't cover the entire hemodynamic complexity. The fundamental advantage comes from the demonstrative influence of the Ea and Ees abnormalities, on stroke volume, ejection fraction, pre-load pressure sensitivity, pressure lability, hypertension and some important aspects of cardiovascular reserve during exercise [32]. However there are also limitations [32]: Ea being influenced by heart rate is not a pure arterial load index being highly dependent on resistances and insensitive to changes in pulsatile load, therefore not measuring the arterial stiffness. Ees disadvantages come from the non-linearity of the ESPVR and from the fact that Ees is in part influenced by preload and afterload; finally Ees doesn't asses myocardial properties (geometry, fibrosis). V0 gets bigger in dilated hearts and may have important variations.

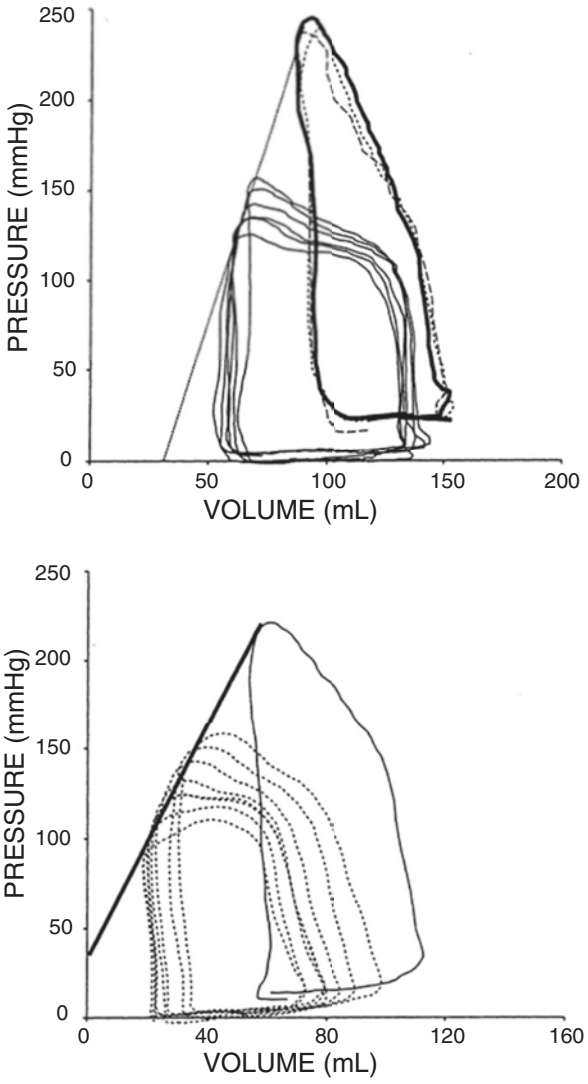

Fig. 7.4 Pressure-volume loops before (*dashed line*) and after (*dark solid line*) sustained isometric handgrip in 2 patients with HF-nlEF. Baseline loops display elevated Ees and Ea, predicting the marked hypertensive response with loading. This was accompanied by increased EDP and prolonged relaxation (see text), supporting a mechanism whereby ventricular-arterial stiffening could couple to diastolic dysfunction (With permission, from Miho Kawaguchi et al. [31]. Copyright © Wolters Kluwer Health, Inc.)

Above those limitations, Ees, Ea and Ea/Ees brought the best definitions in heart failure, providing the understanding of the contractile function and reserve integrated into the VAC. On the other hand, the simple calculation of the ESPVR, simple to use, may easily improve the clinical dynamic tests.

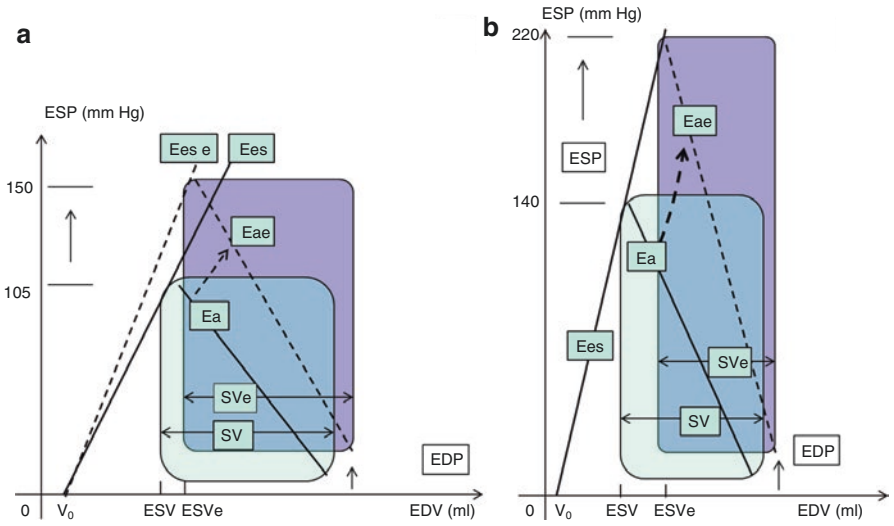

Fig. 7.5 Sketch of two possible ways to not-increase SV at exercise. *ESP* end-systolic pressure, *EDP* end-diastolic pressure, *EDV* end-diastolic volume, *ESV* basal end-systolic volume, *ESVe* exercise end-systolic volume, *SV* basal stroke volume, *SVe* stroke volume at exercise, *Ees* end-systolic elastance, *Ea* basal effective arterial elastance, *Eae* effective arterial elastance at exercise, *A* HFrEF and *B* HFpEF. (**a**) Exercise blunting of the contractile reserve by afterload sensitivity. Starting from a high ventriculo-arterial coupling (high afterload and depressed Ees) an increase of Ees at exercise is counterbalanced by a concomitant increase of Ea (high arterial resistances ± elevated heart rate) resulting in null increase in SV (SV = SVe) and concomitantly augmentation of EDP, leading to dyspnea. (**b**) Inspired from (Kawaguchi et al. [31]). Low ventriculo-arterial coupling but at high values of Ea and Ees. High contractility at rest is needed for basal circulatory requirements leaving therefore to few or no reserve as to increase SV against very high Ea at exercise, leading to a non-augmentation or even a diminution of SV at exercise (Sve<SV), accomagnied by hypertension and elevated EDP. High Ees and Ea at rest may predict hypertensive response at exercise (Kawaguchi et al. [31])

Stroke Volume and Ejection Fraction

Ejection fraction (LVEF) and SV are the most popular volumetric indices of the left ventricle (LV). LVEF represents the ratio between SV and left ventricle end-diastolic volume (LVEDV) as follows: LVEF= SV/LVEDV, it can be also expressed as the ratio: (LVED-LVES)/LVED. LVEF as SV are load dependent. Cohen-Solal et al. [33] demonstrated the inverse relationship between LVEF and VAC: $\frac{Ea}{Ees}$ (VAC) = $\frac{1}{\text{LVEF}} - 1$. Extracting LVEF from the equation will give the same inverse relationship: LVEF = $\frac{1}{\frac{Ea}{Ees}+1}$. Extracting by another way, it gives:

LVEF = $\frac{Es}{Ea + Ees}$. At the first look, it becomes easy understandable. This way to describe LVEF has an advantage over the standard calculation, highlighting, both for the numerator as for the denominator, a much more comprehensive cardio-vascular coupling situation. Examining these fractions, will make understandable, if an abnormal result is due to LV or to arterial alteration or both. Considering that Ees an Ea are fractions, a further simple development, lead to:

LVEF = $\frac{LVESP \times LVESV \times SV}{LVESP \times LVESV \times SV + \left(LVESV^2 \times LVESP\right)}$, where a strong inverse relation is demonstrated, between LVEF versus systolic pressure and the square value of the end-systolic volume, explaining why, in all published studies, LVESV is such a strong predictor.

Why exercise may blunt LVEF? Starting from the inverse relation between LVEF and the coupling ratio: $\frac{Ea}{Ees} = \frac{1}{\text{LVEF}} - 1$, by simplifying the formula we obtain: LVEF= Ees/(Ees+Ea) This way to look at LVEF, indicates a direct relation to Ees (numerator) and inverserelation to the sum of Ees+Ea (denominator).

If we should take, as an example, the published mean values by Asanoi et al. [26], in a group of patients with heart failure and LVEF ≤ 39 % and imagine an exercise echocardiography for contractile reserve estimation.

Basal: Ees = 1.5 mmHg/ml; Ea = 2.7 mmHg/ml.

Calculating basal $\text{LVEF}_{(\text{LVEF} = \text{Ees}/(\text{Ea}+\text{Ees}))}$ = 1.5/(1.5+2.7)= 0.357 (36 %).

Increasing Ees by +25 % (Ees = 1.875) at stable Ea (Ea= 2.7) ➔ LVEF =0.409 (Gain + 5.2 points).

Increasing Ees by +25 % (Ees = 1.875) and +7 % increase for Ea (Ea= 2.889) ➔ LVEF =0.39 (Gain + 3.3 points).

As to get 5 points gain of the LVEF as an indicator of contractile reserve, Ees has to increase by +25 % keeping the Ea constant. In this exercise case, is put in evidence the determining role of the afterload for the LVEF. If Ea should increase by only 7 %, during the study, LVEF will fall by 2 points, in other words, despite 25 % increase of in contractility LVEF is unable to gain more than 3 points, therefore giving a negative result for the test. For a considerable increase of the contraction force, a mild increase in arterial elastance, demonstrates a net blunting effect over the final LVEF augmentation. This simple numerical exercise, tries to promote the understanding that LVEF results from a permanent cross-talk between Ees and Ea, being subordinated to the VAC and might explain the lesser sensitivity of the LVEF to contractility itself. This explains why, LVEF is not a strong contractility discriminator but regarded as a composite result of Ees and Ea, LVEF is as a powerful predictor.

Global function systolic measurements, commonly used, as SV, LVEF, dP/dT, global strain, are load dependent. Contractile reserve investigation in heart failure is confronted to two contrasted situations: high VAC in HFrEF (lower Ees and higher

Ea) and low VAC in HFpEF (high Ees and high Ea). It is not yet, clearly defined, what tests to use for different pathologies, ages or gender. However, low doses Dobutamine at steady heart rate, could be the most appropriate to incite inotropy betting on a not-high peripheral response. On the other hand, exercise, adding or not the handgrip, by its physiological property to provoke an important peripheral response and therefore push to a "face-to-face" Ees-Ea relation, will provide excellent data on LV coupling to systemic circulation.

Leung et al. [34] in a study by exercise echocardiography, in patients with chronic mitral regurgitation, found that an exercise LV end-systolic volume index >25 cm^3/m^2 was the best predictor of postoperative dysfunction, with a sensitivity and specificity of 83 %. At exercise, this finding corresponded to a 3 % LVEF increment, less but also predictive. As it was stated before, it is to underline the powerful prediction role of the end-systolic LV volume. A more recent work [35] on asymptomatic patients suffering of severe mitral regurgitation (MR) started from the assumption that asymptomatic patients with chronic severe (MR) may develop irreversible left LV dysfunction despite a normal resting LVEF, which can hide behind already irreversible myocardial damage. The difference between the resting and post-exercise LVEF was defined as CR: a post-exercise LVEF increment of ~ 4 % was defined as CR+. In patients undergoing surgery, CR was an independent predictor of follow up.

Treadmill exercise echocardiography was performed in patients with severe aortic regurgitation. Contractile reserve was considered positive (CR+) if an increase in LVEF was present at exercise. LV end-systolic volume was an independent predictor of CR+ [36]. Of great interest in this study was that patients with ≥75 LVED and ≥55 mm LVES, compared to those with ≤75 LVED and ≤55 mm LVES had a diminished LVEF (0.67±7.1 vs −3.9±9.9; p= 0.041) accompanied by a higher blood pressure increment after treadmill exercise (181.6 ± 26.6 vs 202.2 ± 17.7 $p < 0.001$) suggesting a much heavier VAC alteration due to a more advanced systemic disease.

The problem we have to face is that LVEF and Volumes Depends on the Imaging Method [37]. Compared to cardiac magnetic resonance (CMR) as a gold standard, LVEDV and LVESV measured with all echocardiographic methods were smaller and showed greater variability than those derived from CMR. Regarding agreement with CMR and reproducibility, all studies showed superiority of contrast 2D echocardiography over non-contrast 2D echo and superiority of the 3D echo over 2D echo. In this study, compared to CMR, 3D echo studies generally had no bias. Another difficulty for LVEF is the beat to beat variability which has been reported up to 5.8 ± 1.7 %. In the absence of 3D echo facilities, LV volume in serial measurements, for contractility reserve, contains some hazard since small tracing errors will become cubic – Simpson's modified rule being based on the sum of a stack of cylinders. During stress echocardiography, the 2-chamber view may not be available due to pulmonary interposition, so one single section is computed in volume, leading sometimes to obscuring discrete variations.

Measuring SV is mandatory for LVEF calculation as well as for small variations during the stress echo-Doppler examination. Considering that LV subaortic area doesn't significantly change with increasing blood flow, measuring the velocity time integral (ΔVTI) variations indicates the Δ SV. Unless the clinical test doesn't significantly increase Ea, like low doses Dobutamine in patients with low LVEF, the result (Δ SV and/or Δ LVEF) will be close enough to inotropy to ascertain a contractile reserve and unveil an afterload mismatch. Pursuing at higher Dobutamine doses or performing exercise tests, will bring into play a much more complex hemodynamic response: chronotropic response, high blood pressure, eventually myocardial ischemia, pulmonary arteriolar resistances, peripheral and myocardial oxygen consumption or global energy reserve. Increasing afterload (Ea) may reinforce the afterload mismatch but also demonstrate the etiology of dyspnea or fatigue and put in evidence an abnormal blood pressure response.

Stroke Volume and Flow Reserve Stroke volume (SV) is a simple and reliable method for contractile reserve estimation. Easy to use, even in difficult clinical conditions, or during stress echocardiography, SV variations (Δ) are a simple evidence of the end-product of all the aforementioned mechanisms. Based on the product between subaortic surface and the Doppler VTI measurement, for serial measurements, it can be simplified to the ΔVTI since the sub-annular region doesn't have significant size variations at flow augmentation. Pibarot and Dumesnil [38] prefer the term flow reserve instead of contractile reserve.

Monin et al. studied 45 patients with aortic stenosis with severe LV dysfunction and low transvalvular pressure gradients using low doses Dobutamine echo-Doppler examination [39]. This study was followed by the French multicenter study on 136 patients on the same pathology, using the same methodology [40]. Dobutamine infusion started at 5 μg/kg/min up to 20 μg/kg per min. The Dobutamine infusion was stopped when the maximal dose or heart rate acceleration ≥10 beats/min was reached. LV contractile reserve was considered positive (CR+) if an increase in SV of ≥20 % was observed. CR+ patients had a low operative risk (5 %) and a good long-term prognosis, whereas operative mortality was high (32 %) in the absence of contractile reserve. However, despite the higher operative mortality, survivors with low/absent contractile reserve had a net improvement in functional status. Tribouilloy et al. studied 81 patients with low-flow/low gradient symptomatic aortic stenosis (mean pressure gradient ≤40 mm Hg, LVEF ≤40 %) without CR on Dobutamine echocardiography, prospectively enrolled in 10 centers [41]. In patients with CR-, aortic valve replacement was associated with a better outcome compared with medical management, indicating that, only on the basis of this criteria, surgery should not be withheld. In our personal series, we have assessed 52 patients with dilated cardiomyopathy having an end diastolic diameter >70 mm. Patients were already or in progress for admission on heart transplant waiting list. As an alternative to heart transplantion, a left ventricle remodeling procedure (Batista procedure) was proposed. Considering the high risk surgery, Dobutamine echocardiography was

performed for patients selection. As we considered this type of surgery at a very high risk, the Δ SV was set high (≥30 %) and was found to be the most powerful predictive parameter for good surgical outcome. Interestingly, patients who underwent the Batista operation showed, on myocardial specimen, mild myocardial fibrosis or none at all. On the other hand, those patients with <30 % SV augmentation, non-included for Batista intervention, who underwent heart transplantation, showed in all cases diffuse moderate or severe myocardial fibrosis [42].

LV Longitudinal Function

Longitudinal contraction, without being a global contraction index is highly sensitive to inotropy modifications and is a major determinant of the global systolic function. Considering the right handed / left handed helix arrangements of the fibers, it is preferably to speak about longitudinal contraction instead of longitudinal fibers. Sub-endocardial layer, the first to suffer in a broad spectrum of pathologies, has a strong impact on longitudinal contraction.

Doppler Tissue Imaging (DTI) Seo et al. [43], compared in an animal study the S′ wave and LVEF against LV dP/dt: S′ had a much stronger correlation to dP/dt than LVEF: r = 0.665 vs r = 0.40, respectively. At the same time S′ was correlated to apical rotation (r = 0.674) leading to the conclusion that *S′* is a more sensitive index of global LV contractility than is LVEF, reflecting both LV longitudinal shortening and torsional deformation. Once again, it has to be underlined that LVEF is determined by the ventriculo-arterial coupling therefore is not a pure contractility index. Meantime longitudinal contraction velocity is much closer to contractility. Without being a global contractility index, it correlates well to global contractility, describing well enough two of three contraction vectors, longitudinal and spiral. DTI will describe the contraction velocity at the place where the Doppler sample is located. Longitudinal contraction velocity recorded at the base of LV (mitral valve annulus) reflects well the LV contractility however as the contraction is unequal, postero-lateral higher versus antero-septal lower, more sampling zones need to be used as to obtain best reliable results. Simple to use, very affordable for Dobutamine or exercise testing, S′ is a good reliable tool for contractile reserve investigation. Ciampi et al. [44] in a prospective study on 89 patients in HFrEF (LVEF < 45 %), compared the S′ variations, during Dobutamine and exercise echocardiography, to the pressure volume ratio (ESPVR) – which was considered for this study a standard of contractile reserve. The cut-off for contractile reserve by ESPVR was set at Δ >0.72 mmHg/mL/m. Patients with a Δ S′ >2 cm/s during the Dobutamine echocardiography had a significantly higher ESPVR, a higher peak VO_2 and a better diastolic filling with a lower E/E' ratio.

LV myocardial strain 2D speckle tracking echocardiography provides reliable data on deformation imaging. Myocardial strain indicates a relative shortening or

lengthening of the myocardium without discrimination between active deformation or passive deformation. Myocardial strain is a shortening or lengthening fraction, measured in the orthogonal planes. The systolic strain rate, meaning length variations over time (contraction velocity) is in theory a pure contractility indicator; however technology is not yet ready to provide a reliable system for a global strain rate assessment. Compared to LVEF or SV, the LV strain suffers from the same load dependency. 2D strain is very imaging sensitive; on the other hand, myocardial contrast agents blur the speckles. Lancellotti et al. [45]. Measured the global longitudinal strain (GLS) at exercise echocardiography, and found GLS predictive for post-operative LV dysfunction in patients with degenerative mitral regurgitation. Chronic LV overload due to mitral regurgitation is accompanied by an increase in LVEF which can mask behind, high or normal values, more severe myocardial damages than expected. Magne et al. [46] tested the predictive power of GLS in patients with > than moderate mitral regurgitation. Exercise improvement of GLS by >2 % and LVEF ≥ +4 % were set as markers of contractile reserve (CR+) and compared to each other in terms of predictability. GLS (CR+) patients had lower BNP levels. CR judged upon LVEF, was not predictive for 2 years event-free survival; on the contrary GLS was an independent powerful predictor. LA volume (cut-off: 40 ml/m^2) was found also an independent predictor but, interestingly, regardless the LA volume, GLS (CR+) patients had a better outcome.

Starting from the idea that deformation and ejection fraction have similarities, Benyounes et al. [47] found a good correlation between LVEF and GLS ($r = -0.53$; $P < 0.001$) which was improved when echogenicity was good ($r = -0.60$; $P < 0.001$). A GLS ≥ − 14 %, allowed detection of LVEF ≤40 % with a sensitivity of 95 % and specificity of 86 %. Using combined measurement may add diagnostic security (Fig. 7.6). In the same perspective, Hasselberg et al. [48] compared GLS to LVEF in a group of patients who underwent cardiopulmonary exercise testing, with peak VO2 measuring. LVEF and LGS, for the all group patients, had the same good correlation to peak VO2 (LVEF: r = 0.62, p < 0.001 and LGS: r = − 0.63, p < 0.001). However, in a HFpEF identified subgroup of 37 patients, LVEF did not correlate to the peak VO2, while LGS had a fair correlation (r = 0.50, p = 0.02). A GLS value of −17.3 % had an excellent sensitivity of 0.89 (95 % CI 0.79–0.95) and specificity of 0.91 (95 % CI 0.71–0.99) to identify patients with a peak VO_2 of <20 mL/kg/min. Wang et al. [49] studied 80 patients with heart failure and preserved ejection fraction (aged 66 ± 8 years; 64 % male) by exercise echocardiography and a 3 years follow-up for all-cause mortality and/or heart failure. Univariate predictors were: decreased resting left atrial ejection fraction, lower peak heart rate, elevated E/e' ratio, reduced TDI myocardial velocities and impaired 2D global longitudinal strain during exercise. In the event group GLS at rest −17.5 ± 3.7 %, increased to −18.2 ± 3.9 % (NS) while in the non-event group GLS increased from −18.8 ± 2.9 to −21.4 ± 3.9 %. On multivariate analysis, only impaired GLS remained an independent predictor of outcome. It appears that impaired sub-endocardial function at exercise is better reflected by speckle strain imaging than by other methods.

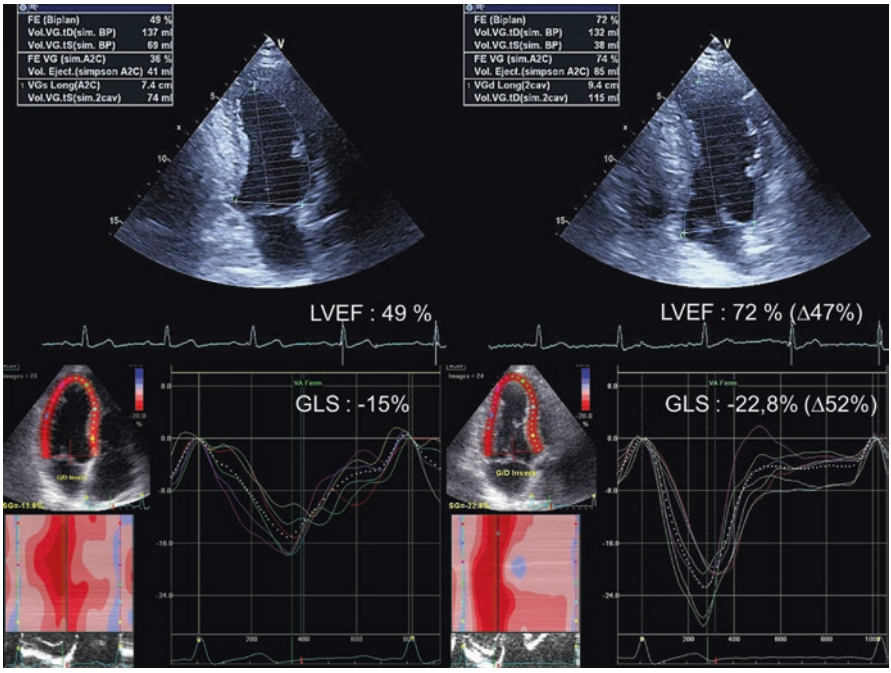

Fig. 7.6 Low doses Dobutamine (5.10 μg/kg/min) echocardiography in a young male adult with mild reduction of the LVEF (47 %) and GLS (−15 %), after myocarditis. Measurements: biplane LVED and LVES, subaortic diameter, subaortic VTI (Doppler), SBP, GLS (speckle tracking), Heart rate (HR). Calculations: SV, LV systolic pressure (SBP*0.9), ESPVR (end-systolic pressure-volume ratio), arterial elastance (Ea) by (SBP*0.9)/SV. ESPVR, being considered ~ Ees (if V0 is ignored) was used for the ventriculo-arterial coupling (Ea/Ees) estimation. LVEF was calculated by three formulas: *1*. Simpson biplane LVEF, *2*. LVEF $_{(SV/LVED)}$ by the SV/LVED ratio, *3*. LVEF= Ees/(Ea+Es). CR+ was demonstrated with nearly threefold increase of the ESPVR; meantime Ea had only a very mild increase (+11 %) leading to an important physiological diminution of the coupling ratio (Ea/Ees), optimizing therefore the LV force to arterial load as to increase SV at low energy cost. Very close results are obtained by calculating LVEF according three different formulas, demonstrating the complex integrative attributes of the LVEF. Note that GLS Δ52 % is very close to ΔLVEF (49 % by LVEF $_{(SV/LVED)}$)

Basal	Dobutamine (10 μg/kg/min) – 5 min	
LVED	137 ml	132 ml
LVES	69 ml	38 ml
Systolic blood pressure	104 mm Hg	169 mm Hg
SV	64 ml	93 ml (+45 %)
Ees = (SBP*0.9)/LVES	1.356 mmHg/ml	4 mmHg/ml (×2.9)
Ea = (SBP*0.9)/SV	1.462 mmHg/ml	1.635 mmHg/ml (× 1.11)
VAC (Ea/Ees)	1.078	0.408 (−62 %)
LVEF $_{(SV/LVED)}$	47 %	70 % (+49 %)
LVEF $_{\text{biplane Simpson}}$	49 %	71 % (+43 %)
LVEF$_{(Es/Ea+Es)}$	48 %	71 % (+48 %)
HR	72/min	62/min
GLS	−15 %	−22.8 % (Δ 52 %)

Future Directions and Possible Developments

Kobayashi et al. [50] predicted already the future, finding that depressed myocardial contractile reserve in dilated cardiomyopathy is related to altered myocardial expression of beta1-adrenergic receptor, altered SERCA2a, and phospholamban genes even in asymptomatic or mildly symptomatic patients with dilated cardiomyopathy. High-Sensitivity ST2 might become a sensitive marker in heart failure [51]. Meantime, cardiologist may hope in a reliable 2D/3D global strain rate imaging.

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Chapter 8
Role of Cardiovascular Magnetic Resonance Imaging in Heart Failure

Anca Florian and Ali Yilmaz

Cardiovascular magnetic resonance (CMR) has evolved as a valuable diagnostic tool by offering comprehensive structural and functional information at a high resolution and practically in any imaging plane without the burden of ionizing radiation exposure. Over the last years, the role of CMR among other non-invasive imaging techniques has been steadily increasing for the whole spectrum of cardiovascular diseases including heart failure (HF) [1–4].

Cardiovascular Magnetic Resonance Techniques

The performance of clinical CMR requires static magnetic fields of 1.5-T or 3.0-T together with a dedicated cardiac coil [5, 6]. Further, a range of fast CMR pulse sequences with different image characteristics – tissue specific relaxation parameters (T1, T2, T2*), motion, flow, perfusion, metabolism etc. – are available using combinations of radiofrequency pulses, magnetic gradient field switches as well as sophisticated data acquisition and reconstruction strategies. Using ECG-gating and breath holding or alternative navigator techniques for compensation of respiratory and cardiac motion, CMR is able to provide anatomical, functional and tissue characterization information in one examination with a duration of approximately 40 min [5, 7].

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M. Dorobanţu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_8

Functional Imaging (cine-CMR)

Currently, retrospective ECG-gated balanced steady-state-free-precession (SSFP) gradient echo sequences are preferably used to acquire cine-CMR loops and they represent the cornerstone of any CMR study. Compared to spoiled gradient echo cine sequences that were mostly used in the past, SSFP achieve better signal-to-noise ratio and temporal resolution together with an enhanced endocardial border delineation ("bright blood imaging") [8]. The acquisition of cine loops in standard imaging planes (similar to echocardiography), including a stack of contiguous short-axis slices completely covering the ventricles, enables a refined assessment of regional and global contractility as well as an accurate and highly reproducible measurement of ventricular volumes, mass and ejection fraction (EF) – free of geometric assumptions and acoustic window limitations [9]. This is particularly valuable for the right ventricle (RV), where echocardiography is limited by the RV's complex geometry [8]. Therefore, CMR is currently considered the non-invasive gold standard for the measurement of left ventricular (LV) and RV volumes and EF [5, 10, 11].

In patients having difficulties in breath holding or a highly irregular ECG rhythm, the use of SSFP can be challenging. In this case, rapid "real-time" cine sequences without synchronization are available, yet with a certain trade-off against spatial and (to a lesser degree) temporal resolution. Additionally, balanced SSFP image quality may be unsatisfactory at 3-T or higher field strengths due to its susceptibility to magnetic field inhomogeneity [7].

Besides the net advantages of evaluating systolic function by CMR, several techniques are also available for the analysis of LV *diastolic function.* Similar to echocardiography, early and atrial mitral inflow velocities can be measured by flow CMR, while myocardial tagging, velocity encoded CMR and newly, feature tracking permit the quantification of diastolic myocardial deformation parameters [12]. Nevertheless, echocardiography is more straightforward and so far remains the standard technique for assessment of diastolic function [13].

Flow CMR

In addition to the visual assessment of cardiac valves in cine images, in/through-plane velocity-encoded phase-sensitive sequences offer accurate blood flow measurement and allow quantification of valvular function. These sequences acquire both magnitude and velocity images in which pixels encode for velocity, enabling the classification of stenotic (peak velocity) valves. Further, by multiplying mean velocity to vessel area in an orthogonal plane relative to flow direction (through-plane), blood volume in the form of valvular output and regurgitant volume as well as regurgitant fraction can be calculated, thereby permitting the quantification of shunts and valvular insufficiencies [14].

Myocardial Perfusion Imaging (MPI)

Myocardial perfusion can be assessed by the timed acquisition of very rapid T1-weighted gradient echo sequences, usually in three LV short-axis slices, during intravenous bolus injection of gadolinium-based contrast agents (0.1–0.2 mmol/kg). This "first pass" imaging technique allows visualization of the dynamic enhancement of the heart (bright) that occurs at first in the cavities and finally in the LV myocardium (via coronary blood supply). The detection of a delayed and/or reduced regional myocardial enhancement (relative dark regions) under hyperemic pharmacological stress (adenosine, dipyridamol or regadenoson) but not at resting conditions – corresponding to one or more coronary artery territories – indicates the presence of inducible ischemia and is usually associated with hemodynamically relevant (>50–75 %) epicardial coronary artery stenosis and/or diseased microvasculature (Fig. 8.3) [7, 14]. MPI-CMR has a considerably higher spatial resolution in comparison to single-photon emission computed tomography (SPECT) or positron emission tomography (PET) and subsequently a higher diagnostic yield for the detection of myocardial ischemia [15]. In some cases, image artefacts (typically a dark endocardial rim artefact) may occur and make image interpretation challenging [16].

New techniques such as accelerated myocardial perfusion CMR can improve spatial resolution (high resolution MPI) or achieve three-dimensional whole heart coverage (3D MPI), while imaging at 3-T offers increased signal-to-noise ratio with high quality images [17].

Myocardial Tissue Characterization

Late Gadolinium Enhancement (LGE) Gadolinium chelates, the only CMR contrast approved for clinical practice, are T1-shortening agents with exclusively extracellular distribution and rapid washout from healthy myocardium. However, the disruption of cellular integrity (inflammation, necrosis) and/or increase in myocardial extracellular space (scar, infiltration, inflammation) lead to retention of gadolinium in the respective areas and subsequent bright signal on T1-weighted gradient echo inversion recovery images, performed 10–20 min after contrast injection (normal myocardium is "nulled" and appears black by manually setting an appropriate "inversion time") [18]. Additionally, phase-sensitive inversion recovery (PSIR) sequences offer increased tissue contrast without the need of manually setting the inversion time [19].

"Black blood imaging" is based on fast spin echo sequences in whom a technique of nulling the blood signal is used in order to better visualize cardiac structure, including the intrinsic characteristics of the myocardium. Among these, pre-contrast (native) and post-contrast ***T1-weighted imaging*** provides an excellent morphologic view of the heart, pericardium, great vessels, and adjacent structures.

Native ***T2-weighted imaging*** detects tissue edema associated with inflammation (acute myocarditis, myocardial infarction, and pericarditis) due to the long T2 relaxation time of increased water content that appears bright. Triple inversion recovery T2-weighted sequences (short tau inversion recovery – STIR) with fat and blood suppression (both appear black) are mostly used nowadays [20]. Insufficient image quality due to arrhythmia or motion artefacts can sometimes limit their diagnostic yield [21]. Alternatively, T2-prepared "bright blood" SSFP sequences are also available and could overcome the problem of "slow flow" artefacts (endocardial bright rim) encountered in the former [22].

T2*-weighted imaging (gradient echo) and the quantification of T2* relaxation time (by T2*-mapping techniques) are validated methods for evaluating excessive myocardial iron secondary to iron overload conditions or myocardial hemorrhage, complicating acute myocardial infarction [23]. Iron depositions alter local magnetic field homogeneity, thereby shortening the T2* relaxation time, a parameter sensitive to iron content.

Evolving CMR Techniques

CMR myocardial deformation imaging techniques have been developed alongside the well-known ultrasonographic methods for quantifying myocardial strain, without the spatial and acoustic window limitations of echocardiography. In the past, *CMR tagging* was considered the imaging gold standard for strain analysis and requires the acquisition of images with a "deformable" superimposed grid (tag lines). However, relatively time-consuming post-processing is the reason why even further optimized tagging techniques are not widely used today. Analogous to speckle tracking echocardiography, *feature-tracking techniques* were more recently introduced as an easier analysis method that tracks the myocardial wall in the standard cine images. The feasibility of CMR feature tracking has been growingly studied in ischemic and non-ischemic cardiomyopathies as well as in adults with complex congenital heart disease and for the assessment of dyssynchrony [12, 24]. However, the diagnostic value of CMR feature-tracking for clinical decision-making is still to be explored.

T1-mapping and extracellular volume (ECV) quantification enable the evaluation of subtle myocardial abnormalities such as diffuse interstitial fibrosis, not depicted by conventional LGE. By performing pre- and post-contrast T1-mapping and determining the respective T1 values, myocardial ECV can be quantified [25, 26]. A modified look-locker inversion recovery (MOLLI) sequence is most often used, but other variants are also available [27]. Native T1 and ECV increase with fibrosis, edema and infiltrations and are rather reduced in lipid and iron deposition. Importantly, native T1-mapping enables a quantitative tissue characterization without the need of gadolinium based contrast agent administration.

Another mapping technique, ***T2-mapping,*** developed to quantify myocardial T2 relaxation, showed promising results in the evaluation of patients with acute

inflammatory cardiomyopathies as well as in patients with acute myocardial infarction [28, 29].

By using the gyromagnetic properties of ^{1}H, ^{31}P, ^{13}C, and ^{23}Na, ***CMR spectroscopy*** offers the possibility to directly measure different metabolites in the myocardium and thus to relate energy metabolism to heart (dys)function. For example, ^{31}P spectroscopy has been used to assess the energy phosphate metabolism of the heart, where a decreased phosphocreatine/ATP ratio was associated with HF and represented an independent predictor of mortality in dilated cardiomyopathy (DCM). Promising future clinical applications of this technique may comprise the detection of early metabolic changes in the myocardium prior to the occurrence of functional impairment in different cardiomyopathies [30]. So far, the widespread use of CMR spectroscopy in clinical practice is hampered by the time consuming techniques with low spatial and temporal resolution [31].

CMR- based molecular imaging permits the visualization of specific tissues or cell types by using functionalized agents. These are magnetic resonance T1- (gadolinium chelates) and more recently, T2-shortening (iron oxide particles) contrast media designed to target either actively or passively specific receptors, molecules or cells and thus enabling the non-invasive assessment of certain biological processes (e.g. phagocytosis of iron oxide particles by macrophages). These methods have been tested mainly for the characterization of atherosclerotic plaques as well as in myocardial infarction or myocarditis. However, the translation of pre-clinical data into clinical studies is still very limited [32, 33].

Safety and Limitations

CMR imaging is a safe procedure and has diagnostic image quality in more than 98 % of cases, as shown by a large European multi-center registry [2]. The use of gadolinium contrast agents was also proved safe in the vast majority of patients [34]. However, due to the risk of nephrogenic systemic fibrosis in patients with an estimated glomerular filtration rate of <30 mL/min/1.73 m^2, only cyclic gadolinium chelates at the minimum dose should be used after a careful risk-benefit analysis [35]. In the same registry, CMR stress testing (adenosine/dobutamine) led to life-threatening complications in only 0.0026 % of cases [2].

In the past, devices such as implantable pacemakers and cardiac defibrillators (ICD) were considered an absolute contraindication to CMR due to the risk of dysfunction, lead heating and induction of arrhythmias. With the growing availability of MR-conditional implants and continuing increase in CMR indications, patients with these devices increasingly undergo successful and safe CMR studies (Fig. 8.1). Nevertheless, the precautions and specifications of each particular device should be carefully considered [36]. Regarding other implants such as sternal wires, cardiovascular prosthesis and stents, the great majority is either MR safe or MR conditional and therefore allowed in the CMR environment at 1.5 and 3-T, while some intravascular clips are considered unsafe (www.mrisafety.com).

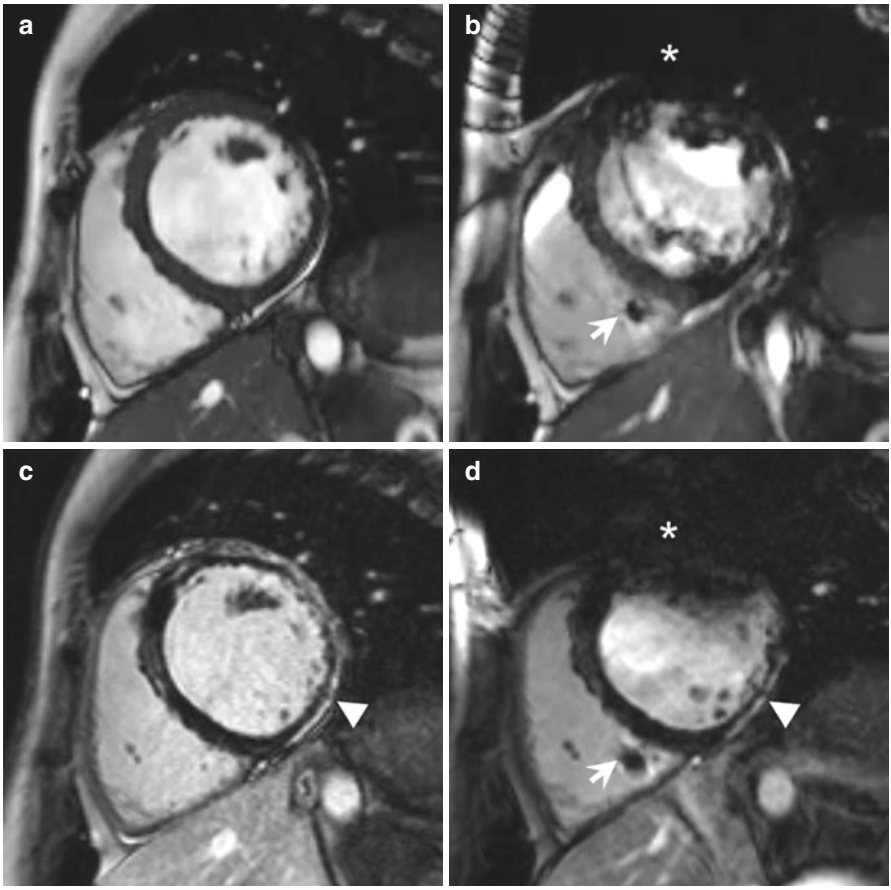

Fig. 8.1 Basal short-axis end-diastolic cine-CMR (**a**, **b**) and LGE (**c**, **d**) before (**a**, **c**) and after (**b**, **d**) primary prophylactic implantation of an "MR-conditional" ICD in a patient with muscular dystrophy type Becker and secondary DCM. The visualization of the anterior LV wall is impaired due to a generator-related artefact (*asterisk*), with typical subepicardial LGE still noticeable after implantation in the inferior wall (**d**, *arrowhead*), but not in the anterior and anterolateral segments. Additionally, the RV-lead is noticeable (*arrow*)

The Role of CMR in Suspected or Confirmed Heart Failure

CMR plays an important role in the work-up of HF, encompassing all stages, from first diagnosis, establishing etiology and risk stratification to guiding therapy and follow-up. While in unselected patients CMR impacted management in 62 % of cases and in nearly 9 % completely changed diagnosis, similar results are shown for HF, where it significantly impacted diagnosis and management in 65 % of cases [1, 2]. According to recently published position statements and guidelines from both European and American societies, today CMR constitutes the alternative and complementary non-invasive imaging technique to standard echocardiography in HF [3, 37–39].

Ischemic Cardiomyopathy

Myocardial Infarction

In ischemic cardiomyopathy, LGE-CMR is considered the non-invasive gold standard to depict irreversibly damaged myocardium with its typical pattern of enhancement, which involves the subendocardium and extends to the subepicardium ("wave front phenomenon") [18, 40]. LGE-CMR was shown to accurately differentiate ischemic from non-ischemic HF and to serve as a potential gatekeeper to invasive coronary angiography (CA) in HF of uncertain etiology [41, 42]. Further, edema on T2-weighted imaging (bright) can differentiate acute from chronic myocardial infarction (MI) and corresponds to the area at risk (AAR) [43, 44].

In ***acute MI***, myocardial salvage by primary percutaneous coronary intervention (PCI) can be quantified by delineating both AAR and LGE [45, 46]. Despite recent controversy, measuring AAR and myocardial salvage has proven utility both clinically and as surrogate endpoint in trials [47]. Microvascular obstruction (MVO), the correlate of "no-reflow" in CA, may be visualized as a dark core within the infarct zone on perfusion imaging as well as on early (2–5 min. post-contrast) and LGE images. Intramyocardial hemorrhage can also be detected as a dark core on T2- or T2*-weighted imaging (Fig. 8.2). Additional to LV-EF, all these aforementioned

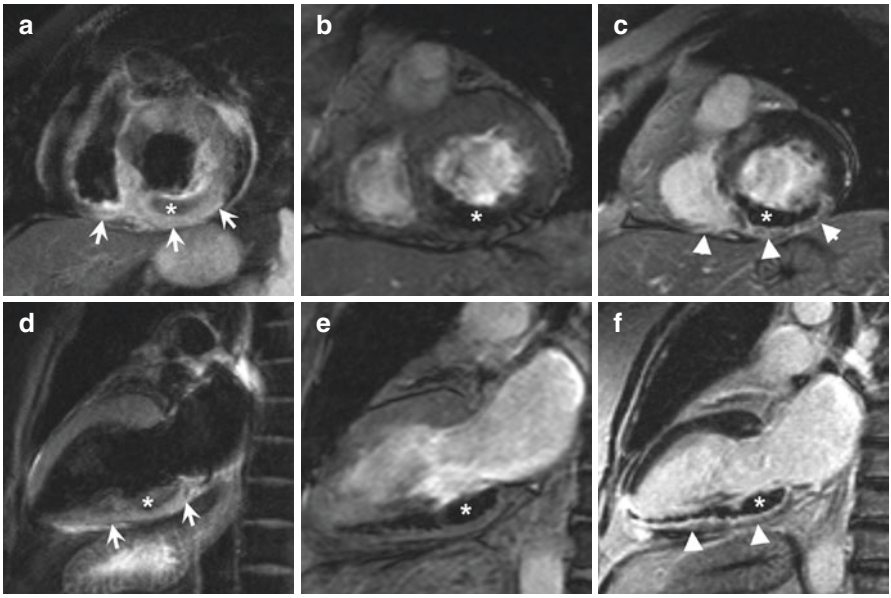

Fig. 8.2 Basal short-axis (*upper row*) and two-chamber view (*lower row*) in a patient with acute inferior wall infarction. Hyperintensity in the inferior wall on T2-weighted imaging corresponding to edema (**a**, **d**) together with depiction of irreversibly myocardial (*arrowheads*) and microvascular (*asterisk*) damage on LGE (**c**, **f**) are seen. The presence of intramyocardial hemorrhage is confirmed by visualization of a large dark core (*asterisk*) in T2*- (**b**, **e**) and T2-imaging (**a**, **d**)

parameters – circumferential and transmural LGE extent, myocardial salvage, presence of MVO or intramyocardial hemorrhage – have been shown to independently exert negative influences on functional recovery and prognosis after MI [48–50].

The excellent visualization of cardiac structures allows detection of post MI complications such as LV thrombus, (pseudo)aneurysms and MI-related pericardial pathology [51, 52]. CMR is particularly helpful in the detection of small apical thrombi coating the endocardium.

Moreover, current recommendations endorse CMR for the work-up of "MI with normal coronary arteries" as it can reveal alternative etiologies like Takotsubo cardiomyopathy or myocarditis [53–55].

The prognostic role of LGE was proven also in ***chronic MI***. Several studies showed that the presence and extent of LGE are independent risk factors for major adverse cardiac events beyond LV-EF (including patients with a nearly normal LV-EF) [56–58]. In addition to scar size, infarct heterogeneity reflected by the extent of the peri-infarct "grey zone" on LGE imaging, appears to serve as potential arrhythmogenic substrate for serious ventricular arrhythmias and was strongly associated with mortality [59]. This positive association was particularly noted in patients with mild or moderate LV dysfunction and may help regarding patient selection for primary prophylactic ICD implantation (when the LV-EF criterion is not met) or regarding VT ablation strategies [59].

Ischemia Testing

The clinical feasibility, safety and high diagnostic accuracy of MPI-*CMR* with vasodilatator stress for the detection of coronary artery disease (CAD) was proven by multiple studies [16, 60, 61]. Stress MPI-CMR demonstrated greater overall diagnostic accuracy (mainly by higher sensitivities) in both the large CE-MARC and the multicenter MR-IMPACT II trials when compared to SPECT [15, 62]. In addition, CMR is more cost-effective than SPECT for the work-up of CAD [63]. As alternative to conventional "stressors", regadenoson – a new selective adenosine A_{2A} receptor agonist – has been shown to be safe and to provide prognostic data similar to adenosine MPI with fewer side-effects [64].

Importantly, in the most recent meta-analysis of 37 studies, stress MPI-CMR had a pooled sensitivity of 89 % and a pooled specificity of 87 % for the detection of hemodynamically significant CAD as defined by invasive CA with fractional flow reserve (FFR). MPI-CMR performed similar to computed tomography or positron emission tomography (PET) and was superior to SPECT and echocardiography [65]. Due to the high negative predictive value, CMR reduced the utilization of invasive CA by 62.4% [66]. Moreover, a recent cost analysis suggests that a strategy of CMR plus invasive CA provided substantial cost reduction vs. one of invasive CA plus FFR in a low to intermediate CAD prevalence population [67]. Thus, stress MPI-CMR gained a well-established role as a gatekeeper to invasive CA and myo-

cardial revascularization. However, specific data on the accuracy, feasibility and on the outcomes of MPI-CMR in patients with HF and low EF are lacking [68]. The evaluation of perfusion defects can be challenging in such cases due to LV remodeling with wall thinning, scar presence and respiratory artefacts.

An alternative for CMR ischemia testing, the detection of inducible regional wall motion abnormalities by high dose dobutamine (± atropine) is superior to dobutamine echocardiography and has confirmed diagnostic and prognostic value [69, 70]. Nevertheless, dobutamine carries an increased risk in HF with severely impaired LV-EF and large amounts of ischemia [70, 71].

The 2013 stable CAD European Society of Cardiology (ESC) guidelines as well as those on myocardial revascularization (2014) recommend the use of stress CMR among the non-invasive stress imaging methods for the diagnosis (for patients with intermediate pre-test probability of 15–85 %), risk stratification and decision regarding revascularization of CAD [72, 73]. Similarly, the 2013 ACCF/AHA appropriate use criteria for multimodality imaging in stable CAD, consider stress CMR appropriate in patients with intermediate to high pre-test probability [74]. For consistent risk stratification across non-invasive imaging modalities, Shaw et al. propose risk-based thresholds to define ischemic burden. Thus, moderate to severe ischemia with stress CMR is defined as ≥2/16 segments with inducible perfusion defects or ≥3/16 dobutamine-induced dysfunctional segments [75].

According to the above mentioned ACCF/AHA recommendations on stable CAD and to those on the management of HF, in de novo HF, non-invasive ischemia testing is appropriate in patients without prior evaluation for CAD and reasonable (together with viability assessment) in patients with known CAD and no angina, unless the patient is not eligible for revascularization [39, 76]. Similarly, in line with the 2012 ESC HF guidelines, non-invasive ischemia and viability testing should be considered in HF patients thought to have CAD and who are considered suitable for coronary revascularization [3].

Viability Assessment

A personalized treatment approach in patients with chronic ischemic HF requires not only testing for ischemia, but also assessment of viability when considering revascularization [77]. Recovery of chronically dysfunctional myocardium is not expected in the presence of transmural scars but may occur in case of viable myocardium as in hibernation or chronic stunning [78].

Among the techniques that are currently available for viability assessment (dobutamine echocardiography, SPECT, PET), CMR has the advantage of assessing multiple aspects of viability at the same time: wall thickness, myocardial scar pattern and degree as well as contractile reserve. Moreover, LGE-CMR performs better than nuclear imaging techniques by accurately depicting not only transmural but also subendocardial infarcts that are undetected by PET or SPECT due to the lim-

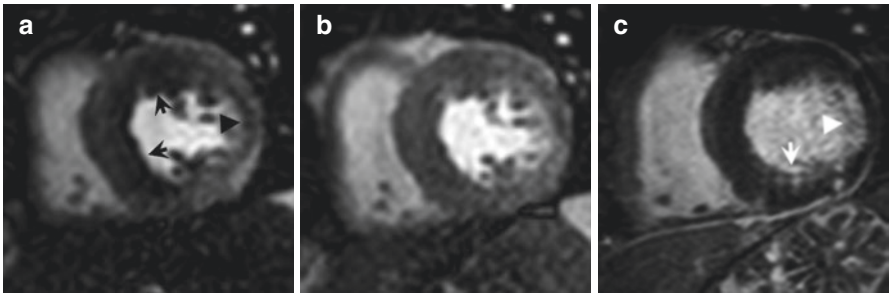

Fig. 8.3 Chronic CAD patient with severe three-vessel disease, including an occluded right coronary artery. Inducible defects due to myocardial ischemia in the anterior segment and septum are seen on MPI-CMR under adenosine stress (**a**, *black arrows*) but not at rest (**b**), in the presence of viable myocardium on LGE (**c**). Additionally, LGE shows a small subendocardial scar with remaining viability in the inferior segment (**c**, *white arrow*) and a larger in the lateral wall (**c**, *white arrowhead*), here with corresponding perfusion defect in the scar (**a**, *black arrowhead*)

ited spatial resolution of these techniques [79, 80]. The transmural extent of LGE allows identifying reversible myocardial dysfunction, since infarcts with a transmurality of >50 % have a low likelihood for functional recovery after revascularization (Fig. 8.3) [18, 81]. For intermediate scars, the addition of low dose dobutamine may improve the results, as contractile reserve was shown to be present in 61 % of segments with 25–50 % transmurality [82].

Unfortunately, the relationship between regional and global functional recovery as well as the "amount" of viable myocardium needed to improve LV-EF are still not well defined. While the 2013 ESC guidelines on stable CAD recommended considering revascularization in chronic ischemic HF patients if the global extent of viability exceeds 10 % of the total myocardium (based on SPECT/PET data), the recommendations from the 2014 ESC guidelines on myocardial revascularization give no numbers as long as LV-EF is ≤35 % and viability is present [72, 73].

Beyond functional recovery, the prognostic role of viability remains a key issue. Myocardial viability on non-invasive imaging (SPECT, PET or dobutamine echocardiography) was strongly associated with improved survival after revascularization in patients with ischemic LV dysfunction in a meta-analysis of 24 retrospective studies [83]. The impact of viability on survival, estimated by CMR prior to subsequent revascularization, was studied by Gerber et al. They showed that in patients with ischemic cardiomyopathy, the presence of dysfunctional viable myocardium by LGE-CMR is an independent predictor of mortality when surgical revascularization is not performed [84]. The STICH (Surgical Treatment for Ischemic Heart Failure) trial recently challenged the role of myocardial viability assessment in deciding whether or not to perform myocardial revascularization in patients with an impaired LV function. However, in this trial with several limitations, viability assessment was only based on SPECT and dobutamine echocardiography – but not on CMR. Hence, no implications can be made on the role of CMR in clinical decision-making based on the STICH data [85].

Non-ischemic Cardiomyopathies

CMR does not only enable the differentiation between ischemic and non-ischemic etiologies, but can also discriminate between different types of non-ischemic cardiomyopathies both based on LGE pattern and other specific features [17, 86]. Accordingly, the second most frequent indication for CMR, following CAD, is the work-up of myocarditis/cardiomyopathies [2].

In relation to endomyocardial biopsy (EMB), still the gold-standard for the diagnosis of non-ischemic cardiomyopathies, CMR plays a complementary role and can even be used as a gatekeeper to EMB [87, 88]. EMB is limited by (a) 'sampling error', (b) the invasiveness of the procedure and (c) the inability to perform one or serial biopsies in patients with preserved LV-EF. In contrast, CMR allows a non-invasive assessment of the entire myocardium with the possibility of follow-up. Moreover, guidance of EMB by CMR can help improving the accuracy and safety of the procedure [87].

Cardiomyopathies Presenting Mostly with a Hypertrophic Phenotype

Hypertrophic Cardiomyopathy

CMR offers a comprehensive evaluation of the heterogeneous hypertrophic cardiomyopathy (HCM) phenotype, including extent and distribution of hypertrophy as well as depiction of RV and apical involvement [89, 90]. CMR is particularly valuable in patients with atypical hypertrophy and/or poor echo window as it depicts characteristic patterns of myocardial disease and is superior to echocardiography [89, 91]. In addition, CMR allows to detect distinctive morphologic features like abnormalities of the mitral valve apparatus (SAM, leaflet elongation, papillary muscle hypertrophy and anatomic variants) or the presence of myocardial crypts, occurring both in HCM patients and in genotype-positive family members [89, 92, 93]. Besides visual assessment, flow imaging is able to directly measure peak velocity in the LV outflow tract as well as to quantify mitral valve regurgitation (Fig. 8.4).

Further, presence of LGE, reflecting myocardial fibrosis and/or disarray, is a common finding in HCM (in ~ 65 % of cases) – with a patchy, mid-wall pattern located mostly in hypertrophic areas and RV insertions in case of HCM forms caused by sarcomere protein mutations (Fig. 8.4) [91, 94, 95]. A series of studies including two meta-analyses have demonstrated that LGE presence is significantly associated with SCD, cardiac and all-cause mortality [94, 96]. However, data regarding the predictive role of total LGE burden in HCM are conflicting. While some studies suggested a positive association between the amount of total LGE and the risk of SCD, other studies could not confirm such an association [94, 97]. Despite its potential role in SCD risk stratification, particularly in non-high-risk patients by conventional riskfactors, currently there are no clear indications for ICD

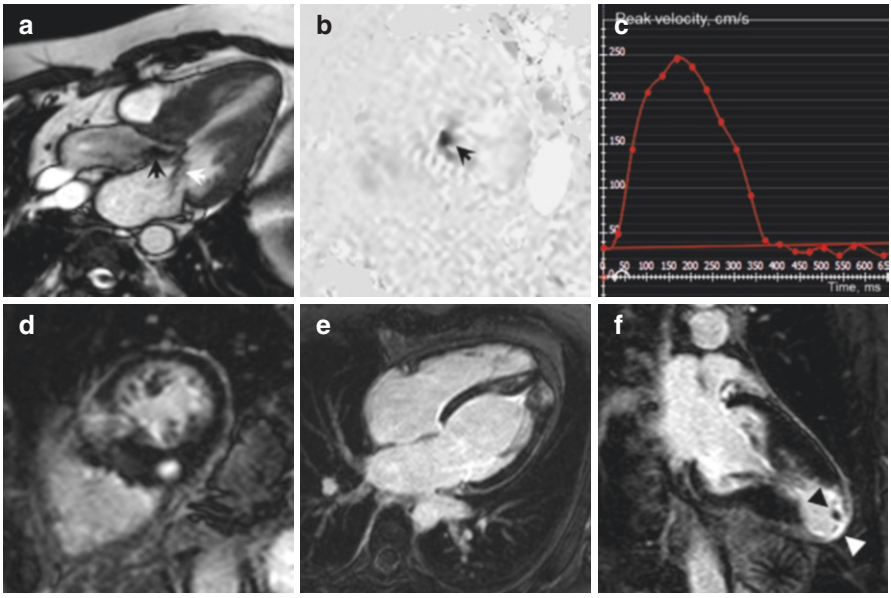

Fig. 8.4 Illustrative CMR images from different HCM patients. In the *upper row*, an obstructive form with SAM leading to LV outflow tract obstruction (**a**, *black arrow*) and secondary mitral regurgitation (**a**, *white arrow*) depicted by cine-CMR. In the same patient, through-plane flow-CMR in LVOT permits the visualization (**b**, *black arrow*) and quantification (**c**; *peak velocity curve*) of obstruction. The *lower row* shows various LGE patterns encountered in HCM: patchy in the hypertrophic area (**d**), including in an apical form (**e**); focal in the RV insertion (**d**); apical aneurysm (**f**, *white arrowhead*) with small thrombus (**f**, *black arrowhead*) due to mid-ventricular obstruction

implantation based on LGE [91, 98]. However, absence of LGE is associated with a low risk for adverse events [97]. CMR can also help in the planning as well as in the follow up after septal reduction therapy [91, 97, 99].

An impaired myocardial perfusion during hyperemic stress, predominantly in the subendocardium and areas of hypertrophy, may be additionally seen in HCM, mirroring the associated involvement of the microvasculature in these patients [100].

According to the current ESC and North American recommendations, CMR should be considered in all HCM patients for baseline evaluation and follow-up according to potential clinical changes or in order to answer specific questions [91, 98, 99].

Most importantly, CMR plays nowadays a major role in identifying the underlying cause of hypertrophy such as storage diseases, neuromuscular disorders (e.g. mitochondriopathies), toxic cardiomyopathies (e.g. hydroxychloroquine) or amyloidosis. For example, Anderson-Fabry is characterized by typical LGE in the inferolateral wall together with shortening of native septal T1 (Fig. 8.5) [101, 102]. The differentiation between HCM and hypertensive heart disease can also be challenging and while asymmetry does not seem to play a role, an increased LV mass and absence of LGE plead for the later. Additionally, an elevated native T1 was also associated to a HCM diagnosis, rather than to hypertrophy secondary to hypertension [103].

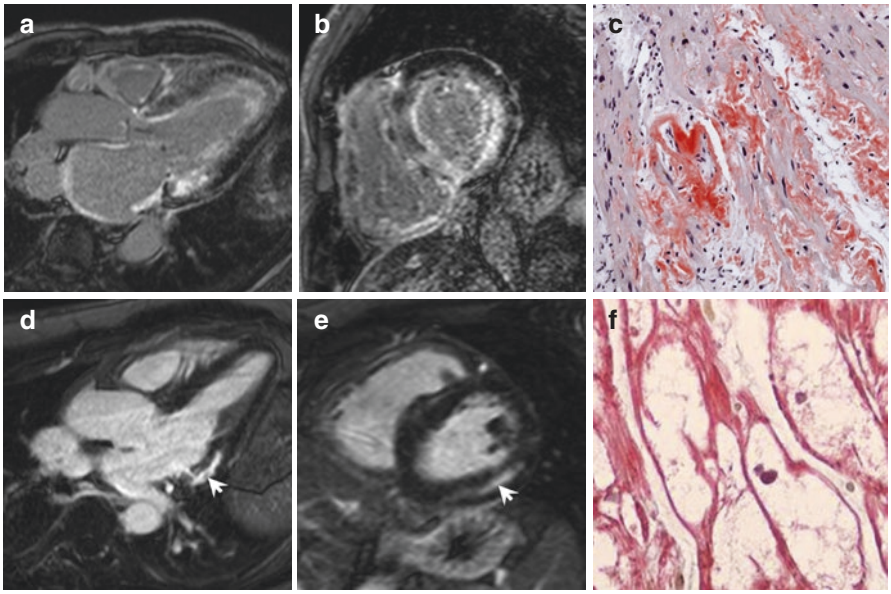

Fig. 8.5 Two CMR examples of patients with LV hypertrophy of different etiologies with corresponding histology findings. In the *upper row*, cardiac amyloidosis with its pathognomonic pattern of diffuse, predominantly subendocardial, LGE in the LV along with hyperenhancement of the atrial and RV walls (**a**, **b**); additionally, confirmation of amyloid depositions in Congo red staining (**c***). In the *lower row*, intramural LGE in the inferolateral wall (**d**, **e**; *arrow*) and identification of vacuolated cardiomyocytes associated with glycosphingolipid deposition (Masson Trichrome staining; **f***) in a patient with Anderson-Fabry (* Reproduced with permission from [175, 176])

Amyloidosis

Congestive HF is a common clinical presentation for cardiac involvement in systemic amyloidosis. An early diagnosis with initiation of therapy is critical in these patients, given that HF occurrence leads to decreased survival [104, 105]. Additionally, in many patients (particularly with senile amyloidosis), cardiac involvement may be the first manifestation of disease [106]. Besides findings of increased wall thickness with normal or reduced contractility, thickened atrial septum and atrial dilatation, post-contrast CMR allows to depict an unique (progressive) LGE pattern of diffuse, predominantly subendocardial but also sometimes more patchy or transmural hyperenhancement (Fig. 8.5) [107, 108]. This characteristic LGE appearance is highly accurate in identifying biopsy-proven cardiac amyloidosis and superior to other non-invasive imaging parameters [106, 107]. Further, in the two most frequent types of cardiac amyloidosis, light chain (AL) and transthyretin (ATTR), a transmural pattern of LGE was predictive for death over a mean of 2 years, independently of parameters like N-terminal pro-brain natriuretic peptide, LV-EF, E/E′, and LV mass index [109]. However, (LGE-) CMR alone cannot differentiate between amyloid subtypes.

More recently, native myocardial T1, a promising surrogate parameter of amyloid load, was shown to be more sensitive than LGE in detecting early cardiac involvement in AL amyloidosis [110]. Moreover, pre- and post-contrast T1 mapping based myocardial ECV measurements independently predicted mortality in systemic amyloidosis [111]. However, careful interpretation of these quantitative parameters is recommended, since a non-neglectable degree of overlap between healthy and diseased myocardium may exist.

Cardiomyopathies Presenting Mostly with a Dilative Phenotype

Dilated Cardiomyopathy

Up to half of the patients with DCM show presence of non-ischemic LGE, most frequently with a mid-myocardial septal pattern that is similar to the one observed in myocarditis (Fig. 8.6) [112–114]. For this reason, a differentiation between "idiopathic" and "inflammatory" DCM is usually challenging based on non-invasive imaging only. A series of studies and a meta-analysis evaluated the prognostic role of LGE in non-ischemic DCM patients [112–114]. Kuruvilla et al. analyzed data from nine studies and found LGE presence to be associated with increased all-cause mortality, HF hospitalizations and SCD [113]. Of note, only the large study from Gulati et al. specifically investigated the role of mid-myocardial LGE and revealed that both its presence and extent provide independent prognostic information beyond LV-EF [112]. Another study focused on patients with idiopathic DCM and suggested that the absence of LGE at baseline is a strong independent predictor of reverse remodeling at 2 years after optimization of medical therapy, irrespective of the initial clinical status and the severity of LV dilation and dysfunction [114]. Conversely, LGE extent was associated with lack of response to treatment and progressive LV dysfunction [114, 115]. Finally, in a recent study by Puntmann et al., native T1 was a significant predictor of all-cause mortality and HF events in non-ischemic DCM [116]. Hence, an approach based on the assessment of both diffuse and regional fibrosis by T1 mapping and LGE may allow improved risk stratification in DCM patients in the future [116].

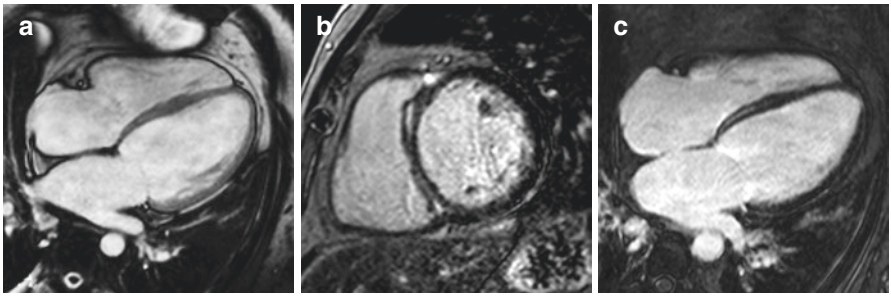

Fig. 8.6 Cine-CMR at end-diastole (**a**) and LGE (**c**) in four-chamber view and in short-axis (**b**) in a patient with idiopathic DCM. A dilated LV with mid-myocardial LGE in the septum (**b**, **c**) can be seen

Iron Overload Cardiomyopathy

Myocardial siderosis either secondary to thalassemia-related repeated blood transfusions or due to genetic hemochromatosis presents with different degrees of diastolic and/or systolic dysfunction. DCM occurs usually in advanced stages, when HF had already developed and the prognosis is poor. T2*-weighted imaging allows not only an early identification and quantification of myocardial iron content (superior to serum ferritin and liver iron) but also provides information on prognosis and response to iron chelation therapy. Hence, in the presence of myocardial iron overload, T2* values are typically <20 ms. Further, in thalassemic patients a direct relationship has been demonstrated between T2* and LV-EF decline, with T2* <10 ms being considered a marker of severe disease and of increased risk for HF and impaired exercise capacity [117]. Additionally, T2* <20 ms was associated with arrhythmia occurrence, mainly atrial fibrillation [117, 118]. As response to chelation therapy, T2* values increase and are associated with an improvement in LV-EF as well as in the risk of developing HF [119]. More recently, similar results were also obtained in genetically confirmed hemochromatosis patients [120].

Cancer Therapy Related Cardiomyopathies

A series of studies aiming to identify more sensitive CMR markers of early cardiac injury after chemotherapy (mainly anthracyclines) found early increases in LV mass, LV end-diastolic volume as well as increases in pre- and post-contrast myocardial signal intensity to predict later decreases in LV-EF [121]. Additionally, some reports describe a myocarditis-like pattern of LGE during and at the end of anthracyclines and trastuzumab therapy. However, data on LGE presence in patients who developed cardiomyopathy after chemotherapy are still conflicting [122] and the reason for the occurrence of focal LGE in some patients is unclear.

CMR might also have a prognostic value in detection of late cardiotoxicity. Reduced LV mass has been shown to be an independent predictor of major cardiac events in cancer patients with anthracycline induced cardiomyopathy, while LGE was an uncommon finding [123]. Moreover, ECV measurements correlated with anthracycline dose as well as with LV functional parameters at a median of 7 years after completion of anthracycline therapy [121, 123].

Muscular Dystrophy

Up to 70 % of Duchenne and Becker muscular dystrophy patients suffer from cardiac involvement with progressive myocarditis-like scarring in the LV lateral wall, leading in a proportion of them to LV systolic dysfunction and DCM (Fig. 8.1). In these patients, LGE enables not only an early diagnosis with timely introduction of cardiac protective therapy but also allows risk stratification for development of HF and potential lethal arrhythmias [124, 125].

Moreover, subtle myocardial fibrosis can be non-invasively detected using T1-mapping and ECV measurement also in myocardial areas without LGE in earlier phases of disease [126].

Arrhythmogenic Right Ventricular Cardiomyopathy

CMR is the preferred non-invasive imaging modality in suspected arrhythmogenic right ventricular cardiomyopathy (ARVC) as it enables a better depiction of subtle RV changes together with the possibility of tissue characterization for identification of fibro-fatty replacement [127, 128].

Unfortunately, the visualization of fibro-fatty infiltration in the RV by T1/T2-weighted or LGE imaging is can be challenging and unreliable due to the rather subepicardial localization and the thin RV wall. Hence, the recently revised task force criteria only considered the presence of regional wall motion abnormalities, microaneurysms or RV dyssynchrony together with clear cut-offs for RV dilation and/or systolic dysfunction as diagnostic imaging findings – but not the presence of LGE per se (Fig. 8.7) [129]. However, since fibro-fatty replacement in case of ARVC does not only occur in the RV but also in the LV in a non-neglectable proportion of patients and since CMR allows LV characterization in ARVC disease variants with left dominant or biventricular involvement, T1- and T2-sequences with and without fat suppression techniques are still suggested and can give important clues in some patients with suspected ARVC or unclear cardiomyopathy [130].

In addition to its role in ARVC diagnosis, the presence of CMR abnormalities was shown to be associated with adverse cardiac outcomes [128, 131]. Therefore, in patients with severe or moderate RV and or LV dysfunction ICD implantation should be considered irrespective of arrhythmias [132].

Compared to the 1994 ARVC task force imaging criteria, the updated 2010 criteria were “more restrictive” and resulted in a marked decrease in the number of patients with any positive CMR criterion [133]. Obviously, there was a high tendency for over diagnosis of ARVC in the past and therefore, an update of the

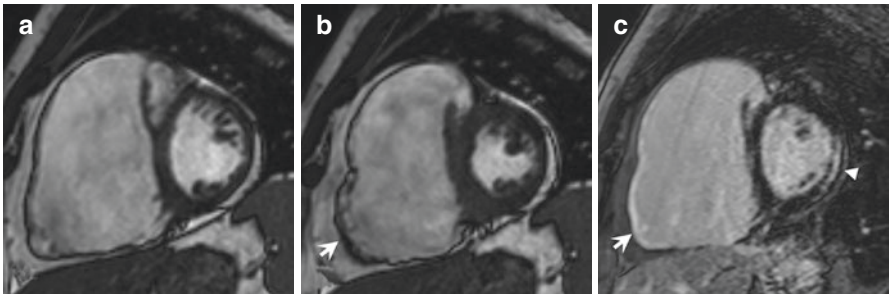

Fig. 8.7 End-diastolic (**a**) and end-systolic (**b**) cine-CMR together with LGE (**c**) in mid-ventricular short-axis in a patient with advanced ARVC. A dilated RV with systolic bulging (**b**, *arrow*) of the basal inferolateral wall is depicted. Additionally to hyperenhancement of the RV wall (**c**, *arrow*), non-ischemic LGE can be seen in the LV lateral wall (**c**, *arrowhead*)

ARVC criteria was essential. However, today the relative low sensitivity of the current criteria for early ARVC phases has led to the search for more sensitive imaging parameters. Among these, feature-tracking CMR measurements of RV deformation and dyssynchrony show promising initial results in differentiating ARVC from RV outflow tract arrhythmias and controls [134].

Inflammatory Diseases and Other Cardiomyopathies

Acute Myocarditis

A correct and timely diagnosis of myocarditis presenting as new-onset HF is of great importance as cardiac function may rapidly deteriorate, requiring supportive therapy [5, 135]. Moreover, myocarditis patients are at increased risk of developing life threatening arrhythmias as well as of progressing to DCM [135–137]. In the context of the limitations (mostly due to sampling error) of EMB, the current diagnostic gold standard, CMR has developed as a reliable non-invasive tool in the work-up of myocarditis [88].

LGE depicts hyperenhancement associated with active myocardial inflammation with characteristic patterns, either mid-myocardial in the septum or subepicardial in the LV lateral wall (patchy distribution) (Fig. 8.8) [86, 87, 138]. Despite the relative

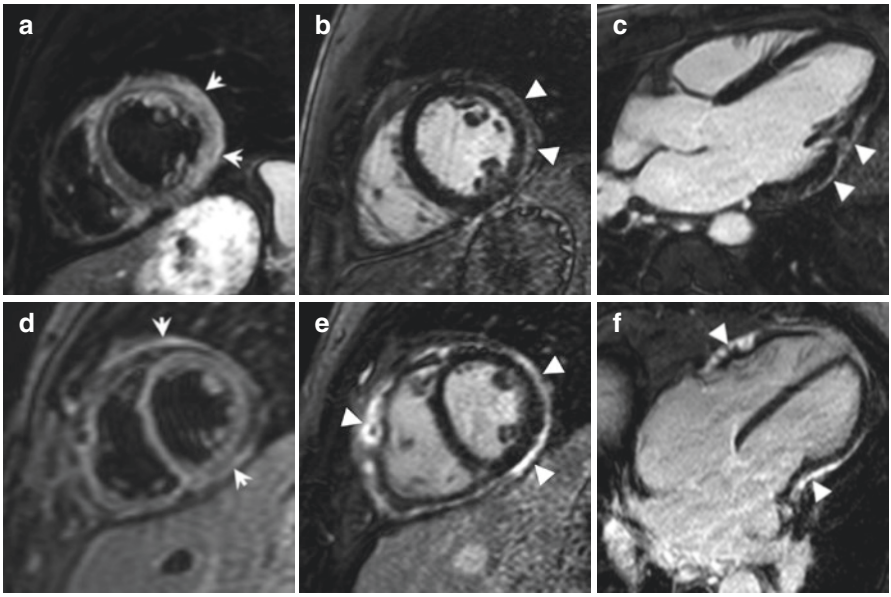

Fig. 8.8 T2-weighted imaging (**a**, **d**) and LGE (**b**, **c**, **e**, and **f**) in a case of acute myocarditis (*upper row*) and in one of pericarditis – evolving towards constriction (*lower row*). Myocardial edema (**a**, *arrows*) and characteristic subepicardial LGE (**b**, **c**, *arrowheads*) can be seen in the lateral wall, typical findings for an acute myocarditis. In the second example, intense circumferential pericardial LGE corresponding to the base of the ventricles (**e**, **f**, *arrowheads*) with milder edema (**d**, *arrows*) are noticeable. Atrial dilatation and a compressed, "tubular" aspect of the LV suggest constriction (**f**)

high specificity of this non-invasive technique, LGE alone cannot completely rule in or rule out myocarditis due to its low sensitivity [88]. In 2009, a more comprehensive CMR approach was proposed by using three tissue markers ("Lake Louise Criteria"): edema by T2-weighted imaging, hyperemia by early gadolinium enhancement and myocyte necrosis/fibrosis by LGE [21]. At least some studies suggested that an improved diagnostic performance can be achieved using a combination of these three methods, with sensitivity and specificity of 76 % and 96 %, respectively, when 2/3 techniques were positive [139]. Today, most centers use simplified protocols including T2-weighted and/or LGE that proved higher sensitivity than the Lake Louise Criteria, however, with similar accuracy [140]. On the other hand, in cases in whom a high positive likelihood ratio is required, the full Lake Louise Criteria should be used. Nevertheless, CMR sensitivity varies with clinical presentation (high for infarct-like and low for chronic dilative cardiomyopathy) and extent of cell necrosis, and the diagnosis may still be missed in a number of patients [141, 142].

Recently, studies using T1- and T2- mapping reported incremental diagnostic performance for native T1, T2 and ECV [143, 144]. However, large multi-center trials with convincing proof of superiority or additional value of mapping approaches in comparison to conventional LGE imaging are still missing.

Regarding disease progression and prognosis, LGE in the lateral wall usually regresses and is often associated with an improvement in LV function, while septal LGE rarely disappears and patients seem to have a worse outcome [86, 88, 145]. Further, in a clinically heterogeneous patient population of biopsy proven viral myocarditis, LGE was the best predictor of long term mortality [137, 146]. On the other hand, positive CMR criteria, especially myocardial edema, were associated with LV functional recovery at 12 months after acute myocarditis [147]. Taken together, the prognostic value of CMR data is dependent on the characteristics of the respective patient population and therefore needs careful interpretation. With respect to the diagnostic approach in suspected myocarditis, combining CMR and EMB achieves aconsiderable diagnostic synergy by overcoming the limitations of each technique [87].

Sarcoidosis

In cardiac sarcoidosis, LGE can accurately detect (even small areas) of myocardial damage even when LV dysfunction or positive diagnostic criteria are absent [148, 149]. This is particularly valuable as arrhythmia and HF secondary to cardiac infiltration are the major cause of death in sarcoidosis [150]. LGE patterns encountered in cardiac sarcoidosis are variable and rather non-specific, usually non-ischemic, with multiple foci involving predominantly the septum and extending into the RV walls (Fig. 8.9) [148]. In addition, T2-weighted imaging may help visualizing areas of active inflammation.

A series of studies investigated the prognostic role of LGE in cardiac sarcoidosis [149–151]. In one study, LGE was present in 26 % of systemic sarcoidosis patients and was the best independent predictor of potentially lethal events [151]. In the larger study by Murtagh et al., the rate of death or ventricular tachycardia at 3 years was 20 times higher in the LGE positive group, all patients having preserved LV-EF. Moreover, LGE burden and RV dysfunction were the best predictors of

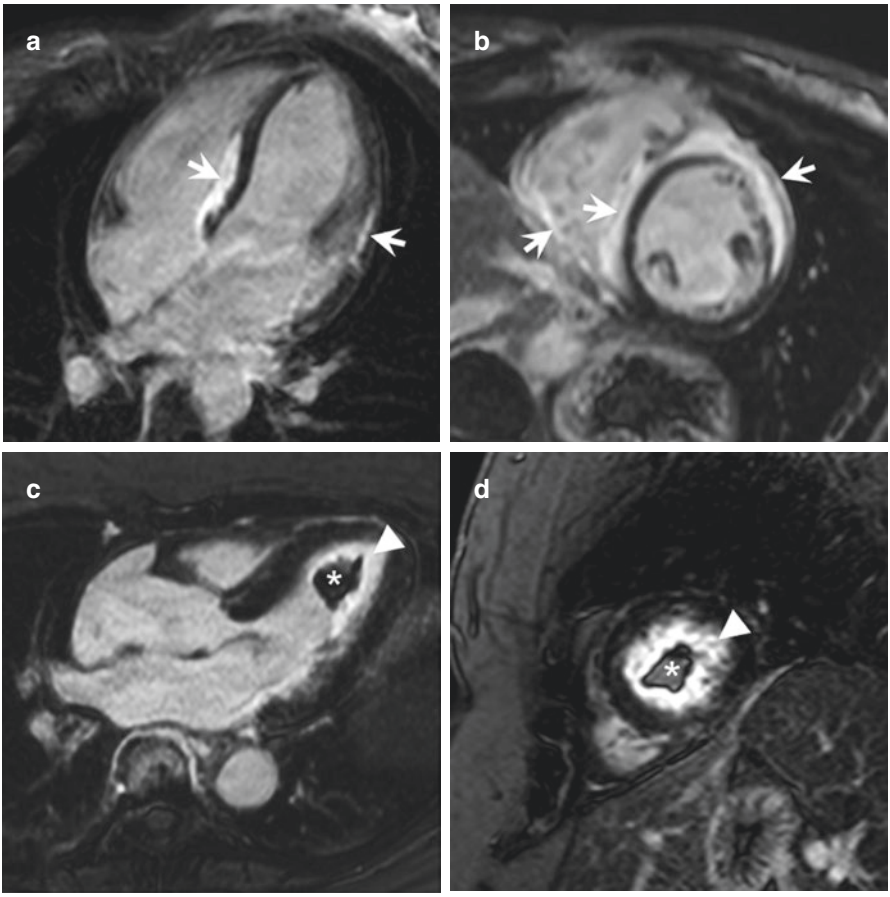

Fig. 8.9 LGE CMR images from two patients with different inflammatory cardiomyopathies. The first (*upper row*) depicts a case of cardiac sarcoidosis with important non-ischemic hyperenhancement involving the anterolateral wall and septum and extending to the RV (**a**, **b**; *arrows*). The second shows a case of hypereosinophilia induced myocarditis with typical association of LGE (**c**, **d**; *arrowhead*) and thrombus (*asterisk*) in the LV apex

adverse events [150]. However, due to the lack of large scale studies, LGE is (so far) not a criterion for primary prophylactic ICD implantation in sarcoidosis [152].

Systemic Inflammatory Diseases

Clinical and subclinical myocardial dysfunction have been described in a wide range of connective tissue diseases. In this context, pathologic processes like myocardial and vascular inflammation with subsequent remodeling and scar formation can accurately be depicted by CMR. However, data on the role of CMR in establishing prognosis and guiding management in these patients needs further investigation [153].

Left Ventricular Non-compaction

Similar to echocardiography, CMR diagnostic criteria for LV non-compaction cardiomyopathy (LVNC) exist [154]. Among these, the Petersen criterion – a ratio between non-compacted to compacted layer thicknesses of >2.3 at end-diastole is usually used [155]. Additionally, parameters like trabecular mass (Jacquier et al.) and the degree of irregularity of the endocardial border (fractal dimension) are reserved mainly for research [154]. Nevertheless, there is poor agreement between the CMR and echocardiographic criteria and both are highly controversial [156, 157]. Therefore, we suggest a careful assessment and interpretation of the degree and pattern of LV and RV trabeculations, always within the clinical context.

Beyond the mere evaluation of trabeculations, CMR allows a comprehensive assessment of LVNC phenotypes: isolated, dilated, hypertrophic or congenital disease associated as well as of LV and/or RV involvement [156]. A series of studies describe some LGE presence in LVNC, even in isolated forms, most frequently non-ischemic, with mid-myocardial predominance and no association to non-compacted areas. Both the presence and extent of LGE seem to be related to clinical disease severity and LV systolic dysfunction [158].

Myocardial trabeculations can be encountered also in DCM patients, in the context of negative myocardial remodeling. Amzulescu et al. questioned the relevance of this LV non-compaction phenotype in non-ischemic HF and showed that the degree of trabeculation did not influence cardiac outcomes [159].

Takotsubo Cardiomyopathy

In Takotsubo, CMR can characterize the typical pattern of wall motion abnormalities; additionally it can depict eventual small apical thrombi as well as RV involvement, the later described in up to one third of cases. In the acute phase, patients may exhibit myocardial edema in the territory of the wall motion abnormalities, usually without LGE. These features help the differential diagnosis to acute myocarditis or myocardial infarction. Hence, as suggested by a very recent position statement, CMR should be considered whenever Takotsubo is suspected or, by limited availability, at least for borderline or indeterminate cases [160].

Valvular Heart Disease

In patients with inadequate echocardiographic image quality or discrepant results, CMR is indicated to assess the severity of valvular lesions – particularly regurgitant – and to assess ventricular volumes and systolic function [161, 162]. In aortic stenosis, both anatomic valve area and peak velocity can be measured, the latter often underestimating the degree of severity. Additionally, (ischemic/non-ischemic) LGE was shown to be an independent predictor of mortality in patients undergoing aortic valve replacement [163].

CMR also allows a reproducible and accurate quantification of valvular regurgitant volume and fraction. In aortic insufficiency, CMR-based regurgitant fraction was superior in predicting development of symptoms and need for surgery at 3 years when compared to LV end-diastolic volume [164]. Further, CMR estimates of mitral regurgitation severity were found to strongly correlate with LV remodeling and clinical outcome post-surgery [165, 166]. Finally, CMR is useful for evaluation of pulmonary valvular disease, which can be difficult with echocardiography.

Adult Congenital Heart Disease

The role of CMR in congenital heart disease, particularly in complex anomalies, has been steadily increasing. Morphological and functional evaluation of the right heart, assessment of vasculature, characterization and quantification of shunts, and detection of myocardial scars, both before and after (often repeated) surgery are indications where CMR is considered superior to echocardiography and should be regularly used when needed [167]. As many congenital heart disease patients will develop at some point HF, CMR offers a non-invasive and non-irradiating tool for follow-up and monitoring of changes in cardiac status.

Pericardial Disease

Pericardial disease can present with HF, particularly due to pericardial constriction. CMR enables the assessment of pericardial thickening as well as effusions or masses. Additionally, while demonstrating ventricular interdependence (on real-time cine's) is a marker of constrictive pericarditis, the identification of pericardial inflammation might suggest potentially reversible forms of constriction (Fig. 8.8) [168]. Moreover, pericarditis can be frequently associated with additional myocarditis. Therefore, in patients with suspected pericarditis careful assessment of myocarditis (and vice versa) is suggested.

The Role of CMR in Guiding Implantable Cardioverter-Defibrillator (ICD)/Cardiac Resynchronization (CRT) Therapy

In line with the current available indications for ICD/CRT implantation, the role of CMR is limited to a reliable alternative to echocardiography for LV-EF assessment [152, 169]. Nevertheless, there are data to support an additional emerging role of CMR for patient selection and follow-up as well as guiding device therapy.

ICD

As presented above, a series of studies support the role of CMR (mainly by LGE) to predict ventricular arrhythmic events in HF of different etiologies [170]. In patients with ischemic cardiomyopathy and a borderline LV-EF of 35–40 %, the presence of a large scar may support the decision for primary prophylactic ICD implantation. Also, in patients with inflammatory diseases (e.g. chronic myocarditis or sarcoidosis), the detection of extensive LGE may help in deciding to implant an ICD. Nevertheless, before LGE-CMR will enter the criteria for primary prophylactic ICD implantation, larger, prospective multicenter trials are required.

CRT

Establishing CRT eligibility in order to ensure a high clinical response rate is challenging and the role of non-invasive imaging is yet to be defined.

Even though assessing dyssynchrony with CMR is possible, it is hardly ever used in practice due to several limitations [170]. More important, information on scar extent and location from LGE CMR can establish prognosis related to CRT [171, 172]. Previous small studies have shown that LGE burden and transmurality as well as pacing a posterolateral scar were associated with a suboptimal response in ischemic cardiomyopathy [173]. Later, a larger study from Leyva et al. including ischemic and non-ischemic cardiomyopathy patients confirmed that LGE CMR-guided lead placement, away from myocardial scar, improved clinical outcomes [171]. More recently, the same research group showed that the presence of mid-myocardial fibrosis in DCM patients undergoing CRT attracts a worse prognosis, similar to that of ischemic cardiomyopathy [172]. In addition to function and scar, a non-invasive characterization of cardiac vein anatomy is possible in the same examination.

Future Directions

Beyond current clinical applications – the tip of the iceberg, experimental CMR is a wide and continuously expanding field. While, for example, molecular imaging reveals new insights into cardiovascular pathophysiology, interventional CMR offers promising imaging guidance for a range of (endovascular, cardiac or electrophysiological) diagnostic and interventional procedures. But most importantly, by combining both, CMR could play a future role in testing, delivering, and monitoring novel biologic treatments in cardiovascular diseases, including small molecule, gene, or cellular agents [174].

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Chapter 9
The Evolving Role of Multimodality Imaging in Heart Failure

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Keywords:
Multimodality imaging
Myocardial perfusion imaging
Myocardial functional imaging
Anatomical imaging
Metabolic imaging
Molecular imaging
Cardiac resynchronization
Arrhythmias
Cardio-oncology
Cardiac amyloidosis

Multi-modality imaging can be defined as the combination of anatomical, morphological, and functional data from non-invasive imaging techniques with the purpose of enhancing the diagnostic accuracy of the single imaging modalities and select more accurately targeted therapeutic interventions, ultimately improving clinical outcome [1].

In this respect, different imaging modalities, providing complementary information, may be performed separately and the information obtained integrated afterwards in a comprehensive anatomical-functional view of the heart or information can be obtained in a single step approach using hybrid systems [2]. In the clinical context of heart failure (HF), multimodality and hybrid imaging can be best applied to define aetiology, assess severity of myocardial damage and ischemia, provide pre-interventional assessment and guide revascularization (in coronary artery disease – CAD – patients) or electrophysiological procedures (CRT) [3]. Moreover,

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M. Dorobanţu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_9

ongoing study of sympathetic and molecular imaging techniques may enable early disease detection, better risk stratification, and ultimately targeted treatment interventions.

This chapter highlights recent observations using different imaging technologies (echocardiography, cardiac magnetic resonance [CMR], cardiac computed tomography [CT], single-photon emission computed tomography [SPECT], and positron emission tomography [PET], but also neuronal imaging with ^{123}I-metaiodobenzylguanidine [MIBG]) in the field of HF.

Imaging of Ischemia: Risk Area and Coronary Arteries

Hybrid SPECT-CT or PET-CT scanners offer the opportunity to perform an integrated evaluation of coronary anatomy and of the functional effects of coronary stenosis, combining the high diagnostic accuracy in detecting luminal narrowings of coronary CT angiography with the functional information of nuclear imaging, either with SPECT or PET, in the evaluation of stress and rest regional and global myocardial perfusion and thus in the evaluation of the area at risk of myocardial ischemia [3] (Fig. 9.1). In patients with HF, combined anatomical-functional imaging using

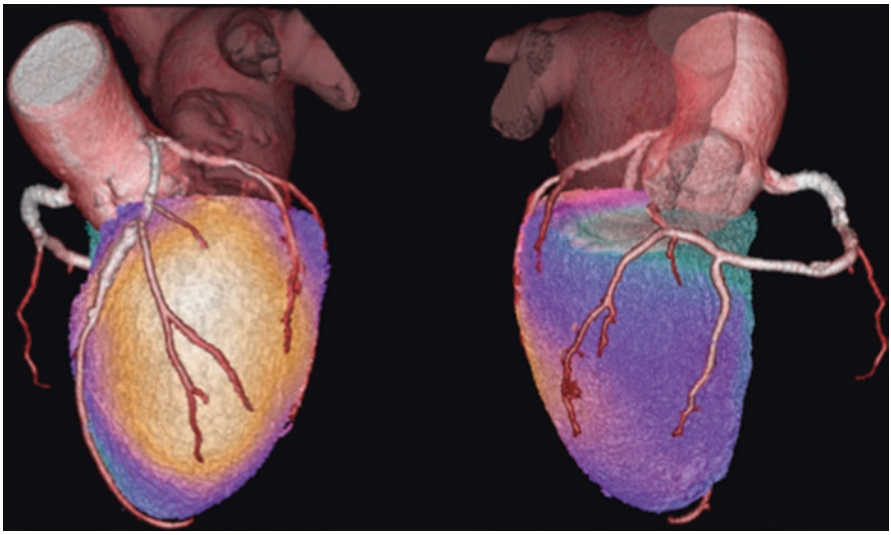

Fig. 9.1 A representative case of hybrid imaging. A 65 years old gentleman with atypical anginal chest pain and an intermediate probability of CAD. He was submitted to computed tomography coronary angiography (CCTA) with evidence of three-vessel CAD with a long 80 % mid LAD calcific stenosis, a 75 % mid RCA mixed lesion, and a 50–70 % distale LCX stenosis. Myocardial perfusion imaging with SPECT was then performed with evidence of extensive anterior distal to apical, as well as inferior to infero-lateral reversible perfusion defect. On hybrid CCTA/SPECT imaging the perfusion defects were reassigned to the LAD and the RCA coronary arteries, excluding the hemodynamic relevance of the LCX stenosis

SPECT-CT or PET-CT may be useful to identify the aetiology of the disease and, in the presence of obstructive CAD, to indicate and guide revascularization. In this context, the 3D fusion of CT coronary angiography images with SPECT or PET perfusion data may allow the unique chance to reassign a specific perfusion defect to the pertinent coronary territory, univocally identifying the presence of haemodynamically significant CAD (i.e. a coronary stenosis with downstream significant myocardial ischemia downstream). As a matter of fact, previous study have demonstrated the existence of a huge inter-individual variability of coronary anatomy that may frequently prevent the correct allocation of a given myocardial perfusion defect to the specific coronary artery [4, 5]. Accordingly, hybrid imaging has been demonstrated to obviate to the most frequent limitations that comes from the side-by-side analysis of two different images modalities such as CT coronary angiography and myocardial perfusion imaging (MPI), by correctly ruling in and out the presence of haemodynamically significant CAD in the majority of patients [5]. As a matter of fact, while in the presence of a matched hybrid finding (i.e. a myocardial perfusion defect subtended by an anatomically significant – >50 % – coronary luminal stenosis) coronary revascularization may be indicated in order to improve patients' symptomatic status and prognosis, a normal hybrid evaluation (i.e. absence of significant coronary stenosis as well as myocardial perfusion abnormalities) is associated with an excellent prognosis. Interestingly, patients presenting a mismatched hybrid finding at SPECT/CT or PET/CT (i.e. either anatomically significant coronary stenosis without evidence of myocardial ischemia at MPI or myocardial perfusion defects without evidence of significant CAD) show an intermediate long-term prognosis, further highlighting the need for aggressive medical treatment [6].

In ischemic HF the indications for and relative benefits of revascularisation remain a source of contention [7, 8].

In fact, the relative effects of medical therapy and revascularization on ischaemia burden as well as the independent prognostic significance of ischaemia change is unclear [9–11]. Moreover, as elegantly suggested by the results of the nuclear substudy of the COURAGE trial, the reduction of global myocardial ischemic burden, by either percutaneous or surgical revascularization might not confer a relevant prognostic benefit, despite frequently having a significant symptomatic impact [11].

In this scenario, since ischaemia is one of the primary drivers of decisions regarding revascularization, clarification of these questions may have significant implications for both patient management as well as healthcare utilization.

Apart from myocardial ischemic burden, in the presence of left ventricular systolic dysfunction and stable CAD another relevant functional factor should be taken into account, the presence and location of residual hibernated myocardium. In fact, those patients usually present a mixture of areas of necrotic myocardium interposed between regions of either prevalently hibernated or mainly ischemic heart muscle. In this context, in order to allow a targeted treatment, an appropriate multimodality cardiac imaging approach should be able to quantitate and localize the different "qualities" of myocardium (i.e. scar, ischemic, hibernated, and normal) and define the pertinent coronary distribution. These information are particularly needed if a revascularization strategy, either surgical or percutaneous, is hypothesized since no

benefit can be expected from the revascularization of necrotic or only partially viable myocardial regions [12].

PET imaging, through the use of widely established perfusion (i.e. ammonia and rubidium) and metabolic (FDG) tracers, still represents the reference standard for the combined evaluation of regional myocardial viability as well as ischemic burden, being particularly suited for the characterization of patients with post-ischemic left ventricular systolic dysfunction. Moreover, particularly when fused with the pertinent CT coronary angiography images, such as in the case of hybrid CT/MPI imaging, PET images may offer the chance to individuate the patients in whom a significant improvement of left ventricular systolic function can be expected after revascularization [13].

Metabolic Imaging

HF is associated with abnormal myocardial metabolism, including energy depletion and reduced mechanical efficiency [14].

These changes may play a role in the progression of HF and may potentially serve as therapeutic targets. In normal conditions, fatty acids represent the major source of cardiac substrate metabolism accounting for the 60-to-90 % of the energy production of a myocardial cell under the resting status. Conversely, in patients with heart failure, glucose becomes the preferred cardiac energy sources, allowing deriving a significant quantity of energy despite relatively contained amount of oxygen [15, 16]. However, while this characteristic metabolic switch may sustain the energetic demands of a failing heart in the short-term, it becomes one of the most relevant counter-adaptive mechanisms in HF, significantly impairing cardiac metabolic reserve. Interestingly, recent evidence has shown how this metabolic adaptation of the failing heart may differ according to patients' sex, with a relative predilection of the "female" heart for the metabolism of fatty acid even during HF [17].

PET imaging, mainly with the use of dedicated carbon 11-labelled radiotracers (i.e. palmitate and acetate) has classically represented the ideal non-invasive imaging modality for the assessment of cardiac metabolism. However, the complex metabolism of fatty acids allows mainly semiquantitative measurements of substrate utilization with PET imaging of carbon 11-labeled palmitate [18].

On the other hand, PET imaging of carbon 11-labelled acetate allows assessment of cardiac oxidative metabolism without the complexity of substrate interaction between glucose and fatty acids [19]. The early rapid clearance of acetate correlates closely with myocardial oxygen consumption, and the relationship of myocardial carbon 11-labelled acetate kinetics to cardiac work offers a noninvasive parameter for cardiac efficiency that can be used to demonstrate the effect of pharmacological and pacing interventions on cardiac energetics [20].

On the other hand, while the non-invasive investigation of fatty acid's metabolism has never entered the clinical arena, fluorine 18-labled fluorodeoxyglucose (18F-FDG) still represent the backbone of metabolic imaging with PET, allowing

to trace cellular glucose uptake and phosphorylation and to quantify regional and global left ventricular glucose metabolism [21]. In this respect, in patients with idiopathic left ventricular systolic dysfunction, glucose metabolism is enhanced as a result of an adaptive mechanism to the increased hemodynamic load. Interestingly, those patients may show a significant regional heterogeneity in glucose oxidation, which may consistently vary in the different left ventricular walls [22]. This aspect may be particularly relevant in the case of patients showing a left bundle branch block (LBBB), in whom the dyssynchronous myocardial mechanical activation appears strictly parallel1ed by an inhomogeneous glucose utilization, lowest at the level of the left ventricular septum and highest in the lateral wall [22, 23].

However, while in patients with idiopathic left ventricular dysfunction 18F-FDG PET may still give relevant pathophysiological information, the most important clinical role of this imaging modality relates to its ability to define the presence of viable tissue within malperfused segments in patients with post-ischemic left ventricular systolic dysfunction [24]. As a matter of fact, still today, myocardial viability assessment with PET, either performed with combined perfusion/metabolism imaging [13, 25, 26] or with the hyperinsulinemic euglicemic clamp technique [27], probably represents the most accurate imaging modality for the evaluation of the indications for coronary revascularization, and for the prediction of patients outcome in post-ischemic left ventricular dysfunction [12, 28].

However, although highly intriguing, metabolic imaging with PET may gain clinical acceptance if dedicated high numbered studies and hopefully clinical trials confirm that a metabolic switch from fatty acids to glucose utilization in the failing myocardium impacts outcomes of patients with HF.

In the last years, the imaging armamentarium in the setting of chronic HF has been enriched by the introduction of a novel multimodal technology, hybrid cardiac PET/MR. In this respect, hybrid imaging with PET/MR dedicated devices combines almost simultaneous anatomic, functional, and metabolic imaging for the improved visualization of cardiac structure function and may provide new quantitative tools to study the pathophysiology of HF in vivo. In particular the excellent tissue characterization offered by cardiac MR, combined with the superior metabolic information given by PET imaging are able to create a new reference standard for the noninvasive assessment of complex cardiac pathologies, such as chronic HF.

Hybrid PET/CMR tomographers were only recently introduced for clinical applications [29]. The integration of PET with structural and functional CMR imaging markers including wall thickness, contractile response to dobutamine, transmural late gadolinium enhancement and perfusion has the potential to improve viability-based prediction of dysfunctional segments after revascularization and deserves to be evaluated in clinical studies.

As a matter of fact, both MR and PET have independently gained wide acceptance for the assessment of myocardial perfusion and viability in different categories of patients [13, 30]. Thus, by combining the strengths of each modality, hybrid PET/MR imaging might ideally become the future “gold standard” for the evaluation of patients with LV systolic dysfunction, especially in the presence of CAD.

While PET/MR imaging offers a clear reduction of radiation exposure, by eliminating CT-based attenuation correction, it might consistently increase workflow complexity and operational costs. Above all, the combination of PET and MR technologies in a unique hybrid device poses the necessity to obtain reliable attenuation correction maps of PET photons, as a mandatory step for PET-based quantification of cardiac functional parameters.

In this respect, after an initial delay due to intrinsic technical limitations, methods for a reliable attenuation correction from MR data have been proposed, showing to be able to replicate the results obtained with the standard CT-base attenuation correction [31]. Ultimately, the great strength of PET/MR will lie in its ability to deliver multimodal quantitative imaging parameters based on dynamic data acquisition with both modalities, offering a simultaneous physiologic and biologic quantitative characterization [32].

Moreover, relatively new acquisitions in the field of cardiac MR imaging seem to allow real time metabolic imaging with an extraordinary accuracy as well as spatial resolution. As a matter of fact, the introduction of MR spectroscopy with hyperpolarized molecules (i.e. carbon-13 pyruvate) in the clinical field might open new fields of pathophysiological investigation centered on the in vivo evaluation of myocardial metabolic pathways (i.e. the Krebs cycle activity) through the quantification of the metabolic flux of key 13C-labelled molecules [33, 34].

While, it is still not clear whether PET/MR will be able to offer added value or generate an additional demand for imaging studies that PET/CT cannot satisfy, we can expect that the combination of molecular imaging with superb functional characterization of cardiac performance will help to better investigate cardiac pathophysiology and to develop predictive parameters for tissue recovery and response to therapy.

Molecular Imaging: The Evaluation of Cardiac Innervation

The cardiac autonomic nervous system comprises the parasympathetic and the sympathetic nervous systems (SNS), which are equally relevant and have specular actions on cardiac function and haemodynamics. The early effects of SNS activation include heart rate and blood pressure elevation as well as increased myocardial contractility. While those mechanisms may support cardiac systolic function in early phases, there are highly detrimental in the chronic setting.

The different functions of the SNS are primarily mediated by the synthesis and release of its dominant neurotransmitter, norepinephrine. Interestingly, after neuronal stimulation only a limited amount of norepinephrine is available to activate adrenergic receptors on the myocyte membranes, since the majority of norepinephrine molecules are recycled into nerve terminals through dedicated transporters.

While these mechanism ensure an optimal norepinephrine turnover at a normal neuronal stimulation frequency, they cannot compensate the physiological norepinephrine spillover in case of prolonged high stimulation frequencies, such as in

patients with HF. In this situation, adrenergic terminals may become depleted of norepinephrine and the heart functionally denervated.

Unfortunately, despite its obvious clinical relevance, the status of cardiac SNS has been classically investigated indirectly, by means of surrogated, modestly reproducible, systemic measures (i.e. baroreceptor function or heart rate variability).

However, modern nuclear imaging offers the chance to shade lights on cardiac sympathetic tone, through the use of a dedicated nervous radiotracer [123I-metaiodobenzylguanidine (123I-MIBG)]. In fact, since the introduction in clinical practice, 123I-MIBG imaging has become the reference radiotracer for the non-invasive evaluation of cardiac adrenergic nervous function by means of planar scintigraphy and SPECT imaging.

From planar images, 123I-MIBG uptake is semiquantitatively assessed by calculating the heart-to-mediastinum (H/M) ratio and the washout rate, which estimates cardiac global adrenergic receptor density and have been associated with adverse prognosis [35].

However, despite their excellent reproducibility, those planar scintigraphic measures are unable to unmask regional alterations of cardiac adrenergic tone, whose presence has been shown to associate with different cardiac pathologies, independently predicting patients' outcome.

In this respect, SPECT imaging offers the chance to evaluate the presence of regional myocardial adrenergic innervation dishomogeneity, allowing, on the other hand, the comparison of regional cardiac innervation and perfusion obtained in the same patient with the same imaging format.

Not surprisingly, some studies have suggested how a regional 123I-MIBG defect score, derived from SPECT images, may be superior to the H/M ratio in predicting patient's adverse prognosis, highlighting the independent detrimental effect of regional adrenergic innervation heterogeneity [36].

Nevertheless, the combined assessment of myocardial innervation and perfusion has never gained wide clinical application, possibly because of the high radiation exposure and long acquisition time of this integrated imaging protocol. The use of new solid-state cardiac cameras with cadmium–zinc–telluride (CZT) detectors, characterized by a higher photon sensitivity and spatial resolution than standard cameras, can easily overcome these limitations and allow a comprehensive assessment of myocardial innervation and perfusion in a single imaging session and with a limited radiation burden. Accordingly, preliminary results obtained with this technique have shown the elevated image quality and possible clinical applications of combined innervation/perfusion CZT cardiac imaging in different patients categories, with and without cardiac pathologies [37, 38].

If SPECT imaging has made the clinical evaluation of cardiac sympathetic innervation feasible, PET still represents the reference standard for the non-invasive evaluation of myocardial adrenergic tone, allowing the absolute quantification of sympathetic nerve terminals activity. However, PET imaging also shows relevant technical disadvantages, mainly related to the short half-life of the Carbon-11 (11C) labelled innervation tracers, which have limited the diffusion of this technique.

Specifically, the versatility of PET radiotracers allows to perform a combined investigation of both pre-synaptic and post-synaptic receptor density. Accordingly, the positron tracers [11C]hydroxyephedrine and [11C]epinephrine permit quantification of the density of sympathetic nerve terminals [39], while postsynaptic-receptor density can be assessed with [11C]CGP12177, which has been shown to independently predict adverse patients' prognosis, particularly related to the incidence of symptomatic HF.

Innervation Imaging of Arrhythmias

Ventricular tachy-arrhythmias represent a leading cause of death in cardiac patients, associating with considerable social and sanitary costs. Structural heart diseases, such as post-ischemic LV dysfunction, are among the major predisposing factors for ventricular arrhythmias whose genesis relies on the combined presence of a triggering mechanism that initiates the arrhythmia and of a anatomic substrates that maintains the arrhythmia ones it is initiated. While the anatomic substrate is mainly identified by the presence of isles of scar tissue (i.e. an old myocardial infarction or the results of a myocarditis) interposed within bands of living myocardium, the triggering functional mechanism may vary. In this respect, cardiac MRI with late gadolinium enhancement technique represents the gold-standard for the evaluation of the presence and extent of myocardial scar, allowing the localization of myocardial fibrosis (i.e. sub-epicardial, sub-endocardial, or transmural) and the definition of the most likely etiology of the underlying disease (i.e. ischemic, inflammatory, infiltrative).

On the other hand, one of the most relevant factors that may trigger ventricular arrhythmias is represented by an abnormality of cardiac sympathetic tone. In fact, it has been shown that the presence of an impairment of cardiac adrenergic innervation may represent a relevant marker of adverse prognosis in different clinical settings, particularly predisposing to the development of malignant ventricular arrhythmias. [40].

In this context, due to an increase in the number of patients with heart failure and ventricular arrhythmias, ventricular tachycardia ablation has a growing clinical role. Long-term success rates remain suboptimal and require creating a detailed electro-anatomic map during the procedure to identify fibrotic areas responsible for arrhythmias. In particular, areas of abnormal cardiac sympathetic innervation can be identified using 123-I MIBG SPECT imaging, which may help in identifying triggers that initiate ventricular tachycardia and also predict successful ablation sites within an otherwise normal myocardium. [41].

Cardiac Resynchronization Therapy

In the last few decades, the evaluation of the presence of LV mechanical dyssynchrony has almost become a mandatory step in the functional assessment of patients with HF, since a dyssynchronous LV mechanical activation has been consistently

associated with adverse patients' functional status and overall outcome [42, 43]. From a theoretical point of view, LV mechanical dyssynchrony should be distinguished by electrical dyssynchrony, the first relating to the inability of the different myocardial walls to contract in unison, while the later describing the delayed propagation of the electric impulse in a portion of the LV myocardium, such as in the case of a left-bundle branch block (LBBB). In this respect, different reports have shown how these two apparently different entities (i.e. electrical and mechanical dyssynchrony) may be independent one from the other, since significant mechanical dyssynchrony may develop even in patients with a normal QRS, still predicting adverse cardiac morbidity [44]. Nevertheless, despite the initial positive results, no convincing data exists on the clinical benefit derived by "treating" mechanical dyssynchrony in patients with a narrow QRS [45].

From a therapeutical standpoint, if LV dyssynchrony has become a new cardiac illness, cardiac resynchronisation therapy (CRT), or biventricular pacing, represents its most effective cure. In fact, this pacing technology aims to restore a physiological myocardial mechanical activation by stimulating different positions of the LV (i.e. the septal and lateral walls).

All the different cardiac imaging modalities offer the opportunity to assess the presence and quantitate the extent of LV mechanical dyssynchrony with similar accuracy and reproducibility. In particular, 2D echocardiography has classically represented the standard imaging technique for the evaluation of patients with suspected myocardial dyssynchrony, and various indices, either based on mono-dimensional, two-dimensional, or Doppler imaging, have been proposed and validated in relatively small numbered studies. However, as clearly shown by the PROSPECT study, almost none of such echocardiographic measures of LV dyssynchrony [46, 47] shows acceptable reproducibility, failing in accurately predict the response to CRT.

Accordingly, in an attempt to overcome the intrinsic limitations of 2D echocardiography, novel indices derived from 3D imaging techniques have been developed, offering the opportunity to characterize LV contraction in a real-time three-dimensional manner. In these 3D echocardiography and single-photon emission computed tomography (SPECT) are undoubtedly the most diffused and clinically relevant technique for the 3D estimation of LV mechanical dyssynchrony. On the one hand, 3D echocardiography offers the opportunity to image the entire LV volume with in real time, allowing deriving three-dimensional measure of global LV deformation (i.e. 3D LV strain) that may significantly better predict cardiac mechanics than 2D indices [48].

On the other hand, nuclear imaging has classically represented the reference standard for the assessment of LV mechanical dyssynchrony, allowing to absolutely quantifying the degree of abnormal myocardial mechanical activation through "phase analysis" [49]. However, those indices of mechanical dyssynchrony (i.e. the phase standard deviation and the histogram bandwidth), initially derived from planar cardiac scintigraphy, have never gained wide clinical diffusion, probably because of the relative rudimentariness of the imaging technique.

SPECT imaging allows obtaining superior measures of LV regional myocardial perfusion, still representing the backbone of the non-invasive evaluation of myocardial ischemia and viability. Moreover, gated SPECT analysis is able to give absolute,

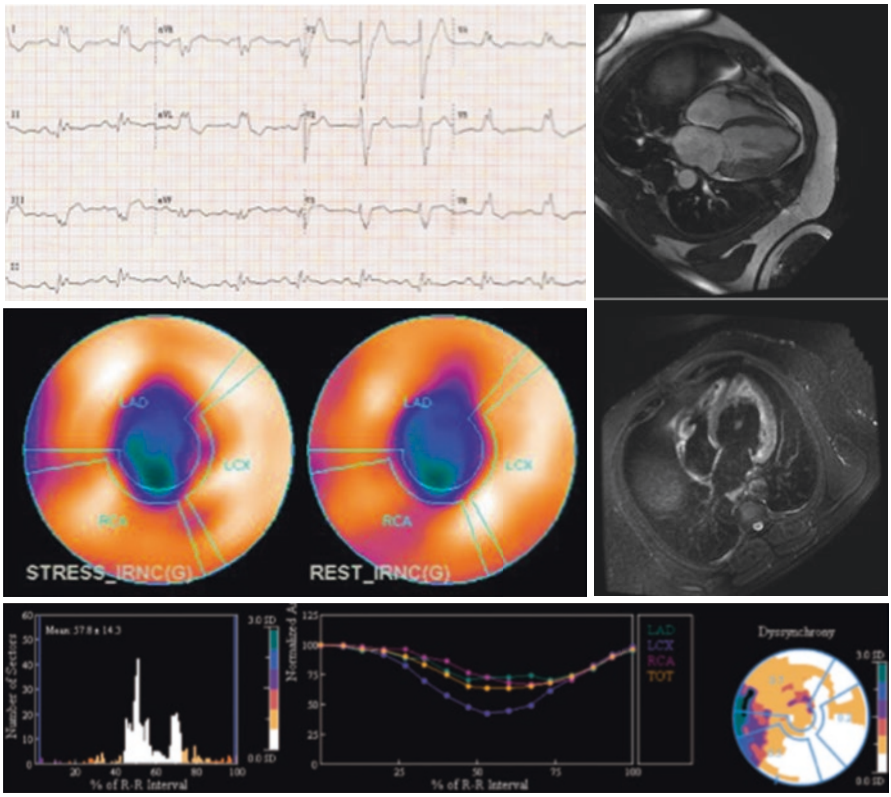

Fig. 9.2 Multimodality cardiac imaging in chronic heart failure. A male patient with post-ischemic left ventricular dysfunction and a previous anterior myocardial infarction treated with PCI on the mid LAD. On ECG a left-bundle branch-block was evident. Cardiac magnetic resonance showed the presence of a moderately dilated LV with depressed systolic function (EF 35 %), while myocardial perfusion imaging at stress/rest SPECT revealed an anterior-distal and apical LV scar gated SPECT images demonstrated the presence of significant mechanical dyssynchrony with delayed activation of the lateral LV wall, suggesting the possible benefit of CRT therapy

highly reproducible and validated, measures of LV structure and mechanics (i.e. LV volumes, ejection fraction, and mass) and to quantitate the presence and extent of mechanical dyssynchrony on a three-dimensional manner [50]. In fact, SPECT derived "phase analysis" represents an almost operator-independent technique to obtain a volumetric evaluation of LV mechanical dyssynchrony on top of the classical SPECT-derived perfusion analysis [51]. As expected, dyssynchrony analysis by SPECT has been shown to correctly identifying patients that will benefit from CRT, allowing obtaining, particularly when performed with dedicated cardiac cameras equipped with cadmium-zinc-telluride (CZT) detectors, a comprehensive evaluation of myocardial perfusion and mechanics with an extremely low radiation burden [52, 53] (Fig. 9.2).

Nevertheless, despite the advancement of the different imaging modalities in the characterization of LV mechanical dyssynchrony, 30–40 % of the patients having CRT do not respond to resynchronization therapy with improved clinical symptom

and cardiac functions, posing a relevant problem of cos-effectiveness of the procedure [42]. Multimodal cardiac imaging offers the chance to overcome the limitations of single-modality imaging, offering the opportunity to characterize different predictors of CRT response, such as the presence and location of myocardial dyssynchrony (i.e. identification of the most delayed LV wall), myocardial viability burden, and coronary venous anatomy.

As a matter of fact, it is capital for CRT response that the LV lead is placed away from a myocardial scar and at or near the site of the latest mechanical activation. Both echocardiographical and nuclear image-guided approaches for CRT have shown significant clinical value to assess LV myocardial viability and mechanical dyssynchrony, recommend the optimal LV lead position, and navigate the LV lead to the target coronary venous site [54].

This is particularly true when imaging modalities that asses and quantitate the presence of LV mechanical dyssynchrony are combined with the non-invasive assessment of cardiac coronary sinus anatomy, as possible with computed tomography (CT) coronary venous angiography in order to preliminarily assess the anatomic feasibility of CRT implantation [55].

Specifically, patients with post-ischemic LV systolic dysfunction might benefit most from this multimodal approach. In fact, those patients are least likely to respond to CRT implantation, probably because of the presence of scared myocardium near the site of delayed LV mechanical activation. On the other hand, patients with an unsuitable coronary venous anatomy (i.e. lacking a venous branch near the site of latest LV mechanical activation) might be spared from the procedure of percutaneous CRT implantation and referred to trans-septal or epicardial lead placement, since they are less likely to respond to traditional implantation techniques.

Accordingly, the ideal approach to patients with mechanical dyssynchrony should theoretically include those three steps: (1) the preliminary 3D assessment of the presence of significant dyssynchrony with the identification of the site of latest LV activation; (2) the definition of regional myocardial scar burden in order to define whether the abnormally contracting LV segments are viable and surrounded by significant viable myocardiaum; (3) the non-invasive evaluation of coronary venous anatomy to ascertain the presence of a suitable coronary venous branch in proximity to the viable dyssynchronous myocardial segments.

Prospective dedicated studies are needed to validate these techniques and demonstrate the clinical opportunity and cost-effectiveness of this multi-modal imaging approach for the management of patients with HF and signs of LV mechanical dyssynchrony.

Rheumatic Disease

Rheumatic diseases (RD) is the result of different pathophysiologic processes that derive from the development of systemic, myocardial, and vascular inflammation. Nevertheless, despite its systemic effects, cardiac specific involvement in RD represents, by far, the most clinically relevant manifestation of this pathology, strongly

effecting patients' clinical status and long-term prognosis. In this respect, at a the cardiac level, RD associates with early coronary atherosclerosis, abnormal coronary vasoreactivity resulting in cardiac ischemia, due to both micro and/or macrovascular lesions, and myocardial fibrosis [56]. On a functional level, patients with cardiac RD may present myocardial, pericardial, and coronary artery diseases, and ultimately systolic and diastolic heart failure, as well as pulmonary arterial hypertension. However, as obvious, the main effect of RD on cardiac structure is represented by the development of, primarily left-sided, valvular pathologies (i.e. mitral stenoinsufficiency or aortic stenosis) that strongly condition the chronic phase of the disease and impact patients' clinical management.

In the initial phase, the symptoms of cardiac involvement in RD are usually subtle, particularly if compared to the prominent acute systemic involvement. On the other hand, cardiac-related symptoms dominate the chronic phase of the disease, underscoring the need for an accurate evaluation of cardiac structure and function through non-invasive imaging. In fact, while having assisted to a significant reduction of disease associated mortality due to targeted pharmacological therapies (i.e. antibiotics), the lifespan of patients with RD remains lower than the general population, predominantly due to the results of cardiac involvement.

Echocardiography still represents the backbone of the non-invasive evaluation of patients with suspected or known RD offering the chance to individuate the initial signs of rheumatic manifestations also in the initial oligo-asymptomatic phase [57]. However, a normal echocardiogram cannot always exclude cardiac involvement and/or identify acuity and pathophysiology of cardiac lesions. Therefore, cardiac magnetic resonance (CMR) imaging is a necessary adjunct, complementary to echocardiography, especially in the case of patients with new onset HF or when there are conflicting data from the initial evaluations. Moreover CMR is the reference standard for the assessment of signs of pericarditis as well as myocarditis and can be used to absolutely quantify the degree of valvular regurgitation and stenosis in patients screened for surgical interventions [58].

Ultimately, cardiac SPECT/PET and coronary CT play a complementary role in patients with cardiac RD, allowing to rule out the presence of other causes of myocardial ischemia in the case of chest pain and to assess the presence and severity of coronary microvascular involvement as a result of the chronic inflammatory process.

Management of Aortic Stenosis in HF

Aortic stenosis (AS) is the most frequent degenerative valvular heart disease in the Western countries and its prevalence increases in parallel with the ageing process of the population. Systolic HF, defined by the presence of reduced left ventricular ejection fraction, may be present in up to a quarter of patients with severe AS, posing diagnostic and management challenges. On the other hand, most of the patients with significant AS show signs of reduced LV compliance with various degrees of

diastolic dysfunction that may consistently reduce effort tolerance even in the presence of a preserved ejection fraction [59].

Multimodality cardiac imaging has two prominent roles in the evaluation of patients with AS: assess coexistent myocardial and coronary pathology in patients with inconclusive symptoms (i.e. angina) or LV systolic dysfunction; perform an in-depth characterization of cardiac structure in a patient candidate to aortic valve replacement, either surgical or percutaneous [60].

In patients with apparently severe AS and LV systolic dysfunction, cardiac imaging can, on one hand, confirm or exclude the severity of the valvular pathology and, on the other hand, individuate other possible causes of HF.

Specifically, 3D imaging modalities, like cardiac CT or 3D echocardiography, may absolutely quantify aortic anulus area and allow a better assessment of the real aortic valve area [60]. Moreover, the calcium score of the aortic valve, as an easy CT-derived measure, has been proposed as an indirect, though specific, signs of anatomic severity of a given AS. Similarly CT coronary angiography can evaluate the extent of underlying coronary artery disease, as a frequent, prognostically relevant, bystander in old patients with AS [61].

From the echocardiographic standpoint, relatively novel imaging techniques, LV deformation analysis through strain imaging, have been proposed for the detection of early signs of contractile impairment in patients with still normal LV ejection fraction [62].

Finally, in patients that will undergo a trans-catheter aortic valve implantation (TAVI) a comprehensive cardiac CT evaluation is currently perform to derive key cardiac and valvular parameters (i.e. anulus dimensions, degree of calcification, relationship with coronary ostia) as well as relevant satellite measures (i.e. anatomy of subclavian, iliac and femoral arteries) that will guide the intervention and define, for example, the best vascular access of the procedure [63].

Cardio-oncology and HF

Decades ago, myocardial biopsy was considered the most accurate method in identifying the myocardial damage induced by chemotherapy, detecting the ultrastructural alteration of cardiomyocytes as well as the alterations of cardiac interstitium [64].

Fortunately, during those years, non-invasive cardiac imaging modalities have emerged as the reference standards in monitoring cardiotoxicity in cancer patients. Nevertheless, despite different techniques and parameters have been proposed, until recently the most diffused parameter for the serial evaluation of patients undergoing chemotherapy and for the early individuation of the presence of cardio-toxicity has been LV ejection fraction [65].

Despite current cardiac imaging modalities may quantify the value of LV ejection fraction with excellent accuracy and reproducibility, it is now clear that the drop of LV ejection fraction represents a late phenomenon in the pathophysiology of the chemotherapy-induced cardiotoxicity.

This evidence has led the clinicians to look for other imaging methods that could evaluate cardiac function independently of the loading conditions, aiming to detect the earliest manifestation of cardiotoxicity and allowing for the appropriate management of the therapy.

Among the different parameters, the evaluation of LV "global longitudinal strain" (GLS) derived by myocardial deformation analysis through 2D-speckle tracking imaging has accumulated evidence supporting its introduction in the clinical evaluation and follow up of patients with suspected chemotherapy-induced cardiotoxicity. As a matter of fact, baseline and periodical evaluation of GLS is recommended by the recent guidelines by ASE/EACVI [66]. Promising techniques such as 3D-STE and tissue characterization performed by CMR are under investigation and could provide new insights into the future for the evaluation of chemotherapy-treated patients.

Cardiac Amyloidosis

Infiltrative heart disease represent a frequently underdiagnosed cause of congestive HF. Among the different etiologies, cardiac amyloidosis represents, by far, the most clinically relevant type of infiltrative heart disease, producing a characteristic type of restrictive cardiomyopathy.

Being a systemic disease with cardiac involvement, the diagnosis of cardiac amyloidosis is based on multiple clinical, bio-humoral, imaging and hystopathological findings. Among the different cardiac imaging modalities, MRI represents probably the one-stop-shop for the non-invasive characterization of patients with suspected amyloidosis. Specifically cardiac MRI can assess the presence and determine the distribution of myocardial infiltration, through the analysis of "late gadolinium enhancement" (LGE) data [67]. Accordingly, the temporal evolution of cardiac involvement can be tracked, with sub-endocardial LGE deposition in the earlier phases, and transmural fibrosis later. Moreover, novel MRI techniques, such as T1-mapping analysis, are able to estimate myocardial extra-cellular volume, giving an idea of the global burden of infiltrative burden and predicting adverse patients' outcome [68]. At the same time, through the analysis of the first-pass kinetics of gadolinium, cardiac MRI offers the chance to assess the presence of regional myocardial perfusion inhomogeneities, early sign of coronary microvascular dysfunction that may develop in cardiac amyloidosis [69].

In addition to cardiac MRI, a new imaging technique has been recently added to the armamentarium for the non-invasive evaluation of cardiac amyloidosis, bone scintigraphy. In fact, it has been shown that Technetium-99m-labelled 3,3-diphosph ono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD), a classical radiotracer employed for bone scintigraphy shows a specific affinity for cardiac amyloid deposits, particularly in the case of transthyretin amyloidosis [70].

Moreover, initial reports have suggested how myocardial ^{99m}Tc-DPD captation might represent a precocious sign of cardiac amyloidosis, even in the presence of inconsistent results from other clinical and/or imaging techniques [71] (Fig. 9.3).

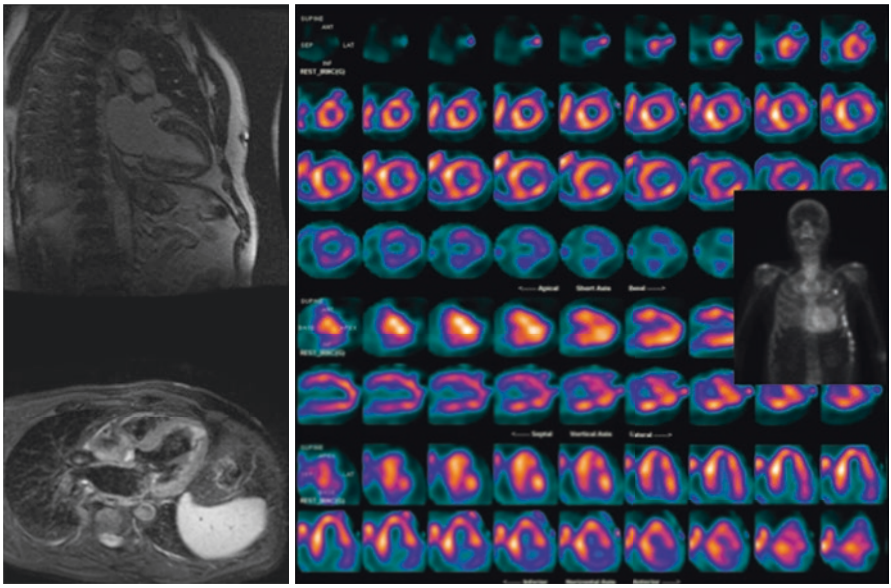

Fig. 9.3 Molecular imaging in heart failure. Representative images of a 85 years old patient with congestive heart failure and preserved ejection fraction. Cardiac magnetic resonance showed the presence of an hypertrophic LV with 50 % ejection fraction and extensive, mainly intra-myocardial, late-gadolinium enhancement (non-ischemic pattern). Because of the suspicion of cardiac infiltration, a diphosphonate (scrivere nome tracciante) whole body and cardiac SPECT scintigraphy was performed with evidence of extensive cardiac tracer uptake consistent with cardiac amyloid deposition

Quantitative Cardiac Imaging: The Need for an Absolute Measurement of Cardiac Parameters

Cardiac imaging, particularly when used in daily clinical practice, is generally used to provide qualitative measures of cardiac structure and function. For example, LV systolic function is described through a visual estimation of the ejection fraction, the presence and degree of LV hypertrophy is characterized with indirect measures (i.e. the interventricular septum thickness), and myocardial perfusion is evaluated in relative terms.

However, particularly in the setting of patients with HF, that frequently require periodic cardiac evaluations to modify targeted treatments (anti-hypertensives, diuretics), the accurate quantification of key LV parameters is necessary. Accordingly, the different cardiac imaging now allow the chance to precisely and reproducibly quantify measures of cardiac structure and function (i.e. LV ejection fraction and mass), LV mechanics (i.e. the global longitudinal strain), and cardiac perfusion (i.e. myocardial blood flow reserve).

Specifically, 3D-echocardiography may offer a to obtain an absolute evaluation of LV volumes, mass and ejection fraction that parallels the results of cardiac MRI,

showing a convincing reproducibility [72]. Moreover, the analysis of LV deformation through 2D (i.e. speckle tracking technique) or 3D echocardiography allows to obtain highly reproducible indices of regional and global LV function, such as the global longitudinal strain, that may additively characterize HF patients [73].

On the other hand, conventional nuclear imaging, particularly in the era of new dedicated cardiac devices equipped with CZT detectors, may become the one-stop-shop for the evaluation of patients with HF, offering the chance to obtain a rapid assessment of LV perfusion and regional viability and cardiac function and structure (i.e. LV mass, sphericity index, and dyssynchrony) within the same imaging session [51, 74]. Moreover, through dedicated molecular imaging, such as in the case of innervation imaging (i.e. 123I-MIBG SPECT) and amyloid imaging (i.e. 99mTc-DPD SPECT), current nuclear techniques allow a precise etiological characterization and risk assessment with contained costs and radiation burden [37, 70].

Finally, when cardiac PET is considered, modern cardiac imaging allows a state-of-the-art evaluation of regional and global absolute myocardial blood flow and perfusion reserve, that still represent some of the most prognostically relevant cardiac functional measures, both in patients with idiopathic LV systolic dysfunction [75] and ischemic heart disease [76], as well as in those with primary (i.e. hypertrophic cardiomyopathy) [77] and secondary (i.e. amyloidosis) cardiomyopathies [78].

Future Perspectives—Hybrid Imaging Using Molecular Targets

Cardiac imaging has been classically used to witness the functional and structural effects of a given pathology, being molecular imaging practically outside the possibilities of most of the imaging modalities. In this respect, nuclear imaging modalities have traditionally represented the only chance to perform molecular imaging in the clinical field, increasingly contributing to the development of imaging strategies which go beyond the sole assessment of myocardial perfusion. Accordingly, cardiovascular molecular imaging aims at the visualization of specific molecules and pathways that precede or underlie changes in morphology, physiology, and function.

Examples are the use of neuronal imaging to identify subjects at risk for ventricular arrhythmia [79, 80], the development of compounds targeting plaque vulnerability before rupture and subsequent myocardial infarction [81, 82], and the analysis of the precocious mechanisms which precede left ventricular remodelling and heart failure development [83, 84]. Additionally, molecular imaging has great potential to facilitate the discovery and development of novel therapies through improved target identification and implementation of more efficient endpoints, as well as visualization of cellular and subcellular target structures. Examples are the development of reporter gene imaging techniques [85], and the implementation of cell labelling for imaging of engraftment after transplantation [86]. This ability to visualize small amounts of molecular-targeted compounds in small target areas has clear translational potentials and may help to design dedicated imaging algorithms

and intrumentations for dedicated molecular analysis. It also provides a strong rationale for hybrid imaging approaches, where the nuclear imaging component is used for molecular targeting and the CT is used for localization of the specific signal [87].

Conclusion

In patients with LV dysfunction, multimodality imaging offers the opportunity to obtain continued information on regional and global cardiac function, myocardial viability, coronary anatomy and regional relative (SPECT) or absolute (PET) myocardial perfusion.

The different modalities may be performed separately and integrated/fused afterwards (i.e. through hybrid imaging) or may be used in a single step approach to define HF etiology, the extent and severity of myocardial damage/ischemia, indicate and predict the response to targeted treatments (i.e. CRT, coronary revascularization) as well as to perform pre-interventional assessment (i.e. to program trans-catheter ablation of arrhythmias or valvular interventions).

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Part III
Treatment of Heart Failure

Chapter 10
Contemporary Pharmacological Treatment of Heart Failure

Justyna Krzysztofik and Piotr Ponikowski

The Goals of Treatment

There are three main goals of treatment in patients with chronic heart failure (CHF):

1. Mortality reduction
2. Improvement in clinical status, functional capacity and quality of life
3. Reduction of hospital admissions (mainly due to acute decompensated heart failure)

Other important objective in the management of CHF patients is an optimal, comprehensive treatment of co-morbidities (i.e. atrial fibrillation, diabetes mellitus, renal dysfunction, iron deficiency, depression). In the recent years, prevention of the occurrence of myocardial damage by optimal management of the disease leading to CHF (coronary artery disease, arterial hypertension, valvular diasese) and slowing-down remodeling of the diseased myocardium have become well recognized aims of treatment in order to prevent development of heart failure [1–3]. As patients with CHF are now living longer and many of them enter very advanced stage of the disease, providing end of life care should also be among important goals of therapy in this population.

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M. Dorobanţu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_10

Pharmacological Treatment in Chronic Heart Failure

Heart Failure with Reduced Ejection Fraction

Differentiation of patients with CHF based on left ventricular ejection fraction (LVEF) into those with heart failure and reduced (HFrEF, LVEF < 40 %), mid-range (HFmrEF, LVEF 40–49 %) and preserved ejection fraction (HFpEF LVEF ≥ 50 %) is important as only in HFrEF patients pharmacological therapies have been shown to reduce mortality and morbidity, favourably changing natural history of this clinical syndrome. We will provide short overview of pharmacological therapy focussing first on disease-modifying therapies followed by therapies recommended for symptomatic relief.

Therapeutic algorithm for patients with HFrEF, recently recommended by the 2016 European Society of Cardiology guidelines is presented in the Fig. 10.1.

Treatments Improving the Outcomes

Intensive research in the pathophysiology of CHF syndrome led to the discovery and better understanding of the compensatory mechanisms elicited during the development of the disease. It became evident that these mechanisms, triggered as an acute, adaptive response to the damage of the myocardium with subsequent deterioration of the left ventricular function and impaired in peripheral perfusion although favorable in an early phase, soon become deleterious leading to disease progression. Neuroendocrine activation involving predominantly adrenergic system and renin-angiotensin-aldosterone system constitutes here a key element resulting in the unfavorable cardiovascular effects namely: myocardial hypertrophy and remodeling, apoptosis/necrosis of the myocardial cells, vasoconstriction, sodium and water retention. The intriguing hypothesis which was put forward comprised overactive neuroendocrine system as a therapeutic target in CHF syndrome. Implementation into clinical practice the *neurohormonal antagonists* (angiotensin converting enzyme [ACE] inhibitors, beta-blockers, mineralocorticoid receptor antagonists [MRA]) was the biggest milestone in the management of HFrEF. Numerous clinical trials subsequently confirmed that they should be used in the treatment of every patient with HFrEF as they improve the outcomes. Only recently a new therapeutic class- *angiotensin receptor neprilysin inhibitor* (ARNI) has shown additional improvement in survival of HFrEF patients with heart failure once compared with ACE inhibitor [4].

Another intriguing pathophysiological concept, recently tested was linked with elevated heart rate as potentially deleterious mechanism being not only a consequence of CHF but itself leading to disease progression. Discovery of a drug which selectively reduces heart rate by inhibiting I_f-channel in the sinus node – ivabradine – allowed to verify this hypothesis. Ivabradine added to optimal treatment with

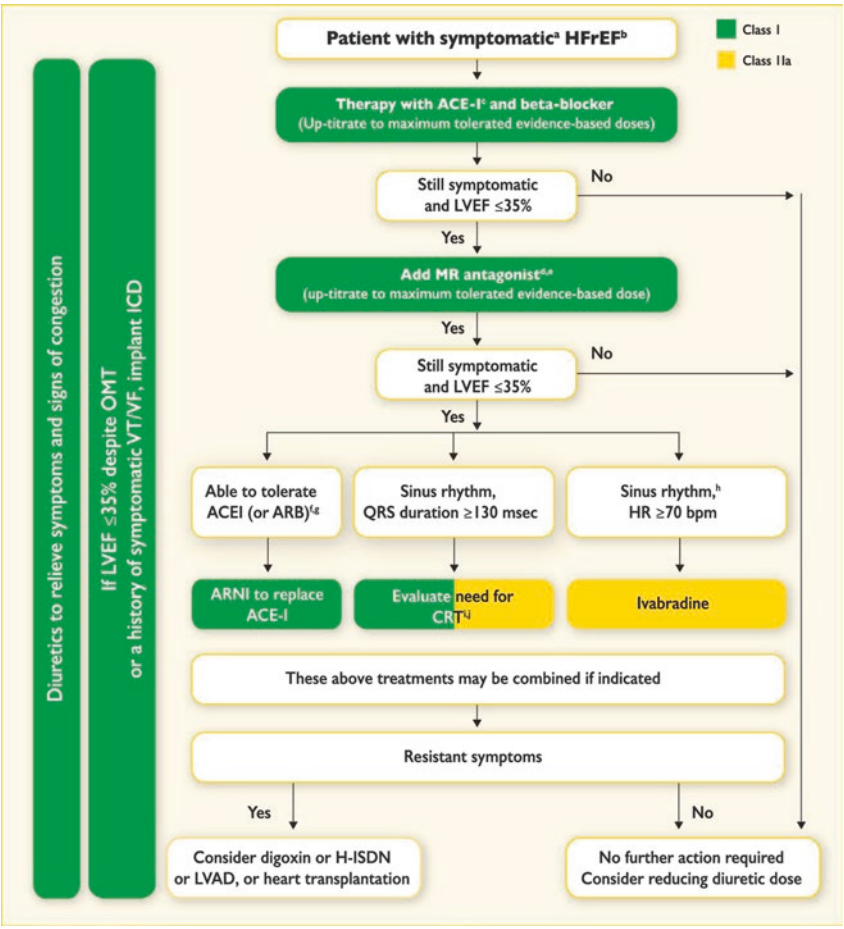

Fig. 10.1. Therapeutic algorithm for patients with symptomatic heart failure with reduced ejection fraction. *Green* indicates a class I recommendation; *yellow* indicates a class IIa recommendation. *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ARNI* angiotensin receptor neprilysin inhibitor, *BNP* B-type natriuretic peptide, *CRT* cardiac resynchronization therapy, *HF* heart failure, *HFrEF* heart failure with reduced ejection fraction, *H-ISDN* hydralazine and isosorbide dinitrate, *HR* heart rate, *ICD* implantable cardioverter defibrillator, *LBBB* left bundle branch block, *LVAD* left ventricular assist device, *LVEF* left ventricular ejection fraction, *MR* mineralocorticoid receptor, *NT-proBNP* N-terminal pro-B type natriuretic peptide, *NYHA* New York Heart Association, *OMT* optimal medical therapy, *VF* ventricular fibrillation, *VT* ventricular tachycardia. [a] Symptomatic: NYHA class II-IV. [b] HFrEF: LVEF<40 %. [c] If ACEI not tolerated/contra-indicated, use ARB. [d] If MR antagonist not tolerated/contra-indicated, use ARB. [e] With a hospital admission for HF within the last 6 months or with elevated natriuretic peptides (BNP> 250 pg/ml or NTproBNP> 500 pg/ml in men and 750 pg/ml in women). [f] With an elevated plasma natriuretic peptide level (BNP ≥ 150 pg/mL or plasma NT-proBNP ≥ 600 pg/mL, or if HF hospitalization within recent 12 months plasma BNP ≥ 100 pg/mL or plasma NT-proBNP ≥ 400 pg/mL). [g] In doses equivalent to enalapril 10 mg b.i.d. [h] With a hospital admission for HF within the previous year. [i] CRT is recommended if QRS≥ 130 ms and LBBB (in sinus rhythm). [j] CRT should/may be considered if QRS ≥ 130 ms with non-LBBB (in a sinus rhythm) or for patients in AF provided a strategy to ensure bi-ventricular capture in place (individualized decision) (With permission of Oxford University Press (UK) © European Society of Cardiology, www.escardio.org [1])

neurohormonal agents further improved the outcomes in HFrEF patients with sinus rhythm and heart rate ≥70 bpm [5].

The most important clinical trials, that has proven to improve the outcomes in HFrEF patients are shown in chronological order in Fig. 10.2.

Treatments Recommended in All Patients with HFrEF- Neurohormonal Antagonists

There are several pharmacological ways to downregulate the sympathetic nervous system and the renin- angiotensin- aldosterone axis, which detrimental chronic activation plays a crucial role in the progression of heart failure:

- Adrenergic receptors blockade
- Renin inhibition (angiotensin I reduction)
- Angiotensin converting enzyme inhibition (angiotensin II reduction)
- Angiotensin II receptors blockade
- Mineralocorticoid receptors blockade.

Benefits from blockade of the renin- angiotensin- aldosterone axis (mainly with ACE inhibitors) in patients with HFrEF are presented in Table 10.1 [3, 21].

Angiotensin- Converting Enzyme Inhibitors

In CONSENSUS trial, which results were first presented in 1987, enalapril used in patients in NYHA class IV was proved to be a first agent, which reduced mortality in heart failure [8, 9]. In next few years ACE inhibitors further strengthened their position in the management of HFrEF across the whole spectrum of the disease, including patients with asymptomatic left ventricular dysfunction [10, 11, 15].

ACE inhibitors prolong survival, increase exercise capacity, decrease rate of hospitalizations, ameliorate symptoms and in patients after myocardial infarction additionally reduce the risk of recurrent myocardial infarction [22, 23].

Indications
ACE inhibitors should be started in all stable patients, already at the very beginning of the development and diagnosis of HFrEF, including also asymptomatic patients with left ventricular dysfunction and continued for the whole life, unless contraindicated. Due to the fact, that fluid retention may attenuate the effects of ACE inhibitors in hospitalized patients with worsening heart failure, the therapy should be started after relieving congestion, but ideally before discharge from the hospital [1, 2].

Contraindications
A history of angioedema is an absolute contraindication for ACE inhibitors. Other contraindications include: allergic or drug- specific adverse reaction, known

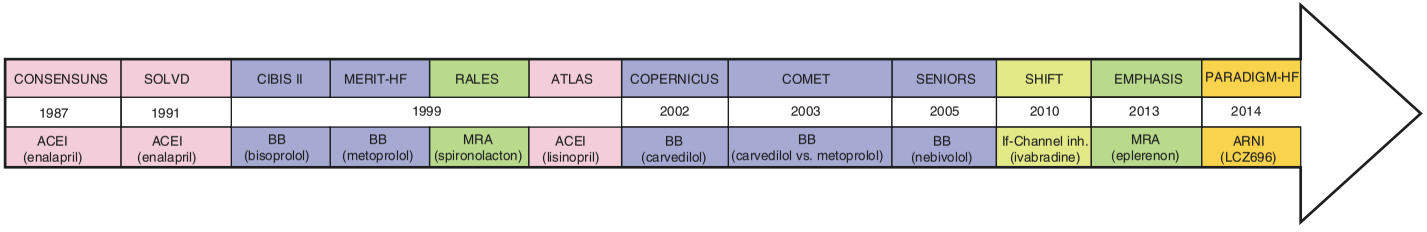

Fig. 10.2. Most important clinical trials (with the year of publishing results) in treatment of HFrEF, that has showed to reduce mortality/morbidity. *ACEI* angiotensin-converting enzyme inhibitor, *ARNI* angiotensin receptor neprilysin inhibitor, *ATLAS* Assessment of Treatment with Lisinopril And Survival, *BB* beta- blocker, *CIBIS II* Cardiac Insufficiency Bisoprolol Study II, *COMET* Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial, *CONSENSUS* Cooperative North Scandinavian Enalapril Survival Study, *COPERNICUS* Carvedilol Prospective Randomized Cumulative Survival, *EMPHASIS* Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure *inh* inhibitor, *MERIT-HF* Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure, *MRA* mineralocorticoid receptor antagonist, *PARADIGM-HF* Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial, *RALES* Randomized Aldactone Evaluation Study, *SENIORS* Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisations in Seniors with Heart Failure, *SHIFT* Systolic Heart failure treatment with the If inhibitor ivabradine Trial, *SOLVD* Studies of Left Ventricular Dysfunction [4–20]

Table 10.1 The main effects of inhibition the renin- angiotensin- aldosterone system by angiotensin converting enzyme inhibitors in HFrEF

Benefits of RAAS inhibition in patients with HFrEF
Mortality and morbidity reduction
Prevention of ventricular remodeling
Decrease of systemic vascular resistance and pre- and afterload; increase in cardiac index
Prevention of the atherosclerotic plaque destabilization and reduction the risk of acute coronary syndromes
Prevention of electrolyte imbalance: hypokalemia during diuretic therapies and hypernatremia due to dilution
Nephroprotective effect- prevention of renal dysfunction and development of proteinuria
Decrease the risk of developing diabetes mellitus type 2

bilateral renal artery stenosis or renal artery stenosis of the only one functioning kidney, pregnancy.

In the following circumstances caution/specialist advice is recommended: significant renal dysfunction (creatinine >221 μmol/L [2.5 mg/dL]), hyperkalemia (>5.0 mmol/L), symptomatic hypotension (systolic blood pressure < 90 mmHg), persistent cough associated causally with ACE inhibitors [1, 2, 6].

Drugs, dosages and rules of applications

Only enalapril was studied in the placebo- controlled trials in chronic heart failure, however class effect of ACE inhibitors was proven in many trials with patients post myocardial infarction and HF. Other studied ACE inhibitors included ramipril, captopril, lisinopril and quinapril hydrochloride [21, 23–28].

Before the initiation of the therapy with ACE inhibitor, renal function and electrolytes should be checked. During the treatment, blood chemistry (creatinine, potassium, urea/blood urea nitrogen) should be re-checked 1–2 weeks after beginning of the therapy and 1–2 weeks after final dose titration. When achieving the highest tolerated dose, blood chemistry should be monitored 4 monthly thereafter [1, 2].

In the ATLAS trial, which was designed to compare high dose versus low dose of ACE inhibitor (lisinopril), it has been shown that there was no difference in all-cause mortality, however in group of patients receiving higher doses a 15 % reduction in combined heart failure hospitalization rate or all- cause mortality was observed. Therefore, it is recommended to initiate the therapy with low doses and up- titrate ACE inhibitor by doubling the dose not less than 2-weeks intervals, until the target dose or the maximum tolerated dose has been achieved [1, 15].

The evidence- based target doses of disease- modifying drugs in heart failure with reduced ejection fraction are presented in Table 10.2.

Problem solving of possible adverse effects

The most dangerous adverse effect is *angioedema*, which occurs in 0.1–0.2 % of patients, usually in first weeks of treatment with ACE inhibitor. In this life- threatening condition emergency treatment is needed to prevent spontaneous eruption and when it has occurred to maintain a patent airway and stop further progression of disease.

Table 10.2 Starting and target doses of disease- modifying drugs in heart failure with reduced ejection fraction

	Starting dose (mg)	Target dose (mg)
ACE-I		
Captopril[a]	6.25 *t.i.d.*	50 *t.i.d.*
Enalapril	2.5 *b.i.d.*	10–20 *b.i.d.*[*]
Lisinopril[b]	2.5–5.0 *o.d.*	20–35 *o.d.*
Ramipril	2.5 o.d.	10 *o.d.*
Trandolapril[a]	0.5 *o.d.*	4 *o.d.*
Beta-blockers		
Bisoprolol	1.25 *o.d.*	10 *o.d.*
Carvedilol	3.125 *b.i.d.*	25 *b.i.d.*[d]
Metoprolol succinate (CR/XL)	12.5–25 *o.d.*	200 *o.d.*
Nebivolol[c]	1.25 *o.d.*	10 *o.d.*
ARBs		
Candesartan	4–8 *o.d.*	32 *o.d.*
Valsartan	40 *b.i.d.*	160 *b.i.d.*
Losartan[b,c]	50 *o.d.*	150 *o.d.*
MRAs		
Eplerenone	25 *o.d.*	50 *o.d.*
Spironolactone	25 *o.d.*	50 *o.d.*
ARNI		
Sacubitril/valsartan	49/51 *b.i.d.*	97/103 *b.i.d.*
***If*-channel blocker**		
Ivabradine	5 *b.i.d.*	7.5 *b.i.d.*

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ACE angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *ARNI* angiotensin receptor neprilysin inhibitor, *b.i.d.* bis in die (twice daily), *MRA* mineralocorticoid receptor antagonist, *o.d.* omne in die (once daily), *t.i.d.* ter in die (three times a day)

[a]Indicates an ACE-I where the dosing target is derived from post-myocardial infarction trials

[b]Indicates drugs where a higher dose has been shown to reduce morbidity/mortality compared with a lower dose of the same drug, but there is no substantive randomized, placebo-controlled trial and the optimum dose is uncertain

[c]Indicates a treatment not shown to reduce cardiovascular or all-cause mortality in patients with heart failure (or shown to be non-inferior to a treatment that does)

[d]A maximum dose of 50 mg twice daily can be administered to patients weighing over 85 kg

[*]From the Corrigendum to current 2016 HF guidelines

In *symptomatic hypotension* dizziness and lightheadedness often resolve with time. Dose reduction or cessation of other antihypertensive medications (like diuretics, nitrates, calcium- channel blockers) might be helpful.

About 10 % of patients (women twice often than men) treated with ACE inhibitor suffer from a *nonproductive cough,* which occurred usually in the first week of treatment, but may develop also much later. As this condition is not related to ACE inhibitor dose and drug class in troublesome, weary cough a withdrawal of ACE inhibitor and substitution of angiotensin-receptor blocker recommended. ACEI-

induced cough usually retreats within 3–5 days, but rarely it may persists even few months after ACEI has been stopped.

Another important possible adverse effects needing management are *hyperkalemia* and *worsening renal function*. Always is such situation, a list of medications taken by patients should be readjusted and concomitant nephrotoxic drugs (i.e. non-steroidal anti-inflammatory drugs), potassium supplements or potassium sparing diuretics should be stopped or at least reduced. In situations, when increase of creatinine by 100 %, or above 3.5 mg/dL (310 μmol/L), or to eGFR below 20 mL/min/1.73 m^2 or increase in potassium level above 5.5 mmol/L is observed, ACEI should be stopped and blood chemistry should be closely monitored.

Abrupt withdrawal of ACEI should be avoided, unless life- threatening complications occurred, because it may lead to clinical deterioration [2, 6].

Beta- Blockers

Beta- blockers play an important role in effective management of HFrEF, which was proven in numerous clinical trials. Beta-blockers reduce detrimental increase in adrenergic activation in chronic heart failure by blocking adrenergic $beta_1$ and $beta_2$ receptors and therefore slow the heart rhythm, reduce renin production and oxygen demand by cardiac cells, reverse the left ventricle remodeling, tackle compensatory decrease in the density of beta-adrenergic receptors, improve the left ventricular filling and the contractility of the "hibernated" areas of the heart muscle and have anti ischemic and antiarrhythmic effects. All this effects of beta- blockers action lead to significant decrease in morbidity, mortality, hospitalizations rate and heart failure symptoms [2, 29, 30].

Indications
Beta- blockers are recommended in all stable patients with HFrEF, also in asymptomatic patients with left ventricular dysfunction [1].

Contraindications
Beta- blockers are contraindicated in patients with second- and third- degree atrioventricular block without permanent pacemaker, critical limb ischemia and in known drug- specific allergic reactions. Asthma is not an absolute contraindication, if cardio- selective beta- blockers may be used, but always required close medical supervision by a specialist [2, 6].

Drugs, dosages and rules of applications
Similarly, as ACE inhibitors, beta-blockers should be started with a low dose in stable patients (as there were not tested in acutely decompensated patients) and double the dose not faster than 2- week intervals to achieve the target dose or the highest tolerated dose. In some patients slower up- titration may be needed.

The evidence- based target doses of beta- blockers in chronic heart failure with reduced ejection fraction are presented in Table 10.2.

There is no class effect within beta- blockers. Three beta- blockers have been shown to reduce mortality in patients with HFrEF: bisoprolol and sustained- release metoprolol succinate (by blocking the beta1 and beta2 receptors) and carvedilol (which blocks also alpha1 receptors). Nebivolol (selective beta1 receptor antagonists with vasodilatory properties) reduces the composite outcome of deaths and cardiovascular hospitalizations, but does not decrease mortality [2, 29, 30].

Problem solving of possible adverse effects
The *increased fluid retention* with worsening heart failure symptoms may occur usually 3–5 days after initiation of the therapy or increase the dose of beta- blocker and increase dose of diuretics or halve dose of beta- blocker may be needed.

The dose of beta- blocker should be halved or in severe deterioration even stopped in case of *bradycardia* (heart rate below 50 bpm) or *symptomatic hypotension*.

Weakness and *general fatigue* may occur in patients receiving beta- blockers, but usually spontaneously resolve within several weeks or months of the therapy. If not, treatment reduction or even cessation should be considered.

In acutely decompensated heart failure beta- blocker can be continuing, however sometimes dose reduction may be necessary [2, 6].

Mineralocorticoid Receptor Antagonists

It has been observed, that despite optimal treatment of ACE inhibitors, in 40–50 % of patients with chronic heart failure the serum aldosterone concentration does not change (mainly due to endocrine, autocrine and paracrine effects). Mineralocorticoid receptor antagonists competitively inhibit receptors for aldosterone and other steroid hormones and therefore they reduce detrimental effects of aldosterone observed in heart failure: vascular and myocardial fibrosis, myocyte hypertrophy and apoptosis, calcification, inflammation, dysfunction of baroreceptors, increased water and sodium retention and excretion of potassium and magnesium with urine. Mineralocorticoid receptor antagonists were proved to reduce mortality and hospitalization rate in two big clinical trials: RALES (1999) designed for spironolactone and EMPHASIS (2013) for eplerenone [13, 14]. Eplerenone was developed to have a greater selectivity for the mineralocorticoid than for steroid receptors and, on this basis, to overcome the sex hormone side effects, that was observed in patients receiving spironolactone. Spironolactone has active metabolite (canrenone) and longer half- life than eplerenone [2, 3, 30].

Indications
MRA should be used in all patients with chronic heart failure with ejection fraction 35 % or lower, who remain symptomatic (NYHA class II- IV) despite optimal therapy with ACE inhibitors (or ARB) and beta- blocker [1, 2].

Contraindications
MRA are contraindicated in pregnancy, during breastfeeding and in known drug-specific allergic or other adverse reactions [2, 6].

Drugs, dosages and rules of applications
It is advisable to start the therapy with low doses (25 mg once daily) and to consider doubling the dose of MRA after 4–8 weeks in order to achieve the target dose of 50 mg once daily, unless not tolerated by patient. The evidence- based target doses of MRA in chronic heart failure with reduced ejection fraction are presented in Table 10.2.

Blood chemistry should be checked at 1, 4, 8 and 12 weeks after initiating or increasing dose of MRA, and then in 3 months' intervals in first year of treatment and 4- monthly thereafter.

In patients with impaired renal function (creatinine >221 μmol/L, 2.5 mG/dL or eGFR <30 mL/min/1.73 m^2), or high level of serum potassium (> 5.0 mmol/L) MRA should be used with caution and systematic blood chemistry should be performed [1, 2].

Problem solving of possible adverse effects
In patients with worsening renal function (creatinine >221 μmol/L, 2.5 mG/dL or eGFR <30 mL/min/1.73 m^2) or when increase in potassium level is observed (> 5.0 mmol/L) the dose of MRA should be halved and blood chemistry must be closely monitored.

In patients with significant *worsening of renal function* (creatinine >310 μmol/L, 3.5 mG/dL or eGFR <30 mL/min/1.73 m^2) or *hyperkalemia* (> 6.0 mmol/L) MRA should be immediately stopped and adequate treatment applied.

Spironolactone has progesterone-like and antiandrogenic effects, and in 10–15 % of patients may cause breast discomfort, gynecomastia or impotence in male patients and menstrual irregularities in women- in such situation it is recommended to consider substitution with eplerenone [2, 6, 30].

Treatments Recommended in Selected Symptomatic Patients

Diuretics

Loop diuretics reversibly inhibit the Na^+-K^+-2 Cl^- cotransporter in the thick ascending loop of Henle, which results in increase excretion of sodium (up to 20–25 % of the filtered load of sodium), natriuresis and diuresis.

Thiazide-type diuretics block the Na^+/Cl^- cotransporter in the distal tube and therefore decrease sodium resorption [2, 3].

Indications
Diuretics should be used together with neurohormonal therapy (ACEI/ARB, beta-blocker, MRA) in symptomatic patients with heart failure (irrespective of the left ventricle ejection fraction) to relieve breathlessness and peripheral edema and can be continued in asymptomatic patients to maintain euvolemia [1, 2].

Most of heart failure patients require treatment with loop diuretics, however thiazide diuretics can be used when renal function is preserved and patient present only mild symptoms of congestion [2, 6].

Contraindications
Diuretics are contraindicated in patients with known drug- specific allergic or other adverse reaction. There should not be used in patients who never had signs and symptoms of congestion.

Drugs, dosages and rules of applications
Dosing should be individually adapted to the patient clinical status (signs and symptoms of congestion, renal function and blood pressure). The effective diuretic dose allows to achieve positive diuresis with daily reduction of body weight by 0.75–1.0 kg.

Furosemide is the most common loop diuretic used in heart failure, however its bioavailability (10–100 % due to extensive bounding to plasma proteins) is much lower than torasemide (80–100 %), which additionally has longer half- life. The starting dose for furosemide is usually 20–40 mg and for torasemide 5–10 mg [1, 2].

Thiazides produce a less intense, but longer lasting diuresis than loop diuretics, however in eGFR <30/min/1.73 m^2 they cease to be effective. The initial dose for hydrochlorothiazide is usually 25 mg. Combination of loop diuretic with thiazides (sequential nephron blockade) might be useful in patients with resistant edema, but frequent monitoring of blood chemistry (electrolytes, creatinine) should be performed during combined therapy [31]. Diuretic resistance is defined as progressively diminished responsiveness to diuretic therapy in the presence of persisting signs and symptoms of congestion and develops in some patients treated with loop diuretics [3].

The starting dose for non-thiazide sulfonamide (indapamide) is 2.5 mg.

Blood chemistry (creatinine, potassium, urea or blood urea nitrogen) should be checked before treatment initiation and after 1–2 weeks after any increase in dose.

Patients should be educated to be able to adjust dose of the diuretic based on changes in weight (advisable is daily weighing), signs and symptoms of congestion [6].

Initial and usual daily doses of diuretics (loop diuretics, thiazides, potassium- sparing diuretics) commonly used in chronic heart failure are presented in Table 10.3.

Problem solving of possible adverse effects

In *symptomatic hypotension* diuretic dose reduction or cessation of other antihypertensive drugs might be helpful.

Patients who experience *hypokalemia* or *hypomagnesemia* may benefit from increasing dose of ACE inhibitor (or ARB) or adding MRA or potassium and magnesium supplements.

In *hyponatremia* with volume depleted it is recommended to stop thiazide, to substitute it with loop diuretics, or to decrease dose of even stop the loop diuretics. Whereas fluid intake restriction, increased dose of loop diuretic and intravenous inotropic support, arginine vasopressin or ultrafiltration should be considered in hyponatremia with volume overloaded.

When renal impairment occurs during therapy with diuretics the following action should be performed: checking for the presence of hypovolemia and dehydration,

Table 10.3 Doses of diuretics used in patients with heart failure

Diuretics	Initial dose (mg)		Usual daily dose (mg)	
Loop diuretics[a]				
Furosemide	20–40		40–240	
Bumetanide	0.5–1.0		1–5	
Torasemide	5–10		10–20	
Thiazides[b]				
Bendroflumethiazide	2.5		2.5–10	
Hydrochlorothiazide	25		12.5–100	
Metolazone	2.5		2.5–10	
Indapamide[c]	2.5		2.5–5	
Potassium-sparing diuretics[d]				
	+ACE-I/ ARB	−ACE-I/ ARB	+ACE-I/ ARB	−ACE-I/ARB
Spironolactone/eplerenone	12.5–25	50	50	100–200
Amiloride	2.5	5	5–10	10–20
Triamterene	25	50	100	200

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ACE-I angiontensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker

[a]Oral or intravenous; dose might need to be adjusted according to volume status/weight; excessive doses may cause renal impairment and ototoxicity

[b]Do not use thiazides if estimated glomerular filtration rate <30 mL/min/1.73 m^2, except when prescribed synergistically with loop diuretics

[c]Indapamide is a non-thiazide sulfonamide

[d]A mineralocorticoid antagonist (MRA) i.e. spironolactone/eplerenone is always preferred. Amiloride and triamterene should not be combined with an MRA

exclusion of other nephrotoxic agents, discontinuing of thiazide diuretic in combination diuretic treatment, reduction of the ACEI (or ARB) dose. If these do not help, hemofiltration or dialysis should be considered [2, 6].

Angiotensin Receptor Neprilysin Inhibitor

The most recent success in the improvement of the pharmacological management of HFrEF is linked to the new class of drugs - angiotensin receptor- neprilysin inhibitor (ARNI) and the first drug in class LCZ696 - which is a molecule that combines the moieties of valsartan and sacubitril (neprilysin inhibitor) in one single substance. ARNI acts on the renin- angiotensin- aldosterone system and neutral endopeptidase system. Neprilysin is a neutral endopeptidase, breaking down natriuretic peptides, bradykinin and a few other peptides in the neurohormonal axis. Therefore, neprilysin inhibitor increases the level of aforementioned vasoactive peptides and by their excessive binding to natriuretic peptide receptors causes the augmented production of cGMP, finally acting anti- remodeling and leading to myocardial relaxation and

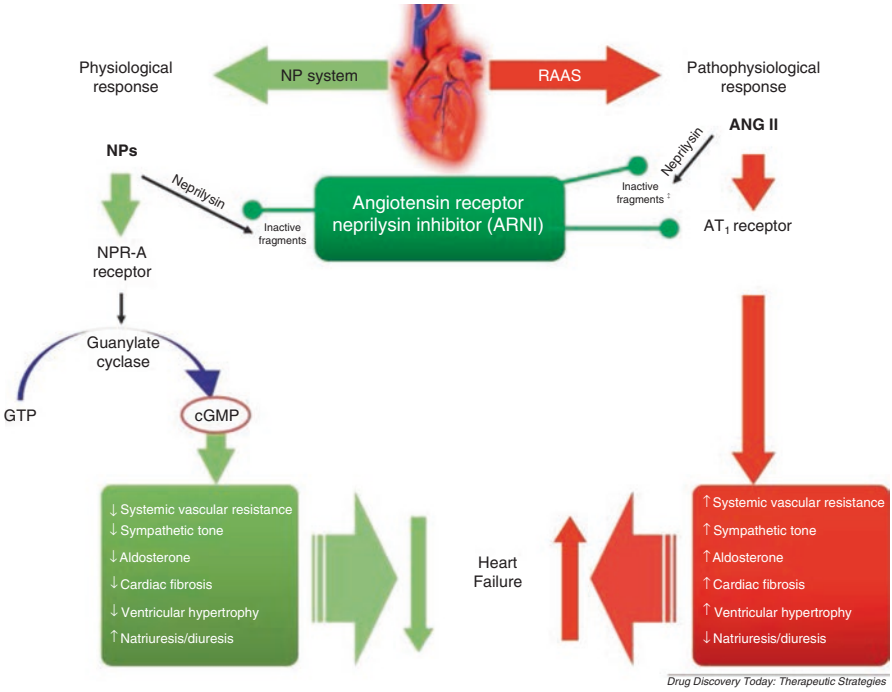

Fig. 10.3. Mechanism of action of angiotensin receptor- neprilysin inhibitor in heart failure. Angiotensin receptor neprilysin inhibitors have the potential to modulate two counter-regulatory neurohormonal systems in HF: the renin–angiotensin–aldosterone system and natriuretic peptide system. *ANG* angiotensin, *ARNI* angiotensin receptor neprilysin inhibitors, *AT1* angiotensin type 1, *cGMP* cyclic guanosine monophosphate, *GTP* guanosine-5′-triphosphate, *HF* heart failure, *NP* natriuretic peptide (e.g. atrial natriuretic peptide [ANP], B-type natriuretic peptide [BNP], etc.), *NPR-A* NP receptor-A, *RAAS* renin–angiotensin–aldosterone system,‡ In vitro evidence (From: Langenickel and Dole [32])

enhancement of diuresis and natriuresis. Increase level of circulating natriuretic peptides inhibits also the secretion of renin and aldosterone. Additionally, ARB reduces water and sodium retention, vasoconstriction and myocardial hypertrophy [2, 3, 32]. The mechanism of action of ARNI is presented also in Fig. 10.3. In 2014 the results of the PARADIGM-HF trial were presented, which was terminated earlier as designed, due to significant decrease on cardiovascular mortality, all- cause mortality and heart failure hospitalization rate in HFrEF patients treated with LCZ696 in comparison to patients receiving ACE inhibitor (enalapril) [4].

It is important to remember than in patients treated with ARNI measurement of natriuretic peptides has low clinical and diagnostic value.

Indications

LCZ696 should be used in symptomatic outpatients with ejection fraction 35 % or less, despite optimal treatment with neurhormonal agents (ACEI, beta- blockers,

MRA), with elevated plasma levels of natriuretic peptides (BNP ≥150 pg/mL or NT-proBNP ≥ 600 pg/mL or, if they had been hospitalized for heart failure within the last year, BNP ≥100 pg/mL or NT-proBNP ≥ 400 pg/mL), with estimated glomerular filtration rate of minimum 30 mL/min/1.73 m^2 (criteria from the PARADIGM- HF trial), who are able to tolerate enalapril 10 b.i.d. (or equivalent) as a replacement of ACE inhibitor [1]. It should be remembered to withdraw therapy with ACE inhibitor for at least 36 hours before initiation of sacubitril/valsartan.

Contraindications
The clinical experience with sacubitril/valsartan is fairly limited to the clinical trial PARADIGM-HF, so the recommendations regarding contraindications are mainly based on the exclusion criteria from this trial. The main contraindications for ARNI use are hyperkalemia (>5.4 mmol/L), end- stage renal disease, severe liver dysfunction, cirrhosis or cholestasis, pregnancy (second and third trimester) and breastfeeding, history of angioedema, hypotension (systolic blood pressure <95–100 mmHg), In patients with systolic blood pressure in range of 100–110 mmHg it seems to be reasonable to consider lower starting dose (24 mg/26 mg twice a day). ARNI cannot be used together with ACEI or ARB and LCZ696 should not be administered before 36 hours after the last dose of ACEI because of the potential risk of angioedema [33].

Drugs, dosages and rules of applications
The starting dose of LCZ696 based on the PARADIGM-HF trial is 100 mg b.i.d. (49 mg of sacubitril and 51 mg of valsartan) which was subsequently up-titrated to 200 b.i.d. (this was implemented in the active run-in phase before randomization to the LCZ696 vs. enalapril phase). In the elderly patients' dose should be adjusted to the renal function [33]. Lower dose of the drug is available - LCZ 50 mg (sacubitril 24 mg/valsartan 26 mg) and can be potentially considered as starting dose in selected cases.

Problem solving of possible adverse effects
In occurrence of hyperkalemia, hypotension (systolic blood pressure ≤95 mmHg), renal dysfunction it may be advisable to re-check medication list, temporary decrease the dose of ARNI or even stop the treatment. The occurrence of angioedema is an indication to immediate cessation the therapy with ARNI, in severe angioedema the adequate emergency management should be performed (such as administration of 1 mg/1 ml adrenaline) [33].

I_f- Channel Inhibitor

Increased heart rate in patients with heart failure is a known risk factor of mortality and benefits from heart rate frequency reduction have been well established in numerous clinical trials with beta- blockers. The cardiac pacemaker frequency is determined by many factors, including a degree of inward I_f ionic current activation,

which regulates the diastolic depolarization of the sinus node. Ivabradine slows the heart rate by specific blocking I*f* open channels in the sinoatrial node and accordingly inhibits I*f* current. I_f- channel inhibitor action is dependent on its concentration and the frequency of channel opening. Therefore, it is effective only in patients with sinus rhythm and particularly favorable in patients with higher heart rates.

In the SHIFT trial, which results were presented in 2010, ivabradine added to optimal therapy with neurohormonal antagonists, was shown to reduce combined endpoint of mortality and HF hospitalization. Use of ivabradine in HFrEF patients with the heart rate frequency 75 bpm or higher was associated with improvement in survival [2, 19, 34, 35].

Indications
Ivabradine should be considered in all stable patients, with ejection fraction 35 % or less, in sinus rhythm, with resting heart rate 70 bpm or more, who are still symptomatic (NYHA class II-IV), despite receiving optimal treatment with maximal tolerated doses of a beta- blocker, ACEI (or ARB) and MRA (all aforementioned conditions must be fulfilled). Ivabradine may also be considered in patients who cannot be receiving beta- blockers because of intolerance or absolute contraindications [1].

Contraindications
The absolute contraindications for I_f-channel blocker use are: unstable cardiovascular conditions (acute heart failure, cardiogenic shock, acute coronary syndrome, stroke, TIA, severe hypotension), arrhythmias and conduction disorders (persistent atrial fibrillation or flutter, third-degree atrioventricular block, sinoatrial exit block, sick sinus syndrome), resting heart rate below 60 bpm, severe liver or renal dysfunction, pregnancy and breastfeeding, known drug- specific allergic reaction or other adverse reaction [2, 6].

Drugs, dosages and rules of applications
Treatment with ivabradine should be started with the initial dose 5 mg twice a day and up-titrate to target dose 7.5 mg twice a day after 2 weeks, if the resting heart rate is above 60 bpm (in some patients slower up-titration may be needed). There is no indication for increase the starting dose when there in resting heart rate 50–60 bpm.

In elderly patients (over 75 years old) beginning with lower dose (2.5 mg twice a day) may be considered [1, 2].

Problem solving of possible adverse effects
Bradycardia occurs in 3–10 % of patients (severe, with heart rate below 40 bpm in less than 1 %), usually in the first 2–3 months. In resting heart- rate below 50 bpm or in symptomatic bradycardia dose should be reduced to 2.5 mg twice a day and beside screening for secondary causes of bradyarrhythmias should be performed. If symptoms still persist it may be necessary to stop the therapy with ivabradine. In severe bradycardia with hemodynamic instability treatment with beta- mimetic might be helpful and it, if necessary, temporary cardiac pacing should be considered.

Drug should also be stopped if patient develop *persistent atrial fibrillation* and in case of *lactose or galactose intolerance*.

Other adverse effect which may occur in more than 10 % of patients receiving ivabradine is transient visual phenomena, which appears usually after 2 months and resolve completely within first few months, therefore there is no need for discontinuation of therapy, unless this is a patient's wish [2, 6].

Angiotensin II Type I Receptor Blockers

Indications

Angiotensin receptor blockers inhibit the effects of angiotensin II on the angiotensin type I receptor. They reduce cardiovascular mortality (candestartan) and worsening of heart failure (valsartan). They should be used only as an alternative for ACEIs in patients, who cannot tolerate ACEIs due to persistent cough, angioedema or allergic reactions [1, 2, 36–38]. Losartan did not reduce mortality in elderly patients with heart failure, but was better tolerated in comparison with captopril (ELITE-II trial) [2, 3, 39].

Contraindications and problem solving of possible adverse effects

Contraindications and possible adverse effects are the same as for the ACEIs, excluding nonproductive cough and angioedema.

Drugs, dosages and rules of applications

The evidence- based target doses of ARBs approved for use in chronic heart failure with reduced ejection fraction in case of ACEI intolerance are presented in Table 10.2. ARB should be started with low dose, and then up titrated every 3–5 days by doubling the dose.

Similarly to ACEI, potassium and renal function should be checked at the beginning of treatment, then after 1–2 weeks and after every changes in dose.

The combination of ACEI with ARB is generally contraindicated and allowed only in some symptomatic patients who do cannot tolerate an MRA, but should be used under very strict supervision because of increased risk of possible adverse effects [1, 2, 40, 41].

Combination of Hydralazine and Isosorbide Dinitrate

Benefits from therapy with combination of hydralazine and isosorbide dinitrate (H-ISDN, used together with ACEI, beta- blocker and MRA) was proven to reduce all-cause mortality and heart failure hospitalizations only in African Americans with heart failure with reduced ejection fraction in NYHA class III- IV. However, observed adherence to H- ISDN therapy has been very poor due to a high number of pills a day and many adverse effects (headache, dizziness, hypotension, nausea, arthralgia and lupus-like syndrome) [2, 3, 6, 42].

Digoxin and Other Digitalis Glycosides

Cardiac glycosides increase concentration of calcium in cardiomyocytes by inhibiting sodium-potassium adenosine trisphosphate pump, and thereby enhance the myocardial contractility. Moreover, by stimulating the parasympathetic system, they have a negative dromotropic impact on atrioventricular node [2].

Indications
Digoxin should be considered in patients with symptomatic heart failure and concomitant atrial fibrillation or atrial flutter with rapid ventricular rate, despite optimal therapy with beta-blockers or when they are contraindicated. The target resting ventricular rate should be in the range 70–90 bpm and <110 bpm during light exercise.

Patients with heart failure and in sinus rhythm may also be treated with cardiac glycosides, provided that they are symptomatic despite recommended treatment with ACEI or ARB, beta-blocker and MRA. In this group digoxin has shown to reduce the hospitalization rate, without affecting overall mortality [1, 2, 30].

Contraindications
Cardiac glycosides throughout increasing calcium concentration may have proarrhythmic effects and should not be used in patients with electrolyte disturbances, especially hypokalemia, hypercalcemia, hypomagnesemia, and in patients with ventricular arrhythmias. The impact on the atrioventricular conduction causes that digoxin is contraindicated in the course of bradycardia, atrioventricular conduction disorders and preexcitation syndrome. The other contraindications are early phase of acute coronary syndrome, left ventricular outflow tract obstruction in hypertrophic cardiomyopathy and amyloidosis [2].

Drugs, dosages and rules of applications
The treatment should be performed under careful control, especially with regular monitoring of serum creatinine and electrolytes levels. The therapeutic serum concentration of digoxin is narrow, and should be in the range 0.6–1.0 ng/mL. Usually, the therapeutic level is obtained after about 1 week from starting dose. The standard dose is 0.125–0.25 mg daily. The lower dose is indicated in older patients, women, patients with kidney dysfunction and hypothyroidism. Usually, the therapeutic level is obtained after about 1 week from starting dose. The standard dose is 0.125–0.25 mg daily. The lower dose is indicated in older patients, women, patients with kidney dysfunction and hypothyroidism [2, 43].

Problem solving of possible adverse effects
The adverse effects of therapy with digoxin are *tachy-* and *bradyarrhythmias with atrioventricular conduction disorders*, *gastrointestinal symptoms* (nausea, vomiting, abdominal pain, diarrhea) and, rarely, *neurological disorders* (dizziness, visual disturbances, confusion). The digoxin intoxication may be treated with digoxin-specific Fab antibody fragments [2, 30].

Heart Failure with Preserved and with Mid- Range Ejection Fraction

Heart failure with preserved or mid-range ejection fraction usually affect elderly patients with many comorbidities.

There are no medications that have yet been proven to prolong survival in patients with heart failure with mid-range or preserved left ventricular ejection fraction, therefore management of these patients focuses mainly on the treatment of cardiovascular and non-cardiovascular diseases (arterial or pulmonary hypertension, atrial fibrillation, coronary artery disease, diabetes mellitus, anemia, iron deficiency, chronic obstructive pulmonary disease, chronic kidney disease, obesity and others). Nevertheless, in the clinical practice majority of patients with heart failure with mid-range and preserved ejection fraction are treated similarly to those with systolic heart failure, because of overlapping recommendations for ACEIs, ARBs, beta- blockers, MRAs and diuretics use. Currently, a few ongoing clinical trials performed in patients with preserved or slightly reduced ejection fraction are looking for treatments that will improve survival. However, not less valid is patients' quality of life, therefore reducing symptoms of heart failure and improving exercise tolerance are important aims of therapy in patients with HFmrEF and HFpEF.

Diuretics improve signs and symptoms of fluid retention in all heart failure patients. There is lack of data supporting beta- blockers and MRAs in symptomatic treatment in patients with preserved or mid-range ejection fraction. Similarly, inconsistent evidence is for ACEIs and ARBs use (excluding candesartan, which has shown improvement in NYHA class in CHARM-Preserved Trial) [44].

Nebivolol, candesartan, digoxin and spironolactone might reduce heart failure hospitalizations in patients with sinus rhythm.

It is important to mention, that in contrast to patients with heart failure with reduced ejection fraction, in patients with mid-range or preserved ejection fraction use of calcium channel blockers (verapamil, diltiazem), as an alternative to beta-blockers in case of patient's intolerance, is not contraindicated [1, 2].

Future Direction Box

The future pharmacological treatment of heart failure seems to be related with personalization of pharmacotherapy and identification of responders and non-responders to recommended therapies. Next few years should bring also medications, that will prolong survival in patients with preserved and mid-range ejection fraction. Advent of therapies focusing on cardiomyocyte function improvement or targeting non-myocytic compartments, such as extracellular matrix, is awaited eagerly.

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Chapter 11
Myocardial Revascularization in Heart Failure

Stephan H. Schirmer and Michael Böhm

Background

Coronary artery disease (CAD) is the cause of heart failure in >60 % of cases [1, 2]. This is particularly true in heart failure with reduced ejection fraction (HF-REF), which will be the focus of this chapter because of the paucity of data on myocardial revascularization in heart failure with preserved ejection fraction (HF-PEF). Of note, part of CAD therapy, i.e. primary percutaneous coronary intervention (PCI) and thereby increased survival in acute myocardial infarction [3], has actually increased prevalence of heart failure. Long-term sequelae of atherosclerotic coronary artery disease, decreased left-ventricular function and heart failure, are projected to affect eight million patients in the United States by 2030 [4].

Understanding the pathophysiology of heart failure (Chap. 2) has paved the way towards contemporary drug treatment of the disease, with inhibition of the renin-angiotensin-aldosterone system (RAAS) and blockade of the sympathetic nervous system forming the cornerstones of treatment (Chap. 10). However, molecular changes (increased RAAS activation, stimulation of the sympathetic nervous system, formation of reactive oxygen species) are often preceded by injury of the myocardium following myocardial infarction or chronic myocardial ischemia secondary to impaired coronary flow. Locally impaired coronary flow as in myocardial infarction or insufficient blood supply because of coronary stenosis can lead to maladaptive remodeling of the whole ventricular myocardium in ischemic cardiomyopathy. Here, loss of myocardial function occurs in myocardium distant to impaired blood

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M. Dorobanţu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_11

flow. Not only cardiomyocyte death following myocardial infarction but also stunning or hibernation of the myocardium can lead to left ventricular (LV) dysfunction. Hibernating myocardium has reduced its contractility, thus reducing oxygen and nutrient demand to a minimum and upholding cardiomyocyte viability in conditions of reduced blood supply [5]. Stunned myocardium refers to akinesia of (parts of) the left ventricle that may persist beyond perfusion restoration. Both hibernating and stunned myocardium, are, however, potentially reversible [6]. Hence, treating impaired coronary flow by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) can be a causal treatment of heart failure. Identifying hibernating or stunned myocardium as viable is central when planning revascularization because scarred myocardium will not benefit.

Revascularization for Treatment of Angina Pectoris

It is essential to divide coronary revascularization in patients with heart failure into approaches aiming at symptom relief versus therapeutic approaches aiming at amelioration of patients' prognosis. Symptoms of angina are undoubtedly improved by revascularization, both in patients with and without heart failure. When revascularization by CABG was tested for its prognostic value in heart failure in the STICH trial (see below), the subgroup of patients suffering from angina pectoris at baseline did not benefit more from CABG than the group without angina [7]. However, CABG did improve angina symptoms to a greater extent than medical therapy alone. Hence, heart failure patients suffering from angina pectoris should be treated for symptomatic relief the same way that patients without heart failure should be treated [1].

Revascularization for Prognostic Purposes

The pathophysiology of maladaptive myocardial remodeling following or during ischemia caused by insufficient blood supply by the coronary arteries is undisputed, particularly when it comes to three vessel disease or stenosis of the left main coronary artery. Most of available data on the prognostic benefit of revascularization in heart failure is derived from surgical trials examining the role of CABG in heart failure patients. Of note, our perception of a beneficial role of (percutaneous) revascularization in stable coronary artery disease – independently of heart failure – is derived from an extrapolation of surgical bypass data: In contrast to primary PCI in myocardial infarction, prospective randomized trials of PCI in stable CAD have hitherto failed to show a prognostic benefit of PCI in terms of mortality reduction [8]. Much more yet not so recent data is available for the prognostic benefit of surgical revascularization: Three large CABG trials (Veterans Administration CABG Study Group, European Coronary Surgery Study and CASS, summarized by Yusuf

et al. in 1994 [9]) unequivocally demonstrated a mid- to long term survival benefit in high risk patients with stable CAD undergoing CABG. Subanalyses of these trials, albeit on a small number of patients, had suggested a benefit also and particularly in patients with a reduced left-ventricular ejection fraction and provided the only scientific bases for the decision-making of revascularization in heart failure before publication of the STICH trial. The investigations mentioned, however, are now more than 30–40 years old, and drug therapy of both stable coronary artery disease and heart failure has much improved, rendering a contemporary comparison with the trial situation difficult. As demonstrated by COURAGE [8], modern medical therapy is increasingly difficult to beat.

The pivotal study on the prognostic benefit of CABG in heart failure was the Surgical Treatment for Ischemic Heart Failure (STICH) trial, published in 2011. In STICH, 1212 patients with an ejection fraction of ≤ 35 % and symptomatic stable coronary artery disease amenable to CABG were randomized to medical therapy or medical therapy plus CABG and followed-up for 5 years. In STICH, patients were eligible for medical therapy alone if there was no left main coronary artery stenosis of 50 % or more, and if they did not suffer from angina in Canadian Cardiovascular Society (CCS) class III-IV. Of the included patients, 30 % had 2-vessel disease, 60 % had 3-vessel disease, and in 68 % the proximal left anterior descending (LAD) artery had a stenosis of at least 75 %.

Importantly, 17 % of the patients randomized to medical therapy crossed over to the CABG group during follow-up (after a median of 142 days), mostly because of progressive symptoms, acute decompensation or patient's or family's decision.

The primary endpoint, all-cause mortality, was not affected in the intention-to-treat analysis (hazard ratio 0.86, confidence interval 0.71–1.04, $p = 0.12$, Fig. 11.1). All-cause death within 30 days was higher following CABG, as expected. Interestingly, the total number of deaths remained higher in the surgery group for 2 years after randomization. Death from cardiovascular was reduced by 19 % with CABG (hazard ratio 0.81, confidence interval 0.66–1.00, $p = 0.05$). All other secondary endpoints (all-cause death or hospitalization for heart failure (− 16 %), all-cause death or hospitalization for cardiovascular causes (− 26 %), all-cause death or all-cause hospitalization (− 19 %), all-cause death or revascularization by PCI or CABG (− 40 %)) were positively influenced by CABG. Also, an as-treated analysis comparing patients medically treated throughout the first year of randomization with those undergoing CAGB in the first year after randomization, showed a 30 % mortality reduction with revascularization (hazard ratio 0.70, confidence interval 0.58–0.84, $p < 0.001$, Fig. 11.1). Another 6 % of patients in the medically treated group were revascularized by PCI, which did not count as revascularization in either intention-to-treat or as-treated analysis. The authors of the STICH trial therefore summarize its results by stating that although the primary endpoint was missed, death of cardiovascular cause and death of any cause or hospitalization for heart failure were lower among patients randomized to CABG [10].

The STICH trial was very carefully conducted, involving surgeons with low operative mortality (<5 % before the trial), losing very few (1 %) of patients to follow-up and carefully overseeing treatment in both treatment arms. However, it has

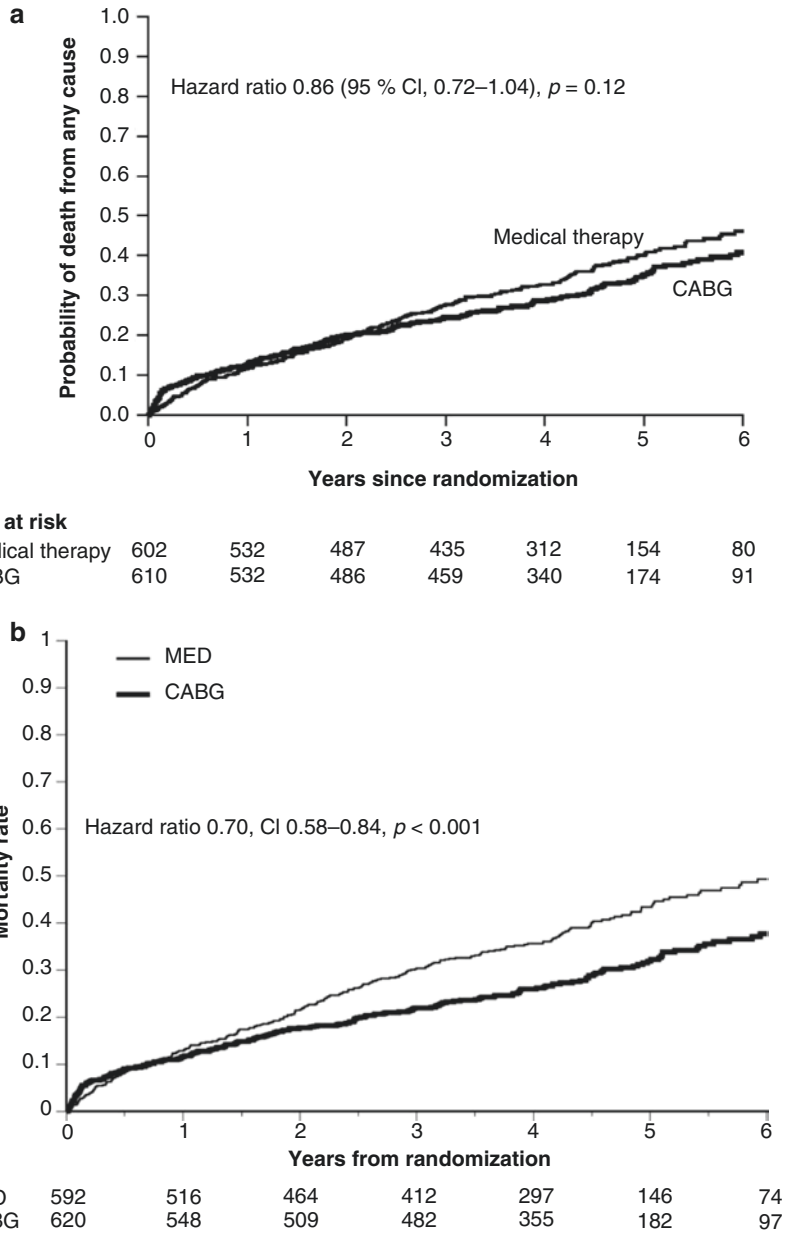

Fig. 11.1 Survival rates in the intention-to-treat (**a**) and as-treated analysis (**b**) in STICH. The primary endpoint, all-cause death, was not significantly different at 5 years follow-up in the CABG group compared to the medical group (**a**). However, because of high rates of changeover between the groups, the as-treated analysis (**b**) revealed that patients actually treated with CABG benefited with a 30 % all-cause mortality reduction (Modified from Velazquez et al. [10])

to be noted that patients were relatively young (average of 60 years old), predominantly male, and had relatively few heart failure symptoms (60 % of patients in New York Heart Association (NYHA) class I or II), while 60 % of patients suffered from angina. This led commentaries to state that STICH was more a trial of angina in reduced LV function than a true heart failure trial.

Recently, in 2016, the Surgical Treatment for Ischemic Heart Failure Extension Study (STICHES) was presented and published [11]. STICHES is a long-term follow-up (median of 9.8 years) of the original STICH study. At the late time-point, the primary endpoint (death from any cause) was now significantly reduced by CABG as compared to medical therapy (hazard ratio 0.84, confidence interval 0.73–0.97, $p = 0.02$, Fig. 11.2). Cardiovascular death was reduced by 21 % ($p = 0.006$), death from any cause or hospitalization for heart failure by 28 % ($p < 0.001$, Fig. 11.2). During the second 5 years of follow-up, few more patients randomized to medical treatment received CABG, resulting in 19.8 % of patients who had CABG before the end of long-term follow-up, of which 11 % of patients underwent CABG after the first year of randomization. PCI was performed in 7.0 % of patients in the CABG group and 8.3 % of patients in the medically treated group. The number needed to treat was calculated to be 14 patients to prevent one death of any cause and 11 patients to prevent one cardiovascular death. Subgroup analyses of STICHES indicate a superior benefit of revascularization therapy in those patients with three-vessel coronary artery disease compared to those with one or two vessel disease.

Not investigating clinical outcomes but left ventricular function is an analysis of the effects of CABG on diastolic LV function: In 2004, Hedman et al. using tissue Doppler presented for the first time echocardiographic data that surgical revascularization improved diastolic function 3 and 12 months after CABG [12]. Before the advent of tissue Doppler, conventional pulse wave Doppler had not provided unequivocal results on diastolic function following CABG.

The Role of Myocardial Viability

From a pathophysiological point of view, it seems obvious that particularly underperfused myocardium (such as stunned of hibernating myocardium) benefits most from revascularization. This understanding has brought along several trials investigating different means of viability testing. Both echocardiographic, scintigraphic and magnetic resonance, all at rest and vasodilator stress, have been described to yield valid results to identify the extent of hibernating myocardium. In general, dobutamine stress echocardiography detecting contractile reserve can be considered more specific in the assessment of cellular integrity, while single photon emission computed tomography (SPECT), late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) and myocardial contrast echocardiography (MCE) are more sensitive, allowing the detection of small amounts of viable myocardium. Novel echocardiographic techniques such as speckle tracking and tissue Doppler-derived

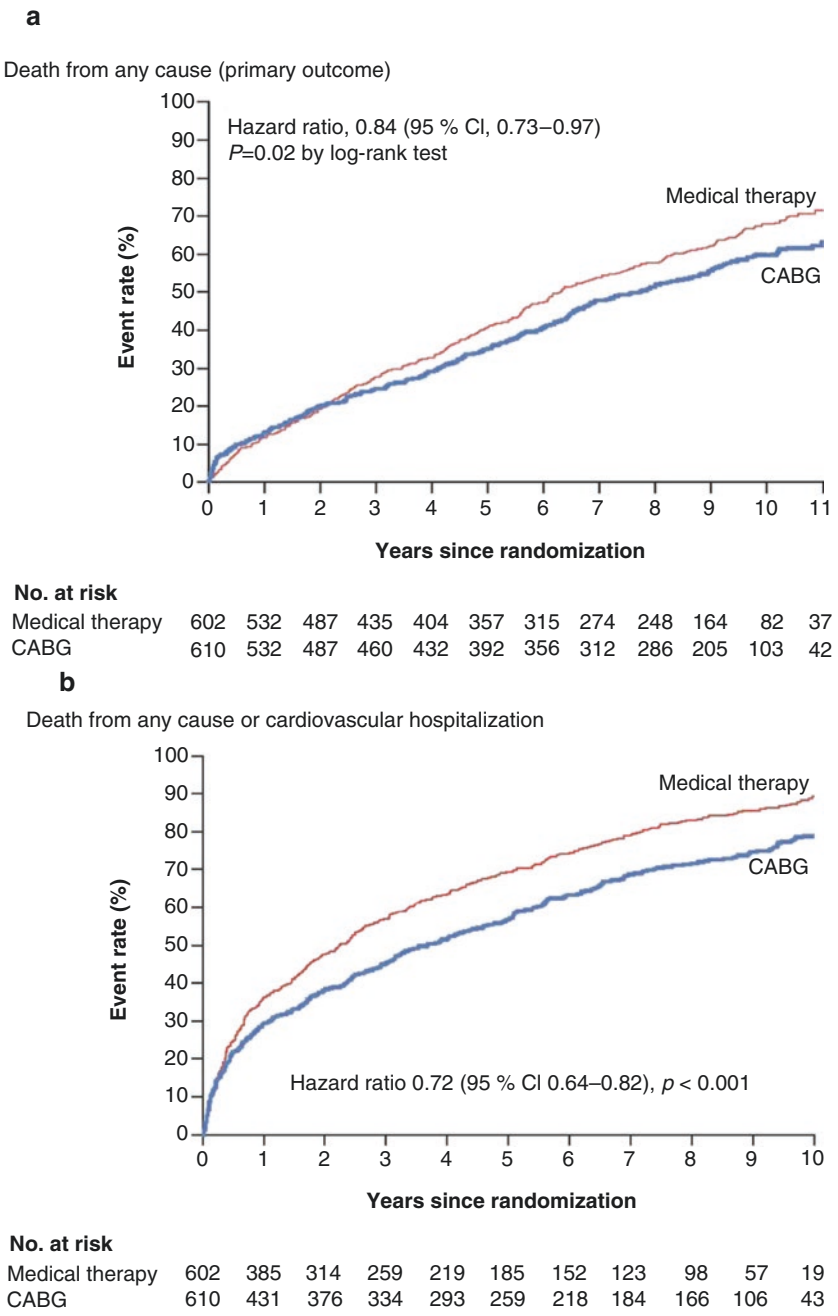

Fig. 11.2 Overall survival in the long-term follow-up of STICH (STICHES) (**a**), and overall survival and cardiovascular hospitalization (**b**). In the extended follow-up (10 years) of the STICH study, intension-to-treat analysis showed that the primary endpoint (all-cause mortality) was significantly reduced by CABG (relative risk reduction 16 %, (**a**)). Several secondary endpoints, such as all-cause death or cardiovascular hospitalization (**b**), were reduced similarly (Modified from Velazquez et al. [11])

strain and strain rate imaging allow quantification of myocardial contractility at rest and during low dose dobutamine. In a study on 57 patients, 72 % of prior dysfunction myocardial segments showed improved dobutamine-induced strain during follow-up 10 months after CABG [13]. Conversely, likelihood of functional recovery following bypass operation was low when there was no or minimal increase in strain. Recent data from nuclear imaging studies (fluorodeoxyglucose positron emission tomography (FDG-PET) in 648 patients with ischemic cardiomyopathy) indicate a threshold of 10 % viable, hibernating myocardium to predict a survival benefit of surgical revascularization [14]. Similarly, CMR can excellently be used for the prediction of benefit from revascularization, as shown in a metaanalysis of 24 trials, where delayed enhancement CMR had the highest sensitivity and low-dose dobutamine CMR the highest specificity [15]. The first randomized prospective analysis evaluating the usefulness of viability imaging in guiding decisions for or against revascularization, the PET and Recovery Following Revascularization)-2 (PARR-2) trial, yielded a neutral result [16]. However, 25 % of physicians did not adhere to the strategy derived from PET scan. When investigators adhered to PET recommendations, hazard ratio (the primary outcome was death, myocardial infarction, or cardiovascular hospitalization at 1 year) was 0.62 (confidence interval 0.42–0.93; $p = 0.019$).

An observational substudy of STICH investigated viability in 601 patients [17]. While initially, all patients in STICH were required viability testing by SPECT, this was loosened during the study due to slow enrolment, low-dose dobutamine stress echocardiography became allowed and viability testing was no longer mandatory. During follow-up of STICH, less patients with evidence of viable myocardium died (hazard ratio 0.64, confidence interval 0.48–0.86, $p = 0.003$, Fig. 11.3) as suggested in an unadjusted analysis. Yet, this difference was no longer significant after adjustment for baseline variables influencing mortality ($p = 0.21$). The predictive value of viability testing for a possible benefit of revascularization was less clear: With respect to mortality, there was no significant interaction between viability status and treatment assignment (Fig. 11.3).

Although the data from the STICH analysis of viability do not clearly favor viability testing, the general consensus remains that in extensive hibernating myocardium, revascularization is of benefit to the patient. Imaging techniques have advanced in recent years, and temporal and spatial resolution has increased significantly. PET and CMR are more and more broadly used and provide superior imaging quality and significance than SPECT or MCE. Recently, a comparison of MCE with SPECT has demonstrated superiority of MCE in the detection of hibernating myocardium in ischemic cardiomyopathy [18]. In a small group of 39 patients, MCE was superior in predicting myocardial functional recovery after revascularization. A further randomized prospective trial, the AIMI-HF trial, aiming to include >1200 patients with ischemic cardiomyopathy, is currently performed to solve the usefulness of advanced imaging techniques (CMR/PET versus SPECT) [19].

Particularly in severe CAD, however, when symptoms of angina are lacking, viability testing should be performed before advancing to revascularization [6].

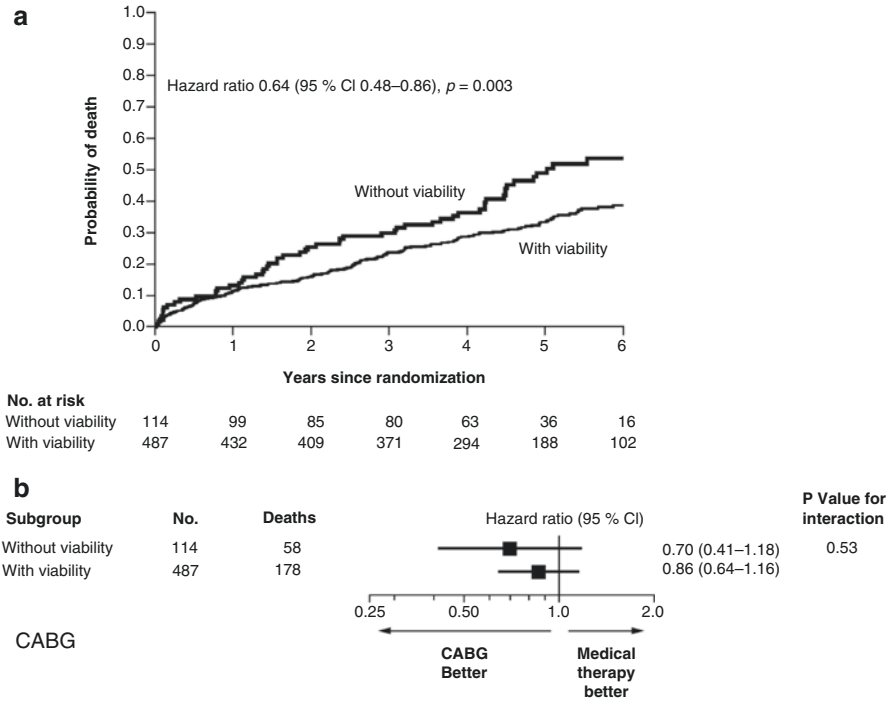

Fig. 11.3 Probability of death, according to myocardial viability status (**a**) and interaction between viability status and treatment (CABG or medical) with respect to mortality. A subanalysis of the STICH trial showed that myocardial viability, as assessed by single-photon-emission computed tomography (SPECT) or dobutamine echocardiograph, predicted mortality (**a**). However, viability status did not predict whether the patient had benefit from CABG (**b**) (Modified from Bonow et al. [17])

In less severe CAD both viability and ischemia testing should be performed, if symptoms of angina are lacking in heart failure patients, before revascularization is planned [6]. European guidelines also rely on the detection of viability, recommending revascularization only in case of angina and viable myocardium. In case a patient has no angina and there is not enough dysfunctional but viable myocardium (>10 %), revascularization is unlikely to benefit the patients, and thus not recommended ("Myocardial revascularization is recommended when angina persists despite treatment with anti-angina drugs") [1].

Similar Value of Percutaneous Coronary Intervention?

STICH and STICHES provide solid data on the benefit of surgical revascularization in heart failure. There is a paucity of data on the prognostic role of percutaneous

coronary intervention (PCI) in heart failure. A trial intending to enroll 800 patients (the Heart Failure Revascularization Trial (HEART) to test all forms of revascularization for their effects on prognosis in heart failure was stopped early due to insufficient inclusion and does not allow to draw reliable conclusions [20].

More than 10 year old data suggest that in heart failure patients (defined as an ejection fraction of less than 40 %) with severe coronary artery disease (three vessel disease or two vessel disease with involvement of the proximal LAD), CABG is superior to PCI in reducing mortality [21]: In the observational New York study that compared 37,212 patients with multivessel CAD who underwent CABG with 22,102 patients with multivessel disease that underwent PCI, 26 % and 19 %, respectively, of patients analyzed had an ejection fraction of 40 % or less. While outcome was similar between CABG and PCI in patients with two-vessel disease and without involvement of the proximal LAD, CABG reduced 3-year mortality as compared to PCI when the proximal LAD was involved or patients had three-vessel disease. As the study is based on patient data from 1997 to 2000, technical developments particularly in the field of PCI, above all the use of drug-eluting stents, makes application of the 2005 published data in today's practice difficult. Although progress has been made in the field of cardiac surgery as well (e.g. standard use of the left internal mammary artery as bypass for the LAD or off-pump bypass surgery), today's use of second or third generation drug eluting stents has considerably reduced restenosis, stent thrombosis, and thus repeat revascularization and mortality. It is conceivable that a prospective randomized comparison of PCI versus CABG in patients with heart failure nowadays shows at least similar mortality rates for both techniques. This, however, remains to be proven. A Japanese registry, the CREDO-Kyoto PCI/CABG registry Cohort-2, encompassed 1064 (out of 15,939) patients with multivessel or left main coronary disease and a history of heart failure. They had an average ejection fraction of 46 % (only mildly reduced) and were treated by PCI in 672 cases versus CABG in 392 cases. Three-year mortality was similar after PCI or CABG in patients with a low or intermediate syntax score below 32. However, in patients with a score of 33 or larger, PCI was associated with a significantly higher mortality (hazard ratio 4.83, confidence interval 1.46–16.03, $p = 0.01$) [22]. Other subgroups such as the subgroup of patients with reduced ejection fraction in the FREEDOM trial of diabetic patients with multivessel disease are difficult to interpret because of their small sample size (32 patients) [23]. Similarly, only 4 % of patients in the pivotal Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial had congestive heart failure at the time of inclusion, and 1.3 or 2.5 % of PCI or CABG patients, respectively, had an ejection fraction of 30 % or less, thereby prohibiting subgroup analyses on this patient group [24]. The authors of the 2016 published STICHES study consistently reason that "It is not known whether percutaneous coronary revascularization as compared with medical therapy alone would result in benefits similar to those that we observed with CABG."

What Do the Guidelines Tell Us?

Current (2016) European heart failure guidelines refer to guidelines for myocardial revascularization in their judgement on the use of revascularization in heart failure. A separate chapter on myocardial revascularization in heart failure, as in the 2012 guidelines, is no longer present in the 2016 version. Instead, because of the "lack of [revascularization] studies including patients who have well-defined HF [heart failure]", angina pectoris and coronary artery disease is listed as a comorbidity of heart failure. Pharmacological treatment with a beta -blocker (indicated in heart failure for the reduction of mortality and morbidity) has received a class I recommendation to relieve angina. In a further step, "Myocardial revascularization is recommended when angina persists despite treatment with anti-angina drugs" (class I, level of evidence A). In fact, the recommendations on CABG in heart failure patients are solely based on STICH. The older (2012) European guidelines had attributed a class I recommendation for angina with left main stenosis or two to three vessel disease in chronic heart failure and LV dysfunction (with level of evidence C only because of neutral results of the intention-to-treat analysis of STICH and the lack of other prospective randomized trials). Essentially, these recommendations from the 2012 ESC guidelines on heart failure were very similar to the 2014 ESC guidelines on myocardial revascularization, that also address patients with chronic heart failure and systolic LV dysfunction (ejection fraction $\leq$35 %). Here, a class I recommendation for CABG is given for heart failure patients with left main or three vessel disease with concomitant LAD stenosis. Revascularization in general is recommended as "should be considered" (class IIa) in the presence of viable myocardium, and PCI "may be considered" (class IIb) if patients are unsuitable for CABG [25]. However, while the approach including a certain size of viable myocardium is sound from a pathophysiological perspective, there is hitherto no study proving this method [1]. In fact, a substudy from STICH failed to prove a mortality benefit when viability was used to predict the effect of revascularization (see above) [17].

Conclusion

From a pathophysiological point of view, revascularization in heart failure is very sensible to do, with the majority of heart failure cases being secondary to ischemic cardiomyopathy, and, hence, coronary artery disease. Data on the prognostic benefit of revascularization largely comes from the surgical field, with the pivotal STICH study and its 5- and 10-year follow-up analyses showing a mortality benefit of coronary artery bypass grafting over medical therapy in patients with an ejection fraction of 35 % or less and multivessel coronary artery disease. Although the totality of investigations on percutaneous revascularization allows the conclusion that PCI is a reasonable alternative particularly when coronary

artery disease complexity is low to moderate, there is a paucity of data on the role of PCI in heart failure. No novel large prospective randomized trials has addressed this issue, but overall experience and several smaller studies unanimously suggest that PCI using recent generation drug eluting stents can well be a match for CABG.

Several parameters concomitantly influence clinical decision making in patients with heart failure. The extent of myocardial disease, age, comorbidities, peri-procedural risk during surgical or interventional revascularization are just the most important [26].

Finally, novel (2016) heart failure guidelines somewhat leave the decision between CABG and PCI to the treating physician, stating that "the choice between CABG and PCI should be made by the Heart Team after careful evaluation of the patient's clinical status and coronary anatomy, expected completeness of revascularization, coexisting valvular disease and co-morbidities [1].

Future Directions

The role of percutaneous myocardial revascularization in heart failure is likely to increase in the future because of the reduction in peri-procedural risk and the technical development (newer generation stents, including polymer-free stents, bioabsorbable stents, and drug-coated balloons). Importantly, prospective outcome data on the prognostic benefit of apparently reasonable interventions rescuing ischemic and /or hibernating still need to be acquired. Similar to the lack of proven prognostic benefit in stable CAD without heart failure, mortality benefit of PCI in ischemic heart disease with heart failure remains yet to be demonstrated.

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Chapter 12
Approach to Arrhythmia in Heart Failure

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Abbreviations

ACE	Angiotensin-converting enzyme
AF	Aatrial fibrillation
AV	Atrioventricular
CRT	Cardiac resynchronization therapy
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
ICD	Implantable cardioverter-defibrillator
LA	Left atrium
LV	Left ventricle
LVEF	Left ventricular ejection fraction
NOAC	Non-VKA oral anticoagulants
NSVT	Non-sustained ventricular tachycardia
NYHA	New York Heart Association
PM	Pacemaker
SCD	Sudden cardiac death
VA	Ventricular arrhythmias
VKA	Vitamin K antagonist
VF	Ventricular fibrillation
VT	Ventricular tachycardia

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M. Dorobanţu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_12

Introduction

Patients with heart failure (HF) frequently present arrhythmias, both supraventricular than ventricular. The treatment of arrhythmias in HF may be challenging because of the particular substrate and comorbidities of these patients. The occurrence of arrhythmias in HF patients may result from advancing disease or appear as the manifestation of acute HF decompensation. In fact, the left ventricular (LV) dysfunction may favour the occurrence of ventricular arrhythmias due to the profound alterations in the ventricular substrate, but it may also increase the incidence of atrial arrhythmias through the increased LV size and filling pressure resulting in mitral valve regurgitation and left atrial dilation. Conversely, rhythm disorders in the presence of underlying structural heart disease represents a negative prognostic factor. In fact, arrhythmias may further impair LV function in patients with structural cardiomyopathies, leading to acute decompensation of chronic HF.

Given these premises, treatment of arrhythmias in the setting of HF warrants significant attention [1]. First, due to their clinical and prognostic relevance, the treatment should be prompt and effective, not only based on patients' symptoms but also on underlying disease and prognosis. Second, the treatment is often challenging, and results are usually worse than in patients without structural heart disease. Attention should be paid in considering patients in their comprehensiveness, addressing treatment not only to the arrhythmia itself but more strongly to the underlying disease and/or to comorbidities.

Brady-Arrhythmias in Heart Failure

The European Heart Survey in 2012 reported an incidence of 6 % of patients with HF and symptomatic bradycardia [2]. Intraventricular conduction system is often affected in cardiomyopathies: a left bundle branch block is common at presentation in dilated cardiomyopathy, and sometimes can be associated to atrioventricular nodal disease, leading to various degrees of atrioventricular block, sometimes requiring pacemaker (PM) implantation. The prevalence of atrioventricular blocks seems however not so different from the general population.

Sinus bradycardia and chronotropic incompetence is conversely more frequent in HF [3]. In fact, autonomic tone is frequently impaired, and may result in symptomatic bradycardia and chronotropic incompetence. Additionally, the prevalence is higher and presents a negative prognostic effect among patients with advanced HF [4]. This phenomenon can sometimes be amplified by beta-blocker or other antiarrhythmic treatments.

Additionally, reversible iatrogenic bradyarrhythmias may occur as a side effect in patients treated with beta-blockers, digoxin or anti-arrhythmic drugs, especially in case of comorbidities such as renal or hepatic impairment that can lead to overexposition to the drugs.

Although PM recommendations are those of the general population [5] patients with HF requiring a PM should be carefully evaluated, bearing in mind that a right apical pacing may be associated with further LV systolic impairment. Biventricular pacing is therefore recommended in case of severe LV ejection fraction (LVEF) reduction.

Approach to Supraventricular Arrhythmias

Epidemiology of Atrial Fibrillation in Heart Failure

Atrial fibrillation (AF) is the most frequent arrhythmia among patients with HF. AF prevalence increases with advancing age, and additional increase is observed in patients with more advanced structural heart disease and New York Heart Association (NYHA) class. The Framingham study reported an incidence of AF among HF subjects of 54 per 1000 person-years [6]. Recently, the Euro Observational Research Programme HF Long-Term Registry reported the concomitant presence of AF in 37.6 % of patients with chronic HF, and in 44% of those hospitalized for acute HF [2].

The prevalence of AF increases along with severity of HF: in fact, 5 % of patients with NYHA Class I present AF, increasing up to 50 % in NYHA Class IV patients [7].

Previous large studies confirmed that HF is an independent risk factor for the occurrence of AF [8]; conversely, other studies reported AF as an independent risk factor for HF [9–11], suggesting the relevance of bilateral self-perpetuating physiopathological mechanisms. Additionally, the development of AF in HF subjects related to increased mortality [6]. A large amount of this risk derives from the incidence of stroke, a relatively common occurrence as HF increases the risk of stroke in AF patients [12].

In addition to worsening the pre-existent HF, AF with uncontrolled ventricular rate may result itself in left ventricular systolic dysfunction with signs and symptoms of HF (tachycardia-induced cardiomyopathy) [13]. This condition is uncommon in the absence of a previous structural heart disease, but it can occur in case of long lasting uncontrolled ventricular rate. In the setting of true tachycardia-induced cardiomyopathy, the diagnosis is made after exclusion of other causes of LV dysfunction and complete recovery of the LV dysfunction after controlling the ventricular rate.

Mechanisms of Atrial Fibrillation Occurrence in Heart Failure

Multiple mechanisms underlie the occurrence of AF in HF. In patients with a structural heart disease involving the LV, complex disadvantageous remodelling mechanism occur as compensation to the LV dysfunction. In particular, electrical, mechanical, metabolic and contractile variations interact for the preservation of

adequate cardiac output [14]. These mechanisms result in elevated filling pressures, increased left atrial (LA) pressure, LA dilation and fibrosis. This substrate, characterized by conduction slowing and heterogeneity, is the ideal substrate favouring AF occurrence and perpetuation [15]. AF onset becomes itself a mechanism of self-perpetuation, as AF begets AF, and longer is AF duration, more relevant becomes electrical and structural remodelling, and more difficult becomes sinus rhythm restoration [16, 17]. Moreover, functional mitral regurgitation is frequently associated with cardiomyopathies, due to the symmetric tethering resulting from LV dilation or asymmetric tethering following ischemic cardiomyopathies. Both these mechanisms are implied in LA progressive dilation and AF occurrence. Additionally, increased LA pressure results also in LA stretch, involving most of all the junction between LA and the pulmonary veins. This stretching results in occurrence of triggered activity sustaining repetitive premature complexes, frequently implied in AF onset [18]. Moreover, HF patients present an increased sympathetic activity and impaired autonomic tone balance: this impairment is also implied in the occurrence of atrial premature complexes and AF onset [19, 20].

In patients with acute HF, other mechanisms may be involved in the onset of AF, as the trigger deriving from the use of catecholamines (dobutamine, dopamine, norepinephrine), associated to new onset of AF in about 10 % of hospitalized patients [21].

Treatment of Atrial Fibrillation in Heart Failure

The mainstay of AF treatment in patients with HF includes prevention of thromboembolic events and symptoms reduction [22]. Concerning symptoms, the optimal treatment can be achieved through rate control or rhythm control strategies, both of them including pharmacological and non-pharmacological options. Whatever is the chosen strategy, the treatment should be patient-tailored, in order to provide the best approach for each single patient. Due to the complexity and variety of the spectrum of cardiomyopathies underlying the clinical condition of HF, each single pathology warrants careful assessment concerning the benefits balanced with the risks of an aggressive strategy, along with the likelihood of a durable efficacy of the chosen strategy.

Prevention of Thromboembolism

Thromboembolic events are the most common and feared complication of AF, affected by a high mortality and morbidity. Guidelines recommend risk stratification based on the CHA_2DS_2-VASc score, to identify patients (score ≥ 1) that will benefit from an oral anticoagulant therapy either with vitamin K antagonists (VKA) or with a non-VKA oral anticoagulant (NOAC) [22]. Due to the fact that congestive HF, moderate-to-severe LV systolic dysfunction on cardiac imaging, or recent

decompensated HF irrespective of LVEF represent the "C" in the acronym of this score, HF patients should all be offered oral anticoagulation treatment. The choice between VKA and NOAC should be based on patients' characteristics, including compliance/efficacy, comorbidities such as renal or hepatic impairment, and risk of bleeding as assessed by the HAS-BLED score [23]. Guidelines recommend NOAC as first-line choice in non-valvular AF, due to their higher compliance and reduced pharmacological interaction careful monitoring of renal function is however required, and a progressive impairment of renal function, along with gastrointestinal side effects, may sometimes lead to NOAC discontinuation, favouring treatment with VKA. Patients with contra-indications to any kind of oral anticoagulation and concomitant high thromboembolic risk (such as previous major bleeding during anticoagulation therapy) may be offered percutaneous LA appendage closure, demonstrated to be non-inferior to oral anticoagulation in patients who could not undergo this treatment [24–26].

Acute Management of Atrial Fibrillation in Acute Heart Failure

AF may become a medical emergency in the setting of acute HF, both as precipitating factor or as a consequence of acute hemodynamic deterioration. In this setting, patients may present with signs of hypoperfusion, including symptomatic hypotension, oliguria, multi-organ damage and lactate acidosis. New onset AF may be a precipitating factor, contributing to accelerate hemodynamic deterioration, especially in case of very fast ventricular rates. This situation requires urgent electrical cardioversion to restore sinus rhythm [22]. Due to the high risk of arrhythmic recurrence after cardioversion, sometimes rate-control strategy as first-line treatment can be adopted safely. Beta-blockers however may cause haemodynamic deterioration, and should be given cautiously, with strict blood pressure monitoring. Alternatively, digoxin can be administered, even if its efficacy can be lower in acute HF compared to beta-blockers [27, 28].

Rate Control: Pharmacological and Interventional Treatments

Large randomized studies during the past years investigated the superiority of rate or rhythm control strategy in patients with HF. All these studies did not find significant benefits in terms of survival, quality of life and hospitalizations between rhythm or rate control strategies [29, 30], even specifically among patients with HF [31], so current guidelines recommend rate control as the first line strategy in patients with HF, reserving rhythm control to patients still symptomatic despite adequate rate control [22, 27]. However, these results were mainly driven by the adverse effects of antiarrhythmic drugs in patients with HF: rhythm control was pursued only by pharmacological treatment, and, additionally, in the AFFIRM study rhythm control arm

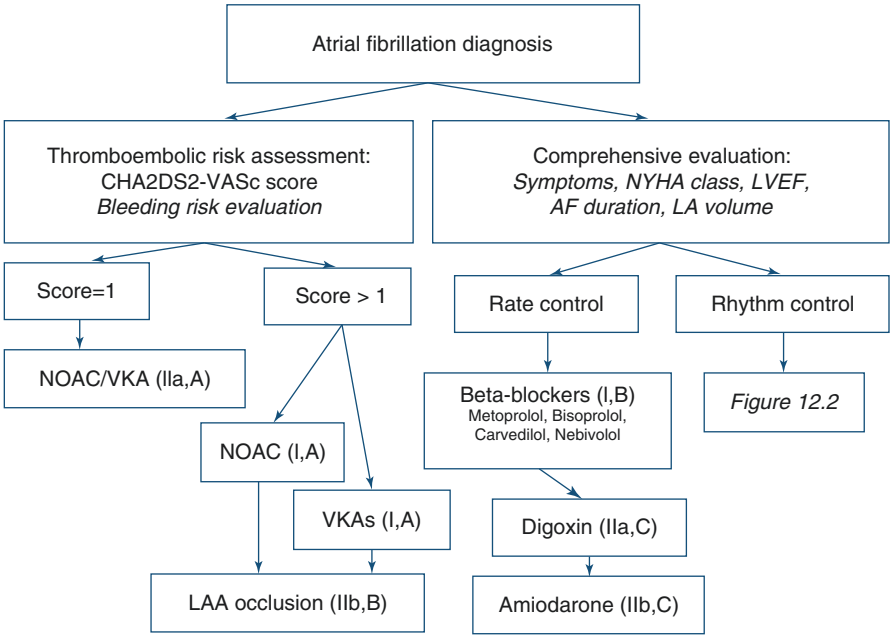

Fig. 12.1 Flow-chart for thromboembolic risk assessment and rate control management in patients with heart failure and concomitant atrial fibrillation. *LVEF* left ventricular ejection fraction, *AF* atrial fibrillation, *LA* left atrial, *NOAC* novel oral anticoagulant, *VKA* vitamin K antagonist, *LAA* left atrial appendage

patients were less commonly treated with anticoagulation compared to rate control arm [32]. Moreover, recent computational models and registries conducted among general population identified a benefit for rhythm over rate control in terms cardiac output [33], survival [34] and stroke incidence [35, 36], suggesting that an appropriate patient selection, leading to a higher likelihood of rhythm control efficacy (short arrhythmia duration, LA dimension), and the choice of the correct method to pursue the target leads to significant benefits for rhythm control, at least within selected subgroups.

Pharmacological rate control should always be applied for these patients: in fact, beta-blockers although not to be recommended with the sole aim to improve prognosis, may be effectively used [37]. Additionally, digoxin can be used as an alternative drug or associated to beta-blockers [22, 27, 28]. Eventually, amiodarone may be considered in non-responsive patients [38]. The approach for thromboembolic risk management and AF rate control in HF patients is represented in Fig. 12.1.

Finally, in patients refractory to pharmacological rate control and still symptomatic, atrioventricular (AV) node ablation with PM implantation may be considered to improve symptoms [39]. Given the reduced LV function, the need of continuous ventricular stimulation after atrioventricular node ablation and the symptoms of HF,

biventricular PM implantation is recommended in patients with HF and reduced LVEF [40, 41]. Additionally, implantable cardioverter defibrillator (ICD) function should be included as recommended by guidelines in patients with LVEF lower than 35 % [27].

Rhythm Control: Pharmacological and Interventional Treatment

Rhythm control strategies are currently recommended in patients symptomatic from AF despite adequate rate control [22]. As previously stated, however, this recommendation relies on randomized trials in which rhythm control was pursued only by means of antiarrhythmic drugs. In fact, HF patients are more prone to develop adverse events such as pro-arrhythmia or worsening HF. Therefore, Ic class drugs, sotalol and dronedarone are not recommended in patients suffering from symptomatic HF [42]; dronedarone can be considered only in stable NYHA class I patients, as was related to increased mortality in symptomatic HF [43]. The only available drug among patients with HF remains amiodarone, affected however by a high incidence of systemic adverse effects [44], such as thyroid dysfunction, cutaneous effects, hepatic and pulmonary toxicity, requiring periodical monitoring of these patients during the treatment.

Given these limitations, growing interest has been directed towards transcatheter ablation. Current guidelines suggest AF catheter ablation in patients refractory to or intolerant to antiarrhythmic drugs. Recently, some studies have been performed aiming to assess the safety and efficacy of AF catheter ablation in the specific population of patients with HF [45–58], including few small randomized trials [59–62] and meta-analyses [63–65] (see Table 12.1).

All studies consistently described promising results in terms of safety and efficacy, with a long-term efficacy and incidence of complications similar to that reported among the general population [65]. Additionally, an improvement in NYHA class and LVEF was found in these patients, suggesting the usefulness of this procedure in interrupting the vicious circle by which AF can further impair LV function in the presence of a pre-existent cardiomyopathy [66, 67]. The rationale of AF ablation in this setting is, in fact, based on the potential of acting directly on atrial substrate, interrupting or slowing the progressive impairment of LV and LA function sustained by the vicious circle that links AF and HF. Interestingly, the largest meta-analysis reported improved efficacy especially when AF ablation is performed early in the natural history of AF ($p = 0.030$) and HF ($p = 0.045$),reducing the proportion of patients who would subsequently experience a LVEF decrease to < 35 % ($p<0.001$) [66]. Additionally, the benefits in terms of LVEF improvement are maintained over follow-up, and are markedly higher in patients maintaining sinus rhythm, supporting the usefulness of rhythm control in those patients [64]. Caution should be made, however, in patients' selection: the large amount of fluids administered during AF ablation [68] and the frequent need for extensive LA ablation require careful monitoring of the patients' hemodynamic status in order to avoid predictable complications.

Table 12.1 Observational and randomized studies investigating the role and effects of AF catheter ablation in CHF

Author, Year (Ref)	Design	N. pts	Age, years	Paroxysmal AF (%)	NYHA class	Follow-up, months	Success single (%)	Redo (%)	Success final (%)	LVEF (%)	Other parameters
Chen et al. (2004) [45]	Obs	94	57	51	2.8	14	52	22	73	36➔41	↑QoL
Hsu et al. (2004) [46]	Obs	58	56	9	2.3	12	28	50	78	35➔56	↓ LV diameter, ↑QoL, exercise capacity and NYHA
Tondo et al. (2006) [47]	Obs	40	57	25	2.8	14	55	33	87	33➔47	↑exercise capacity and QoL
Gentlesk et al. (2007) [48]	Obs	67	54	70	–	6	55	31	86	42➔56	–
Nademanee et al. (2008) [49]	Obs	129	67	40	–	27	–	21	79	30➔37	–
Lutomsky et al. (2008) [50]	Obs	18	–	100	–	6	50	–	–	41➔52	–
De Potter et al. (2010) [51]	Obs	36	52	39	–	16	50	31	69	41➔58	–
Cha et al. (2011) [52]	Obs	111	55	28	–	12	–	–	76	35➔56	↑QoL
Anselmino et al. (2013) [53]	Obs	196	60	22	2.1	46	45	30	62	40➔50	↑NYHA and mitral regurgitation
Calvo et al. (2013) [54]	Obs	36	52	24	–	6	70	31	83	41➔48	–
Nedios et al. (2014) [55]	Obs	69	61	33	2.4	28	40	46	65	33➔48	–
Bunch et al. (2015) [56]	Obs	267	66	–	–	60	39	–	–	27➔42	↓ death and CHF hospitalization vs. AF, no ablation

Rillig et al. (2015) [57]	Obs	80	60	20	2.0	72	35	–	57	35➔56	↑ NYHA, ↓ LA diameter
Ullah et al. (2016) [58]	Obs	171	58	36	2.3	43	26	60	65	34➔46	↑NYHA, ↓ death and stroke in SR patients
Khan et al. (2008) [59]	RCT	41	60	49	–	6	71	20	88	27➔35	↑QoL and 6MWT distance vs. AVN ablation
MacDonald et al. (2010) [60]	RCT	22	62	0	2.9	10	–	30	50	36➔41	QoL and 6MWT: no difference vs. medical treatment
Jones et al. (2013) [61]	RCT	26	64	0	2.4	10	69	19	88	21➔32	↑QoL and peak VO2, ↓ BNP vs. rate control
Hunter et al. (2014) [62]	RCT	26	55	0	2.7	6	38	54	81	32➔40	↑QoL, NYHA class peak VO2, ↓ BNP vs. rate control

Obs observational, *RCT* randomized controlled trial, *QoL* quality of life, *LV* left ventricle, *LVEF* left ventricular ejection fraction, *CHF* congestive heart failure, *AF* atrial fibrillation, *SR* sinus rhythm, *6MWT* 6-minute walking test, *LA* left atrium, *BNP* brain natriuretic peptide, *AVN* atrioventricular node

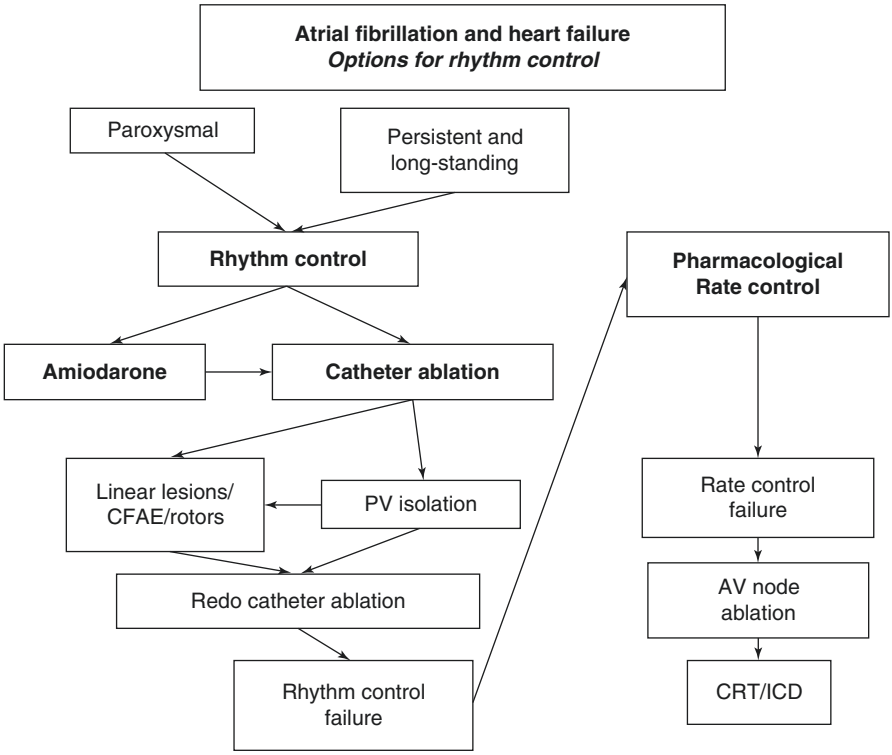

Fig. 12.2 Flow-chart for rhythm control strategies in patients with heart failure and concomitant atrial fibrillation. *PV* pulmonary vein, *CFAE* comlex fractioned atrial electrograms, *ICD* implantable cardioverter defibrillator, *CRT* cardiac resynchronisation therapy

Recently, a randomized trial compared catheter ablation to amiodarone for AF treatment in patients with HF and an implanted device, reporting a higher efficacy for AF ablation, along with a lower incidence of significant adverse effects compared to amiodarone [69]. This and other ongoing studies, such as the CASTE-AF [70], may lead to a further extension of recommendations to perform AF catheter ablation early in patients with HF.

Some issues however remain to be addressed. First of all, catheter ablation protocol: pulmonary vein isolation is the mainstay of the procedure, as demonstrated in the general population [71, 72], but patients with an altered atrial substrate such as HF patients often require additional lesions, like linear lesions (left atrial roof, mitral isthmus) [73], complex fractioned atrial electrogram ablation, right atrial lesions (cavo-tricuspid isthmus, superior vena cava) [74] or drivers/rotor ablation [75]. No randomized studies are currently available, in HF populations and the optimal first-line protocol needs to be further evaluated. Additionally, specific cardiomyopathies, such as hypertrophic cardiomyopathy [76, 77], present a peculiar anatomic substrate, and require extensive LA ablation to achieve satisfactory efficacy. A simplified approach for AF rhythm control strategies in HF is represented in Fig. 12.2.

Other Supraventricular Arrhythmias in Heart Failure

The presence of a structural heart disease can favour the occurrence of any supraventricular arrhythmias, in particular atrial flutter and atrial tachycardia. The prevalence of these arrhythmias among HF patients is less defined, but it has been reported in up to 30 % of patients [2], increasing along with more advanced disease.

Atrial flutter presents the same thromboembolic risk of AF; therefore, the same scores identify patients requiring oral anticoagulation treatment [22]. Additionally, recommendations towards rate control and rhythm control strategies are the same as for AF. However, particular consideration should be made in typical atrial flutter: catheter ablation of cavo-tricuspid isthmus is in fact a simple, safe and effective procedure, that can be safely performed with limited risks in HF patients and is much more effective than antiarrhythmic drugs [78]. Therefore, catheter ablation for typical atrial flutter should be considered early in these patients [1].

Atrial tachycardia, conversely, does not carry thromboembolic risk. However, it may be strongly symptomatic in patients with HF, leading sometimes to worsening HF and acute decompensation [79]. Additionally, patients with ICD may receive inappropriate shocks, and patients with resynchronization devices (CRT) may be affected by suboptimal resynchronization rate [80]. Pharmacological treatment is often required, including beta-blockers as first line treatment, or anti-arrhythmic drugs (mainly amiodarone) when beta-blockers are ineffective. Catheter ablation can be considered in patients with frequent sustained episodes refractory to pharmacological treatment [1, 81].

Ventricular Arrhythmias

Epidemiology of Ventricular Arrhythmias in Heart Failure

Patients with HF present a high incidence of a wide spectrum of ventricular arrhythmias (VA). In particular, the prevalence is higher among patients with severely depressed LVEF and those with ischaemic aetiology. Ventricular premature beats and asymptomatic non-sustained ventricular tachycardias (NSVT) are very common. In particular, their prevalence range up to 87 % and 30–60 %, respectively [82, 83], progressively increasing along with more advanced NYHA class.

Conversely, sustained ventricular tachycardia (VT) and ventricular fibrillation (VF) are the most feared arrhythmic complications of HF. The recent Taiwan registry reported an incidence of VT and VF around 2 % per year in patients with HF [84]; predictors of increased risk were advanced age, NYHA class, ischaemic aetiology, male sex and renal failure. VT and VF are responsible for almost 50 % of all deaths in HF [85]. Additionally, the occurrence of previous VT or VF doubles mortality compared to patients without previous sustained VA [86, 87]. These data underline the importance of a comprehensive approach to correctly treat and prevent sudden death in HF patients.

Patients admitted to hospital for acute HF present an even higher incidence of VA. In the ADHERE registry, the incidence of in-hospital VT or VF was 10 % [88], while in the EuroHeart Survey 2 % of acute HF patients presented VT ad admission [2].

Mechanisms of Ventricular Arrhythmias in Heart Failure

Patients with HF progressively undergo significant ventricular remodelling. This is characterized by electrical, structural, metabolic and contractile changes of the myocytes aiming at preservation of an adequate cardiac output. These processes are however maladaptive, resulting arrhythmogenic, due to the over-activation of the beta-adrenergic pathway, renin-angiotensin-aldosterone system and Ca-Calmodulin-dependent kinase II signalling [89]. Mechanical stretch resulting from volume overload, along with neurohumoral activation, play a relevant role in arrhythmias onset (Fig. 12.3).

In fact, the inotropic response from this activation results in a compensatory contractile performance, effective in short-term maintenance of pump function, but finally leading to myocardial hypertrophy and fibrosis. Initially, myocytes present electrical remodelling characterized by prolonged action potentials, larger Calcium transients and heterogeneity in repolarization, due to increased function in Na/Ca exchanger, reduced function of K channels and increased Calcium turnover from sarcoplasmatic reticulum. This is the underlying mechanism of triggered activity resulting in ventricular arrhythmias onset: Calcium release from the sarcoplasmatic reticulum of cells that cannot maintain a proper Calcium equilibrium creates delayed after-depolarization and premature beats occurrence. Arrhythmias can be perpetuated by the altered excitability, changes in cell-to-cell connectivity and repolarization dispersion resulting from fibrosis, that favours re-entrant arrhythmias onset.

Progressive cellular dysfunction resulting from these maladaptative changes finally results in LV dilation. Conduction in a dilated LV is further slowed, leading to increased fibrosis, oxygen stress due to mythocondrial dysfunction, and cellular apoptosis.

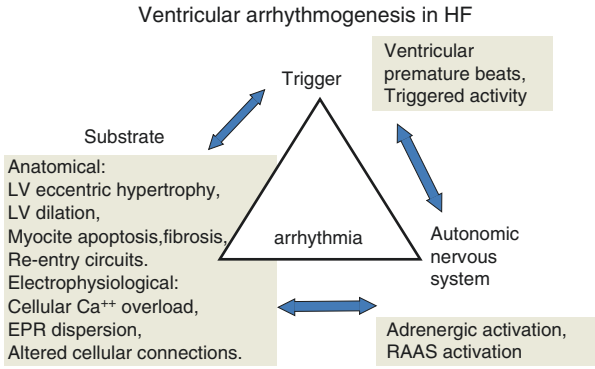

Fig. 12.3 Mechanisms of ventricular arrhythmogenesis in patients with heart failure. *HF* heart failure, *LV* left ventricular, *ERP* effective refractory periods, *RAAS* rennin-angitensin-aldosterone system

These changes are particularly evident in ischaemic cardiomyopathies: both acute and chronic ischaemia lead to myocyte dysfunction creating the optimal substrate and triggers for VA. While arrhythmias in the setting of an acute coronary syndrome can be treated addressing acute ischaemia, patients with chronic ischaemic cardiomyopathy present a significant risk of arrhythmia and need to be evaluated to assess the need of aggressive preventive treatment [1].

Treatment of Ventricular Arrhythmias in Heart Failure

The objective of the treatment of VA in patients with HF is the prevention of sudden cardiac death (SCD). Several randomized studies have been conducted to assess the effectiveness of pharmacological and non-pharmacological treatments. The mainstay includes maintaining a stable hemodynamic status, including treatment with beta-blockers, ACE inhibitors or angiotensin receptor antagonists, mineralocorticoid receptor antagonists [27, 90]. In fact, a complete, titrated and continuously monitored treatment will stabilize patients reducing the risk of life-threatening VA. Additionally, avoiding precipitating factors such as electrolyte imbalance, myocardial ischaemia, hyperthyroidism, drug-related adverse effects reduce the risk. On the other side, VA may be related to the progression of underlying structural heart disease and their prevention may deserve specific treatment such as antiarrhythmic drugs, ICD or transcatheter ablation [1].

Prevention of Sudden Cardiac Death in Heart Failure

Risk stratification is the first-line assessment to optimally detect patients obtaining benefits from aggressive treatment, balancing the benefits and risks [91]. Several studies investigated the efficacy of ICD implantation for secondary prevention, demonstrating improved survival with ICD compared to antiarrhythmic drugs [92, 93];subsequently, the same advantages over antiarrhythmic drugs were confirmed in asymptomatic high risk patients with ischaemic cardiomyopathies [94–96]; evidence, instead, is less solid in non-ischemic cardiomyopathies, but ICD is recommended also in this setting [97]. Current recommendations to select patients for ICD and/or CRT implantation are discussed in detail in Chaps. 13 and 14.

Pharmacological Treatment for Ventricular Arrhythmias

Beta-blockers act specifically reducing the risk of VA and SCD by blocking the adrenergic triggering mechanisms, slowing the sinus rate and possibly reducing calcium release from ryanodine receptor. They are the only drugs that demonstrated in

large populations a significant survival improvement, with a relative risk reduction of about 30–35 % in mortality and 40–45 % in SCD [98, 99]. These outcomes are more evident in patients with ischemic cardiomyopathies, but also patients suffering from HF of different aetiologies benefit from this treatment. The mechanisms include reduction in the adrenergic tone, often over expressed in HF patients, and able to increase triggers for sustained VA, and modulation of the substrate, constituted by the underlying structural cardiomyopathy. Beta-blockers in fact act more specifically reducing repetitive VA, reducing therefore the risk of SCD. Of note, not all beta-blockers are recommended in HF patients. In particular, metoprolol, a selective B1 blocker, demonstrated to reduce mortality in HF patients [100]. Bisoprolol, another selective B1 blocker, also improved outcome in HF patients in the study [99]. Carvedilol, a non-selective beta-blocker, and nebivolol, a selective beta-blocker with nitrous oxide-mediated action on the endothelium, have also proven efficacy in HF patients [98, 101]. All HF patients should receive a beta-blocker treatment at the maximal tolerated dose aiming to reduce the risk of arrhythmias and SCD. The choice should be based on each patient's profile, comorbidities, concomitant therapy and hemodynamic status [27]. Further dosage adjustments may be required during the follow-up.

However, HF patients frequently suffer from VA despite optimal medical treatment including a maximal dose of beta-blockers, ACE-inhibitors and mineralocorticoid receptor antagonists. In these patients, a more aggressive antiarrhythmic pharmacological treatment is needed. Amiodarone, a class III antiarrhythmic agent presenting abroad spectrum of action, including blockade of depolarizing sodium currents and potassium channels that conduct repolarizing currents, leading to electrical stabilization of the cellular membranes, has been widely used in HF patients to reduce the risks of VA. Results are heterogeneous, as the GESICA trial [102] and meta-analyses including randomized studies [44, 103] demonstrated a benefit on mortality reduction, while the SCD-HeFT trial [104] and CHF-STAT [95] reported no benefit from amiodarone treatment. In particular, due to its mild negative inotropic effect, patients characterized by advanced HF and poor hemodynamic status can receive limited benefit. Additionally, chronic administration of amiodarone is associated with complex drug interactions and extracardiac side effects, as previously stated. Regular monitoring of lung, liver and thyroid function is needed, as the longer is the therapy and the higher the dose of amiodarone, the greater is the likelihood of adverse effects occurrence. However, it should be noted that amiodarone is the only antiarrhythmic drug available in HF patients: class I (quinidine, flecainide, propafenone) and other class III drugs (sotalol, dronedarone) related to increased mortality in HF patients due to pro-arrhythmic effects [42, 105]. Amiodarone may be a reasonable choice for optimally treated HF patients presenting with sustained VT, who are not candidates for an ICD (Class IIb, level C indication). Additionally, in HF patients treated with an ICD presenting with symptomatic VAs or recurrent ICD shocks, despite optimal HF treatment, amiodarone is recommended (Class I, level C indication) [91]. In such patients, association between amiodarone and beta-blockers can be more effective in reducing appropriate shocks [106].

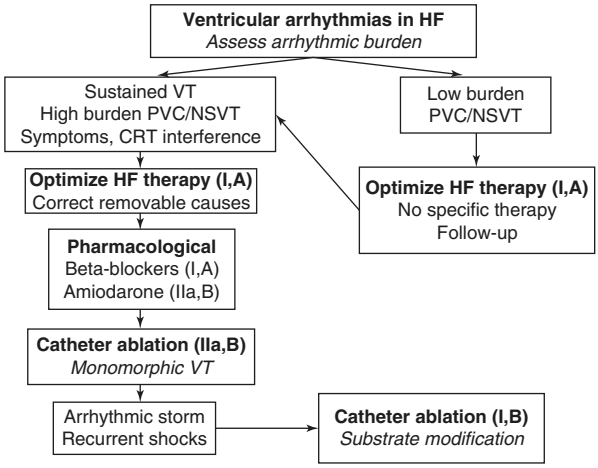

Fig. 12.4 Flow-chart for pharmacological and non-pharmacological treatments for ventricular arrhythmias in heart failure. *HF* heart failure, *PVC* premature ventricular contraction, *NSVT* non-sustained ventricular tachycardia, *VT* ventricular tachycardia

Although no randomized trials are available, Mexiletine, a IB class antiarrhythmic drug acting as Na^+ channels inhibitor, also appears safe and effective in post-myocardial infarction VTs, especially in combination with other drugs as amiodarone [107, 108].

Conversely, frequent ventricular premature contractions and non-sustained VT should not provide recommendation for amiodarone treatment, as risks may become more relevant than the benefits provided in terms of arrhythmic burden reduction (Fig. 12.4). These recommendations should be applied both for patients suffering from ischemic cardiomyopathies than for patients with different aetiologies of HF [1].

Interventional Treatments for Ventricular Arrhythmias

Patients with HF may experience symptomatic VA despite optimal medical treatment, including antiarrhythmic drugs. In particular, multiple recurrent ICD shocks may occur, leading to disabling symptoms. In this setting, catheter ablation has been proposed as an optional treatment for patients suffering from VT related to myocardial scars, aiming to improve patients' symptoms and quality of life (Class IIa, level B). Two randomized studies demonstrated that catheter ablation decreased the number of appropriate ICD shocks preventing recurrent VT in patients with ischaemic heart disease [109, 110]. Moreover, catheter ablation is recommended to control incessant VT or electrical storms (Class I, level B) [91, 111, 112].

Catheter ablation holds the potential to target both areas of triggered activity as, more frequently, the critical isthmus of slow conduction within the VT reentry circuit [113]. Scar-related VT are typically monomorphic, but multiple VT morphologies may be induced in the same patient. The QRS morphology at 12-leads ECG helps to identify the exit site of the reentry wave front, that may be endo-, mid-, or epicardial, to identify patients suffering from epicardial VT and

requiring epicardial ablation [114]. Conversely, polymorphic VT, frequently incessant and refractory to drug treatment, may be treated with catheter ablation because frequently triggered from Purkinje fibres [112].

Mapping and ablation of the VT may be performed during ongoing VT (activation mapping) for well-tolerated VTs, while electro-anatomical mapping systems may aid in localization of ventricular scars and areas of slow/late conduction, enabling ablation during sinus rhythm (substrate ablation) without induction of hemodynamically unstable VT. The alternative techniques include point-by-point ablation at the exit site of there-entry circuit, linear lesion sets or ablation of local fragmented electrograms aiming to homogenize the scar [115–117]. Epicardial mapping and ablation can be required especially in patients with non-ischaemic cardiomyopathies [118], and require careful evaluations because of potential complications of epicardial access, damage to the coronary vasculature or other surrounding organs.

Patients with post-myocardial scar VT experience a better outcome following catheter ablation than non-ischaemic cardiomyopathies [119]. The success rate is determined by the amount of infarct-related scar burden [120], and dedicated units for this treatment may positively affect outcome [121]. Moreover, recently a better outcome has been demonstrated for extensive substrate ablation, compared to ablation limited to stable monomorphic VT [122, 123].

At present, catheter ablation is therefore a strong recommendation for arrhythmic storm and recurrent VT in patients in optimal medical treatment, aiming to improve symptoms and reduce ICD shocks [1, 91]. It should also be considered in patients suffering from monomorphic scar-related VT. No data concerning hard endpoints such as survival are however available at present, so this procedure cannot be considered as alternative to ICD implantation. The risks related to these procedures are not negligible, with possible complications including stroke, valve damage, cardiac tamponade, AV block or death (ranging, the latter, from 0 to 3 %) and should therefore be performed under careful monitoring and by trained centres.

Arrhythmias in Heart Failure with Preserved Ejection Fraction

The subgroup of HF with preserved LVEF (HFpEF) is a specific population with peculiar pathophysiological features compared to HF with reduced LVEF. In this setting, electrical and mechanical remodelling is secondary to a significant diastolic dysfunction, characterized by increased LV stiffness, impaired relaxation and concentric hypertrophy [124].

These diastolic alterations induce a significant increase in LA pressure, creating the ideal substrate for AF onset and perpetuation. AF is in fact very common and presents a negative prognostic factor, being related to increased mortality [125] and risk of stroke and HF worsening [126, 127]. In this setting concerning oral anticoagulation, patients with HFpEF should be considered as those with reduced LVEF [27] and, concerning rate control, no evidence currently favours one class over the others.

Due to the negative prognostic impact of AF in HFpEF patients, however, rhythm control strategy is often adopted aiming to maintain stable sinus rhythm. At present current recommendations are limited to amiodarone, while class Ic drugs, sotalol and dronedarone present the same limitations as in patients with HF and reduced LVEF [22, 27], while catheter ablation of AF, although attractive, has been investigated in only one study, showing similar results compared to the general population [128].

Patients with HFpEF, instead, seem to present a lower incidence of ventricular arrhythmias compared to those with reduced LVEF. Large studies reported in fact a relatively low incidence of SCD [129]. Conversely, the risk of VA and SCD is high in patients with hypertrophic cardiomyopathy, that can present clinically with HFpEF [130].

Future Directions

Some areas of uncertainties are still present concerning the treatment of arrhythmias in HF.

First of all, further studies are required to define the optimal treatment of AF in patients with HF. Antiarrhythmic drugs failed to demonstrate superiority over rate control strategies. Catheter ablation, however, holds the potential to interrupt a vicious circle: the evaluation of the impact of this procedure on strong outcomes, such as mortality and stroke incidence, is required to better define the role of AF ablation. Additionally, alternative anticoagulant drugs should be studied more extensively among HF patients, aiming to better define the safety and efficacy of the NOACs compared each other. Finally, the role of brief and sporadic episodes of AF detected by implanted devices should be further evaluated concerning their real thromboembolic risks.

Concerning VA, instead, the definition of VA and SCD risk remains somewhat unclear. The relevance of NVST and frequent premature beats needs to be further evaluated, as antiarrhythmic treatments other than beta-blockers are affected by non-negligible risks. The role of frequent ventricular extra systoles in impairing LV function is also a matter of debate, as it is not clear if a cut-off can be used to detect VA requiring treatment, aiming to reduce HF progression. Finally, the impact of LV assistance devices on the arrhythmic risk of patients with advanced HF needs clarification, as a growing number of patients is being treated with such devices.

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Chapter 13
Devices for Heart Failure: Implantable Cardioverter Defibrillator

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Abbreviations

AF	Atrial fibrillation
ATP	Antitachycardia pacing
CAD	Coronary artery disease
CRT	Cardiac resynchronization therapy
CRT-D	Cardiac resynchronization therapy with an ICD function
CVD	Cardiovascular disease
HF	Heart failure
ICD	Implantable cardioverter defibrillator
LV	Left ventricle
LVEF	LV ejection fraction
QOL	Quality of life
SCD	Sudden cardiac death
S-ICD	Subcutaneous implantable defibrillator
VF	Ventricular fibrillation
VT	Ventricular tachycardia

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M. Dorobanţu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_13

Implantable cardioverter defibrillator is an implantable battery-powered device, which consists of a device and lead(s), and aimed to convert life threatening ventricular tachyarrhythmias (ventricular tachycardia, ventricular fibrillation) to a sinus rhythm by means of an antitachycardia pacing and direct biphasic current shock. The implantable cardioverter defibrillators usually have pacemaker function as an additional function.

Heart failure is a chronic disease with a high prevalence and incidence worldwide. Despite the current approach to the early diagnosis and treatment, heart failure associated morbidity and mortality is still high and will continue to rise in the future. The progression of heart failure is irreversible. Current approach to the treatment of heart failure with an optimal medical therapy and device therapy can slow down the progression of the disease, but not reverse or stop the progression. Consequently, efforts should be made to decrease heart failure incidence and prevalence and improve survival among heart failure patients. The main two causes of death among heart failure patients are ventricular tachyarrhythmias and progressive pump failure. A significant advance in the use of implantable devices (implantable cardioverter defibrillator, cardiac resynchronization therapy with and without defibrillation function) to monitor and treat HF patients has been performed. During the last decades the large randomized studies have demonstrated that implantable cardioverter defibrillators are highly effective for primary and secondary prevention of sudden cardiac death in heart failure patients.

Nowadays, implantable cardioverter defibrillators are considered the standard therapy for patients at high risk for ventricular tachyarrhythmias, both for primary and secondary prevention.

Implantable cardioverter defibrillator (ICD) is an implantable battery-powered device, which consists of a device and lead(s), and aimed to convert life threatening ventricular tachyarrhythmias (ventricular tachycardia, ventricular fibrillation) to a sinus rhythm by means of an antitachycardia pacing (ATP) and direct biphasic current (DC) shock. The ICDs usually have pacemaker function as an additional function.

Development of ICDs has started since mid of twentieth century when Claude Beck performed the first electrical defibrillation of ventricular fibrillation (VF). The first human implantation of an ICD was performed at the John Hopkins Hospital by the group of Mirowski in the early 80s [1, 2]. During the last decades ICDs have evolved from bulky pulse generators which were placed in the abdominal region with epicardial patches requiring thoracotomy to a sophisticated rhythm management devices with an endocardial defibrillation leads. The implantable cardioverter defibrillator has been proven to be a highly effective tool for primary and secondary prevention of sudden cardiac death in selected patients. The annual number of implantations have increased substantially during the last years. A worldwide cardiac pacing and implantable cardioverter-defibrillator survey with 61 included countries was conducted in 2009 and was compared with the results of 2005. This survey demonstrated a significant increase in the number of ICD implantations among all involved countries [3].

The effectiveness of ICDs in the primary and secondary prevention of sudden cardiac death (SCD) among HF patients has been demonstrated in large randomized studies [5, 19] and will be discussed in details in this chapter.

Epidemiology of Heart Failure: Insight into the Device Therapy

According to the current definition of the European Society of Cardiology "Heart failure is a clinical syndrome in which patients have typical symptoms and signs resulting from an abnormality of cardiac structure and function" [4].

Heart failure (HF) and atrial fibrillation (AF) are considered to be new cardiovascular epidemics over the last decades and are considered to be an increasing healthcare problem worldwide due to a high morbidity and mortality and the high rate of disability among HF patients. HF affects nearly five million patients in the USA and more than 550,000 patients are diagnosing with new HF annually. The incidence of HF remained stable over the last decades, meanwhile the prevalence of disease has steadily increased worldwide due to an ageing of the population and high incidence of coronary artery disease (CAD) which is among the main risk factors of HF. Approximately 15,000,000 patients have HF in the USA and Europe [5–9].

According to the Framingham Heart Study, the 5-year survival of HF patients is less than 40 % after the first manifestation of the disease [10]. The absolute mortality of HF is still high, nearly 50 % within 5 years [9, 11]. The ARIC study, which was published in 2008, has demonstrated that 1- and 5-year mortality among HF patients after hospitalization for HF were 22 % and 42.3 %, respectively [12].

Another important aspect of the current problem of HF is the HF-related costs. Treatment of HF is associated with a repetitive, prolonged and costly hospitalizations and expensive treatment, such as a therapy with an implantable devices, heart transplantation, etc. (i.e. HF related direct and indirect annual costs were estimated around $30,000,000,000 in the United States in 2006 and $33 billion in 2007) [13, 14].

The above mentioned data predispose to understand the fact that, despite the current approach to the early diagnosis and treatment, HF associated morbidity and mortality is still high and will continue to rise in the future. It is important to emphasize that the progression of HF is irreversible. Current approach to the treatment of HF with an optimal medical therapy and device therapy can slow down the progression of the disease, but not reverse or stop the progression.

Consequently, efforts should be made to decrease HF incidence and prevalence and improve survival among HF patients. The early prediction of the outcome of HF is as important as the early identification of the disease itself and the group of patients who will benefit from the certain intervention and might allow more rational or cost-effective use of specific heart failure medications and devices. Different risk factors and multivariable risk scores, such as a brain natriuretic peptide (BNP) and the Seattle Heart Failure Model (SHFM) have been prescribed during the last decades and recommended for the risk stratification of HF patients [15].

To summarize, HF is a chronic disease with a high prevalence and incidence worldwide, the prognosis of which is remaining poor and mortality among affected patients is still high.

Evolution of the Implantable Cardioverter Defibrillator from Thoracotomy to the Subcutaneous Implantable Defibrillator

The first implantation of a defibrillator was performed in a patient with two previous cardiac arrests in 1980 at the John Hopkins Hospital by the group of Mirorowski. Thereafter ICD implantation was performed in a few centers in patients with a history of cardiac arrest (i.e. secondary prevention). In 1985 the US Food and Drug Administration (FDA) approved commercial implantable cardioverter-defibrillators.

The ICD-system consists of a pulse generator and lead(s). The ICD can be divided into three groups: single-chamber ICDs, dual-chamber ICDs and cardiac resynchronization therapy (CRT) with an ICD function (CRT-Ds). The generator consists of the battery, capacitor and the circuit (pacing pulse and shock generation, signal filtering and analysis, data storage). The basic components of ICDs have not changed during the last decades. Initially, the pulse generator was a single-chamber device and placed in the abdominal region with epicardial patches requiring thoracotomy to implant the system. A significant improvement was the shift from epicardial defibrillation patches to endocardial defibrillation leads, which simplified the implantation procedure (Fig. 13.1). The dual-chamber ICDs were produced and represented thereafter. During the last decades, technology evolved from shock boxes to a sophisticated rhythm management devices. Defibrillation efficacy has been improved by invention of biphasic shock waveforms and by using the generator as one of the electrodes for defibrillation. Modern ICDs can perform a variety of sophisticated functions, including atrial and ventricular therapy, ATP, bradycardia pacing, biventricular pacing, electrogram storage, and diagnostics e.g. HF, burden of AF [16, 17].

The concept of the biventricular pacing (i.e. CRT) was introduced more than 20 years ago. CRT was developed as a technique to provide a synchronize pacing of right and left ventricles and reduce the morbidity and mortality of HF patients by improving the whole contractility of the left ventricle (LV) and ejection fraction of the left ventricle (LVEF).

Recently, subcutaneous implantable defibrillator (S-ICD) was introduced into the clinical practice. Both the generator and the lead of an S-ICD are implanted subcutaneously, and logically avoid of the use of endocardially placed leads [18]. Both the rationale and the scientific data regarding the CRT-Ds and S-ICDs will be discussed in details in this chapter.

A significant advance in the use of implantable devices (ICD, CRT-P/D) to monitor and treat HF patients has been performed during the last decade. Nowadays, ICDs are considered to be the standard therapy for patients at high risk for ventricular

Fig. 13.1 Original implantable cardioverter defibrillator pulse generator, on the *left*, and a modern device on the *right* (Gasparini and Nisam [17]. [16] Copyright 2016 by Springer)

tachyarrhythmias, both for primary and secondary prevention. The current state of art of the device therapy of HF patients will be discussed in details below in this chapter.

Current Tendencies in the Treatment of Heart Failure (Prevention of Sudden Cardiac Death): From Optimal Medical Therapy to the Idea of Implantable Cardioverter Defibrillators

The main guidelines focused on the diagnosis and treatment of HF, primary and secondary prevention of SCD are represented by the European Society of Cardiology, the American Heart Association and the American College of Cardiology [4, 19–21, 68].

The current management of HF targets the modification of the existent and the identified risk factors and elimination of their influence on the natural course of

disease, treating the main heart disease, improving the quality of life (QOL) and reducing the mortality, and including the following approaches: optimal medical therapy (OMT), device based therapy (ICD, CRT-P/D), LV assist devices (LVAD) and heart transplantation. Prevention of SCD among HF patients is the most challenging issue in the treatment of HF.

The main two causes of death among HF patients should be emphasized. More than half of HF associated deaths are due to ventricular tachyarrhythmias (ventricular tachycardia (VT), VF) and the rest is due to a progressive pump failure (progressive failure of cardiac function) [22].

Several studies have been performed to demonstrate the effect of OMT on the reduction of HF mortality. Among medications used for the treatment of HF only beta blockers has shown to have an impact on the reduction of HF mortality. The US Carvedilol trial has showed a 65 % reduction in mortality with carvedilol in patients with HF with systolic dysfunction (LVEF <35 %). Arrhythmia associated death had decreased from 3.8 to 1.7 % [23]. The CIBIS-II trial has demonstrated a significant reduction of arrhythmic mortality from 6.4 to 3.6 % with bisoprolol. All-cause mortality was reduced by 34 % [24]. The MERIT-HF study has showed a significant 41 % relative risk reduction of arrhythmia associated mortality with metoprolol [25]. The impact of carvedilol on the reduction of SCD among severe HF patients was checked in the COPERNICUS trial, which showed a significant reduction in SCD from 6.1 % in the placebo group to 3.9 % in the carvedilol group, all-cause mortality has significantly reduced by 35 % [26]. A meta-analysis of a randomized controlled trials of the role of beta-blockers in the prevention of SCD in HF patients were recently performed by Al-Gobari et al. 30 randomized controlled trials with the comparison of the use of beta-blockers vs. placebo/control for the prevention of SCD in HF patients were included. The total number of involved patients was 24,779. Beta-blockers were effective in the prevention of SCD (OR 0.69; 95 % CI, 0.62–0.77, $P < 0.00001$), cardiovascular death (OR 0.71; 95 % CI, 0.64–0.79, $P < 0.00001$) and all-cause mortality (OR 0.67; 95 % CI, 0.59–0.76, $P < 0.00001$). The results of the analysis have suggested that beta-blockers reduce the risk of SCD by 31 %, cardiovascular death by 29 % and all-cause mortality by 33 % [27].

The usefulness of amiodarone as an antiarrhythmic medication in the reduction of the incidence of SCD among HF patients was evaluated in several studies. A total of 1013 patients resuscitated from SCD or presenting with VT and/or VF patients were enrolled in the AVID study to compare the effectiveness of ICD versus antiarrhythmic drugs (mostly amiodarone). The primary endpoint of the study was overall mortality. A total of 45 % of the patients in the defibrillator group and 40 % of patient in antiarrhythmic drug-group had a HF at the time of inclusion to the study. ICD was superior to antiarrhythmic drugs for increasing overall survival among patients. Overall survival with an ICD was 89.3 % vs 82.3 % with an amiodarone at 1 year, 81.6 % vs 74.7 % at 2 years and 75.4 % vs 64.1 % at 3 years respectively ($p < 0.02$ %). The effect of an ICD was not significant in a patients with LVEF > 35 %, which is a very important point to emphasize [28]. Authors had concluded that the implantation of an ICD should be offered as a first-line therapy to survivors of SCD.

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) had a crucial role on the future understanding of the possible ways of the prevention of SCD

among HF patients, e.g. the role of antiarrhythmic drugs and ICDs [29]. The ability of amiodarone to decrease the mortality among HF patients and the primary prevention effect of ICDs especially among patients with non-ischemic cardiomyopathy were not clarified before. A total of 2521 consecutive patients with New York Heart Association (NYHA) class II-III HF (70 % class II, 52 % ischemic HF) and an impaired systolic function (LVEF < 35 %) of the LV (median LVEF 25 %) were randomized into three groups: conventional therapy plus amiodarone, conventional therapy plus placebo and conventional therapy plus a conservatively programmed, shock-only, single-lead ICD. The primary end point was death from any cause.

The median follow-up was 45.5 months. 244 (29 %) patients were died in the placebo group, 240 (28 %) and 182 (22 %) were died in the amiodarone and in the ICD group, respectively. There was no significant difference in the reduction of risk of SCD in amiodarone and placebo groups (HR 1.06; 97.5 %, 0.86–1.30; P = 0.53). ICD therapy was associated with a decreased risk of death of 23 % (HR 0.77; 97.5 %, 0.62–0.96; P = 0.007) and an absolute decrease in mortality of 7.2 % points after 5 years in the overall population.

Prevention of Sudden Cardiac Death Among Heart Failure Patients

As it was mentioned above the primary and secondary prevention of SCD in patients with HF is the greatest challenge in the management of HF patients.

The following concepts have to been clarified at this point. The term SCD is used when a congenital, or acquired, potentially fatal cardiac condition was known to be present during life; OR an autopsy has identified a cardiac or vascular anomaly as the probable cause of the event; OR no obvious extra-cardiac causes have been identified by post-mortem examination and therefore an arrhythmic event is a likely cause of death [21].

A primary prevention of SCD includes therapies to reduce the risk of SCD in individuals who are at risk of SCD but have not yet experienced an aborted cardiac arrest or life-threatening arrhythmias [21].

A secondary prevention of SCD comprises of therapies to reduce the risk of SCD in patients who have already experienced an aborted cardiac arrest or life-threatening arrhythmias [21].

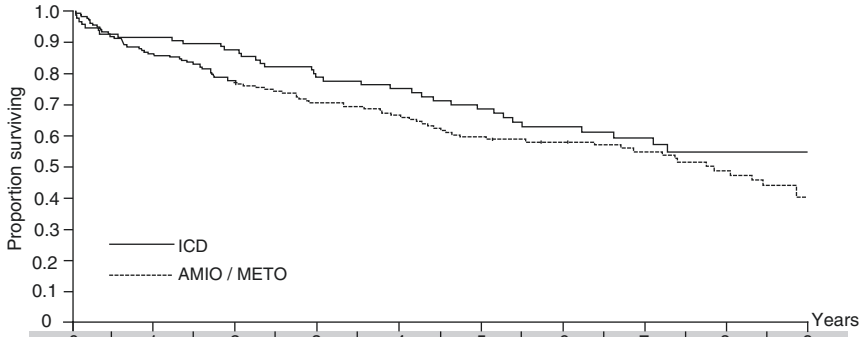
Secondary Prevention of Sudden Cardiac Death Among Heart Failure Patients

Several studies were performed at the beginning of the “ICD-era” with the intention to demonstrate the effectiveness of such a therapy in the reduction of mortality among survivors of SCD (secondary prevention).

One of the first studies which were performed among SCD survivors was the above mentioned AVID study [28]. Among SCD survivors (VT, VF) ICD was superior to an antiarrhythmic drugs for increasing overall survival among patients. It is important to emphasis one more time that the study showed that the effect of an ICD was not significant in a patients with LVEF > 35 %.

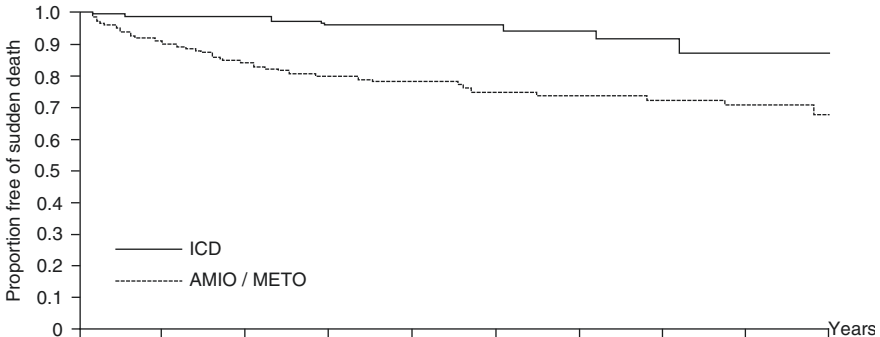
The next study which was performed among survivors of SCD was the Cardiac Arrest Study Hamburg (CASH) study [30], which was published in 2000. A prospective, multicenter, randomized comparison of ICD vs. antiarrhythmic drug therapy among survivors of cardiac arrest was performed. An inclusion criteria was a cardiac arrest secondary to documented sustained ventricular arrhythmias. Patients with cardiac arrest within 72 h of an acute myocardial infarction (MI), cardiac surgery, electrolyte abnormalities or pro-arrhythmic drug effects were excluded from the study. Included patients were randomized to ICD-group and antiarrhythmic drug group (amiodarone-, metoprolol- and propafenone-group). The primary end point of the study was all-cause mortality. The secondary end points were sudden death and recurrence of cardiac arrest at 2-year follow-up. All the patients included in the ICD-group had received an epicardial ICD until June 1991 and an endocardial ICD from July 1991. Appropriate functioning of the devices was proved by the pre-discharge DFT-test. The recruitment of patients was performed from 1987 to 1998. Assignment to propafenone was discontinued in 1992 due to a high prevalence of all-cause mortality among propafenone-group as compared with an ICD-group. The remained of included patients (n = 288) were randomized into ICD- (n = 99), metoprolol- (n = 97) and amiodarone-group (n = 92). The minimum follow-up was 2 years. The baseline parameters of the recruited patients were similar in an ICD- and antiarrhythmic drug-group (metoprolol + amiodarone). The mean LVEF of the recruited patients were higher compared to the patients included in the AVID study. Fifty-nine percent and 56 % of patients in the ICD-group and antiarrhythmic drug-group were in NYHA functional class II, respectively. During the mean follow-up of 57 ± 34 months the overall mortality rates were 36.4 % (CI 26.9–46.6 %) in the ICD-group and 44.4 % (CI 37.2–51.8 %) in the antiarrhtyhmic drug-group. Overall survival was non-significantly higher in the ICD-group compared to the antiarrhythmic drug-group. The overall mortality rates among metoprolol- and amiodarone –group was 45.4 % (CI 35.2 % to 55.8 %) and 43.5 % (CI 33.2 % to 54.2 %) respectively (P = 0.845).

The secondary analyses demonstrated that the overall sudden death rates were 13 % (CI 7.9–19.6 %) in the ICD-group and 33 % (CI 27.2–41.8 %) in the antiarrhythmic drug-group. The sudden death free survival was significantly higher in the ICD-group as compared to the antiarrhythmic drug-group [1-sided P = 0.005, HR 0.423 (97.5CI upper bound 0.721)]. The overall rates of nonfatal cardiac arrest were 11.1 % (CI 6.9–16.5 %) in the ICD-group and 19.5 % (CI 12.2–25.6 %) in the antiarrhythmic drug-group. In ICD patients, the percent reductions in all-cause mortality were 41.9, 22.8 and 24.7 % at years 1, 5 and 9 of follow-up. Kuck et al. had concluded that therapy with an ICD was associated with a non-significant 23 % reduction in all-cause mortality as compared to the treatment with metoprolol/amiodarone. The benefit of an ICD implantation as secondary prevention was more visible during the first 5 years after the index event (Figs. 13.2 and 13.3).



	0	1	2	3	4	5	6	7	8	9
ICD	99	91	82	68	61	50	36	29	15	9
AMIO/METO	189	161	142	115	90	79	64	51	34	22
% reduction in all-cause mortality of ICD ptd		41.9	39.3	28.4	27.7	22.8	11.4	9.1	10.6	24.7

Fig. 13.2 Long-term overall survival in ICD and drug arms. *AMIO* indicates amiodarone, *METO* metoprolol, *pts* patients. (Kuck et al. [30] Copyright 2016 by Springer)



	0	1	2	3	4	5	6	7	8	9
% reduction in sudden death of ICD pts		81.8	86.7	76.2	78.3	80.8	73.1	64.3	56.7	60.6

Fig. 13.3 Long-term survival free of sudden death in ICD and drug arms. *AMIO* indicates amiodarone, *METO* metoprolol, *pts* patients (Kuck et al. [30] Copyright 2016 by Springer)

The Canadian Implantable Defibrillator Study (CIDS) had similar design and have been performed in Canada. Six hundred and fifty nine resuscitated patients (with documented VF, sustained VT, unmonitored syncope) were included in the trial and were randomized in an ICD-group and an amiodarone-group [31]. During the 5-years of follow-up arrhythmic mortality was reduced by 33 % with an ICD therapy compared with amiodarone, which was not statistically significant. 50.5 %

of patients in an amiodarone group and 48.8 % of patients in an ICD group had a congestive heart failure.

Meta-analysis of the above mentioned AVID, CASH and CIDS secondary prevention trials was performed by Connolly et al. in 2000, which has demonstrated an overall reduction of arrhythmia induced mortality with ICD by 50 and 28 % relative reduction in death [32]. All three trials have demonstrated consistent results regarding the comparison of an ICD vs. amiodarone. A significant reduction in death from any cause with an ICD was demonstrated with these trials, with a summary hazard ration (ICD: amiodarone) of 0.72 (95 % confidence interval 0.60, 0.87; P = 0.0006). For the outcome of arrhythmic death, the hazard ratio was 0.50 (95 % confidence interval 0.37, 0.67; P < 0.0001). Survival was extended by a mean of 4.4 months by the ICD over a follow-up period of 6 years. Patients with an impaired systolic function of LV (LVEF ≤ 35 %) benefit more from an ICD implantation as compared with those with a better preserved systolic function of LV.

Consequently, based on these trials current guidelines suggest that "an ICD is recommended to reduce the risk of sudden cardiac death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing hemodynamic instability, and who are expected to survive for >1 year with good functional status" (Class of recommendation – I, Level of evidence – A) [4, 21, 68].

Primary Prevention of Sudden Cardiac Death Among Heart Failure Patients

According to the major guidelines on the management of HF and prevention of SCD ICD implantation is indicated for the primary prevention of SCD among HF patients who have an estimated life expectancy at least 1 year and more [4, 19–21, 68]. These recommendations are based on the major trials performed during the last decades.

ICD therapy was compared to amiodarone therapy in a patients with NYHA class II-III HF and LVEF < 35 % in the Sudden Cardiac Death in Heart Failure (SCD-HeFT) trial in improving 5-year survival [29]. The primary endpoint of the study was all-cause mortality. All the included patients were randomized into a placebo-, an amiodarone- and an ICD-shock only-group. ICD therapy was associated with a 23 % reduction of all-cause mortality as compared with placebo.

One of the earliest trials which has compared ICD therapy with an OMT was the Multicenter Automatic Defibrillator Implantation (MADIT) Trial [33]. A comparison of an ICD vs conventional medical therapy among high-risk patients was investigated. A total of 196 consecutive patients with ischemic cardiomyopathy, NYHA class I-III HF, LVEF ≤ 35 %, a documented episode of asymptomatic unsustained VT and inducible, non-suppressible ventricular tachyarrhythmia on electrophysiological study (EP study) were included in the study and randomized into an ICD-group (n = 95) and conventional medical therapy group (n = 101). The mean follow-up of the trial was 27 months. A total of 15 deaths (11 cardiac deaths) were

registered in the ICD-group as compared with the 39 deaths in the conventional therapy group (HR 0.46, 95 % CI, 0.26–0.82, P = 0.009). Antiarrhythmic therapy (amiodarone, beta-blockers, etc.) in the involved population were not associated with the improved survival. Hence, all-cause mortality was reduced by nearly 60 % over the 27-month of follow-up in the ICD-group.

The second Multicenter Automatic Defibrillator Implantation Trial (MADIT II trial) was conducted later and involved patients with ischemic cardiomyopathy and prior myocardial infarction (at least 1 month or more before inclusion in the study), LVEF < 30 %, NYHA class I-III HF (59 % of involved patients were in NYHA class II-III HF, patients with NYHA class IV HF were not included in the study) who were randomized in a 3:2 ratio to receive an ICD (n = 742) or a conventional medical therapy (n = 490). ICD implantation was associated with a 31 % relative risk reduction in mortality [34]. The most important aspect of the MADIT II trial which has to be emphasized is the fact that due to a very poor predictive value EP studies were not performed for risk stratification and current guidelines are focused on class of HF (NYHA) and LVEF.

According to the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [68], which has been published recently, an ICD implantation is indicated for the primary prevention of SCD among HF patients in the following settings:

1. An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA Class II-III), and an LVEF ≤ 35 % despite ≥3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status, and they have:
   - Ischemic heart disease (unless they have had an MI in the prior 40 days) – Class I, Level A.
   - Dilated cardiomyopathy – Class I, Level B.
2. ICD implantation is not recommended within 40 days of an MI as implantation at this time does not improve prognosis – Class III, Level A.
3. ICD therapy is not recommended in patients in NYHA Class IV with severe symptoms refractory to pharmacological therapy unless they are candidates for CRT, a ventricular assist device, or cardiac transplantation – Class III, Level C.
4. Patients should be carefully evaluated by an experienced cardiologist before generator replacement, because management goals and the patient's need and clinical status may have changed – Class IIa, Level B.
5. A wearable ICD may be considered for patients with HF who are at risk of sudden cardiac death for a limited period or as a bridge to an implanted device – Class IIb, Level C.

Unless patients after MI are at high risk of SCD due to life-threatening ventricular tachyarrhythmias, as it was mentioned above, ICD implantation is indicated at least 40 days after MI. The hypothesis that patients with an acute MI can benefit more in case of an early implantation of ICD was checked in randomized trials.

Patients at 6–40 days after an acute MI (LVEF ≤ 35 % and impaired cardiac autonomic function, manifested as depressed heart-rate variability or an elevated average 24-h heart rate on Holter monitoring) was involved in the Defibrillator in Acute Myocardial Infarction Trial [35] and randomized in an ICD therapy group (n = 332) and no ICD therapy group (n = 342). The primary endpoint of the study was mortality from any cause. The secondary endpoint was death from arrhythmia. No significant difference in overall mortality was observed during a follow-up period of 30 ± 13 months (62 vs 58 patients died in the ICD and in the control group, respectively; HR for death in the ICD group 1.08, 95 % CI, 0.76–1.55, 9 = 0.66). However, the prevalence of nonarrhythmic deaths were significantly higher in the ICD group as compared with the control group (50 vs 29, HR in the ICD group 1.75, 95 % CI, 1.11–2.76, p = 0.02).

A total of 898 consecutive patients at 5–31 days after an acute MI (LVEF ≤ 40 %, heart rate≥90 bpm on the first available electrocardiogram, nonsustained VT (≥150 bpm) during Holter monitoring or both criteria) were randomized in the ICD treatment group (n = 445) and medical therapy group (n = 453) in the study of Steinbeck et al. [36]. No significant difference in the overall mortality during a follow-up of 37 months was observed (116 vs 117 in the ICD and control group, respectively, p = 0.78). Though the prevalence of SCD in the ICD group was less than in the control group (27 vs. 60; HR, 0.55; 95 % CI, 0.31 to 1.00; p = 0.049) the number of non-SCD was higher in the ICD group (68 vs. 39, HR, 1.92; 95 % CI, 1.29 to 2.84; p = 0.001).

Hence, prophylactic ICD implantation early after an acute MI (≤40 days) among HF patients is not associated with a better survival.

Cardiac Dyssynchrony

Many of HF patients have a LV contraction dyssynchrony associated with conduction delay which led to the reduction of systolic function of LV [13]. The presence of the mentioned dyssynchrony worsens contraction of LV due to heterogeneity of LV contraction and reduces the LVEF which leds to the increasing of mortality among HF patients. According to the studies performed at the beginning of the noughties dyssynchrony is an independent risk factor of HF patients' mortality. According to some studies the prevalence of dyssynchrony among HF patients varies from 25 to 30 % based on the ECG and up to 60 % based on echocardiography [37, 38]. In the EuroHeart Failure survey 41 % of those patients who had an EF < 35 % had a QRS duration ≥ 120 ms. (7 % – RBBB, 34 % – LBBB or the intraventricular conduction delay) and 17 % had a QRS ≥ 150 ms. [39]. In the Italian Network on congestive heart failure (IN-CHF) 25 % of the involved patients had complete LBBB, 6 % had complete RBBB and 6 % had other forms of intraventricular conduction delay [40].

Two levels of cardiac dyssynchrony are present: electrical dyssynchrony, which is mainly represented by a prolonged PR interval and widened QRS complexes, and

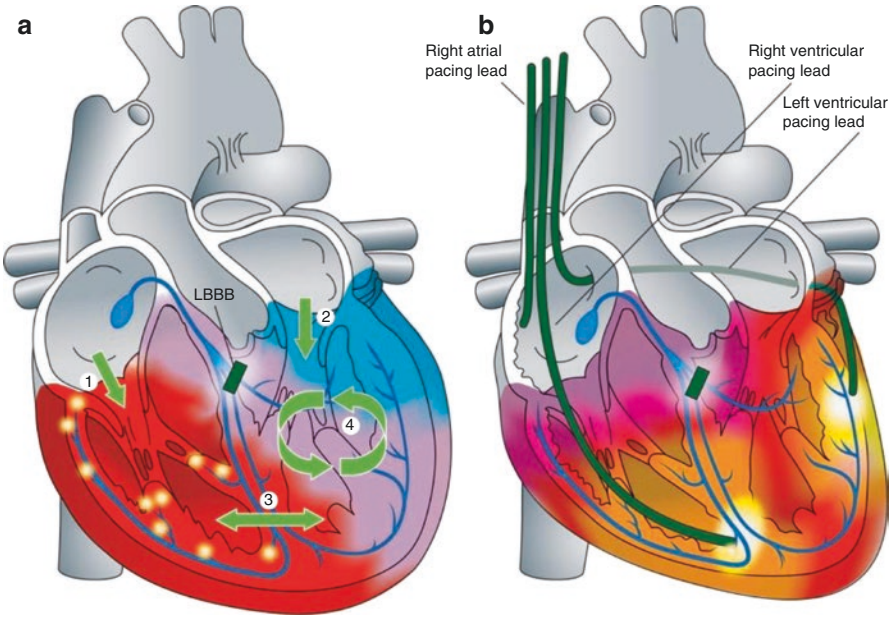


Fig. 13.4 Relation of the cardiac conduction system, mechanical dyssynchrony, and CRT. (**a**) Electrical disturbances induce mechanical dyssynchrony at different levels: atrioventricular (1, 2), interventricular (3), and intra left ventricular dyssynchrony (4), resulting in an impaired mechanical efficiency of the cardiac cycle and decreased cardiac output. LBBB has been indentified to have an effect most on mechanical dyssynchrony. Early electrical activation is marked in *red*, whereas late electrical activation is marked in *blue*. (**b**) A standard CRT system consists of a right atrial lead, a right ventricular lead (in CRT pacemaker systems) or a right ventricular defibrillation lead (in CRT defibrillator systems), and a left ventricular lead. The left ventricular lead is placed in a tributary of the coronary sinus on the left lateral or posterolateral wall. CRT works by biventricular pacing and subsequent resynchronisation of the impaired mechanical contraction patterns. *CRT* cardiac resynchronisation therapy. *LBBB* left bundle branch block (Holzmeister and Leclercq [41] Copyright 2016 by Springer)

mechanical dyssynchrony, which is the result of an electrical dyssynchrony and represented by interatrial dyssynchrony, AV dyssynchrony, interventricular dyssynchrony and intraventricular dyssynchrony.

Current main approaches to diagnose the dyssynchrony are ECG (based on the QRS widening), echocardiography and magnetic resonance imaging. 12-lead ECG is considered to be a basic tool, which can suggest the presence of a broad QRS complex. The above mentioned abnormal electrical activation, mainly represented by the prolonged PR interval and widened QRS complexes, which is mostly attributable to a left bundle branch block (LBBB), frequently detected in HF patients lead to the concept of biventricular pacing (i. e. synchronize pacing). HF patients with broad QRS complexes (which suggests LV contraction dyssynchrony) have a worse prognosis than those patients with a narrow QRS complexes. According to the MADIT CRT trial patients with an intraventricular conduction delay, RBBB and LBBB had 3-year mortality rates of 4 %, 7 % and 8 % respectively [42]. Figure 13.4

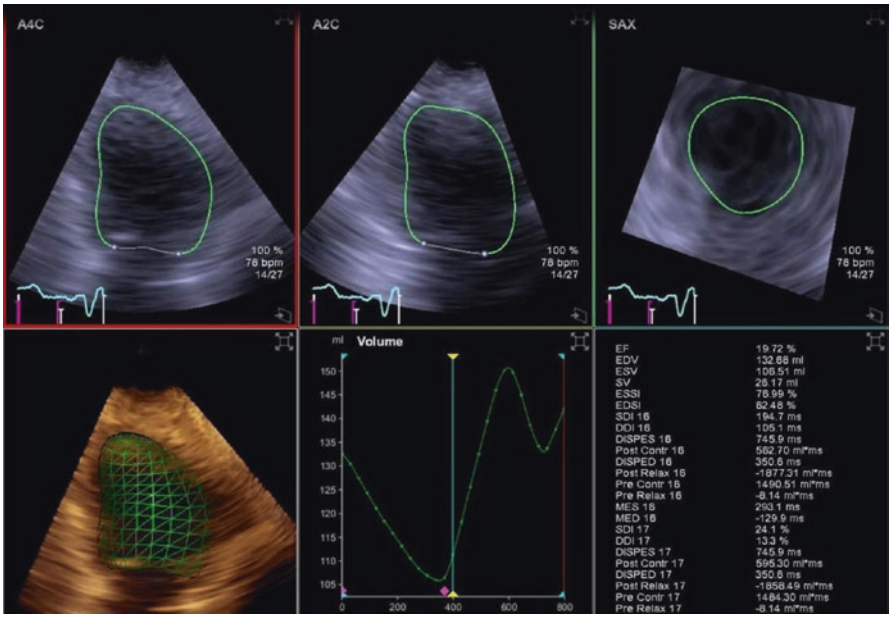


Fig. 13.5 3D echocardiography in a patient with LBBB. A substantial systolic dyssynchrony represented by SDI 17 = 24.1 %. LVEF = 20 %. *SDI 17* systolic dyssynchrony index of 17 segments of LV

represent the relation of the cardiac conduction system, mechanical dyssynchrony, and the concept of CRT [41].

One of the easy reproducible tools to visualize dyssynchrony is an echocardiography. During the last decades echocardiography evolved and developed as one of the modern and developed tools, which plays an important role in the diagnosis and risk stratification of HF patients. Currently, 3D echocardiography (along with M-mode, 2D echocardiography and tissue doppler imaging) plays an important role in the assessment of LV dyssynchrony and evaluation of the CRT response after an implantation [43]. Figure 13.5 shows a 3D transthoracic echocardiography of a patients with LBBB, QRS duration is 160 ms., no CAD, who reffered for CRT implantation.

The Concept of Biventricular Pacing: Cardiac Resynchronization Therapy

Cardiac resynchronization therapy was developed in the mid of ninetieth with the intention to improve the quality of life (QOL) and survival of HF patients by synchronizing LV contraction. The concepts of the short-term hemodynamic effects of a synchronize stimulation of right and left ventricles, or left ventricle alone were published in 1960–1970 by Vagnini et al., Tyers et al., Gibson et al. and De Teresa et al. [44].

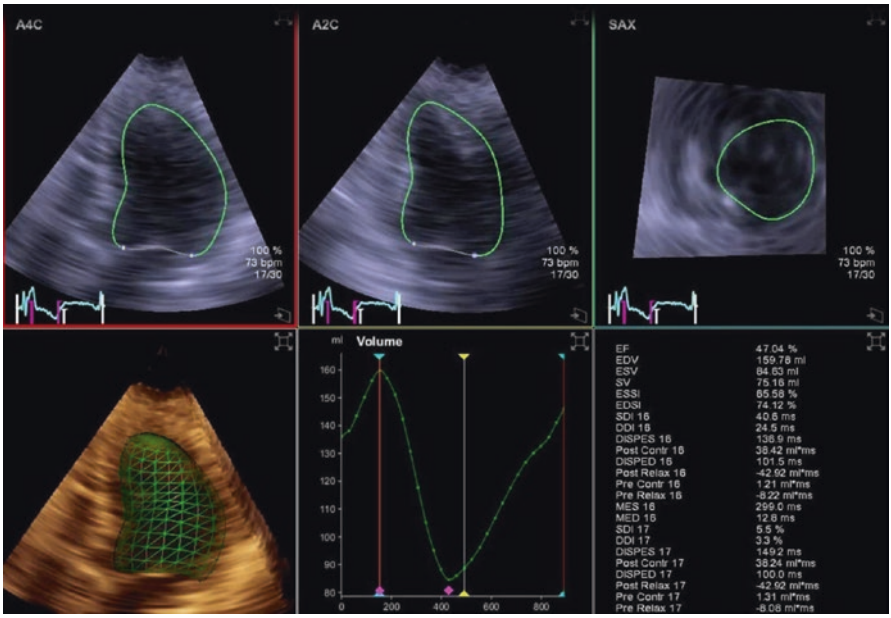


Fig. 13.6 3D transthoracic echocardiography after CRT implantation. A substantial improvement of systolic function of the LV (LVEF = 47 %) and synchronize contraction of the LV (SDI 17 = 5.5 %) was registered within a 24 h after implantation

The first steps of resynchronization were done in the early 90s. Gazeau et al. have performed an epicardial stimulation of LV in 1994 and the first endocardial stimulation of LV through the coronary sinus was done in 1996 by Bakker et al. in the Netherlands [45, 46]. In 2001 CRT was approved by the FDA of the USA to use in selected patients with HF. During the last two decades several studies have been performed and the substantial effect of CRT implantation on the improvement of the mechanical synchrony of LV, energetic efficiency and regional metabolism have been demonstrated. CRT-therapy aimed to influence on the most of the above mentioned mechanisms of cardiac dyssynchrony and led to the improvement of LV function, reduction of the functional mitral regurgitation and induction of LV reverse remodeling [47]. Figure 13.6 represents a 3D echocardiography of the same patient after CRT implantation, as was discussed above in Fig. 13.5 (<24 h after implantation). A substantial improvement of the LVEF (LVEF = 47 %) and narrowing of QRS complex (QRS = 130 ms) was registered with 24 h after implantation of a CRT.

According to the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [68] the following patients have an indication for CRT-therapy:

1. CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 ms and LBBB QRS morphology and with LVEF ≤ 35 % despite OMT in order to improve symptoms and reduce morbidity and mortality – Class I, Level A.

2. CRT should be considered for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 ms and non-LBBB QRS morphology and with LVEF ≤ 35 % despite OMT in order to improve symptoms and reduce morbidity and mortality – Class IIa, Level B.
3. CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 ms and LBBB QRS morphology and with LVEF ≤ 35 % despite OMT in order to improve symptoms and reduce morbidity and mortality – Class I, Level B.
4. CRT may be considered for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 ms and non-LBBB QRS morphology and with LVEF ≤ 35 % despite OMT in order to improve symptoms and reduce morbidity and mortality – Class IIb, Level B.
5. CRT rather than RV pacing is recommended for patients with HF with reduced EF regardless of NYHA class who have an indication for ventricular pacing and high degree AV block in order to reduce morbidity. This includes patients with AF – Class I, Level A.
6. CRT should be considered for patients with LVEF ≤ 35 % in NYHA Class III–IV despite OMT in order to improve symptoms and reduce morbidity and mortality, if they are in AF and have a QRS duration ≥130 ms provided a strategy to ensure biventricular capture is in place or the patient is expected to return to sinus rhythm – Class IIa, Level B.
7. Patients with HF with reduced EF who have received a conventional pacemaker or an ICD and subsequently develop worsening HF despite OMT and who have a high proportion of RV pacing may be considered for upgrade to CRT. This does not apply to patients with stable HF – Class IIb, Level B.
8. CRT is contraindicated in patients with a QRS duration < 130 ms – Class III, Level A.

Clinical benefits of biventricular pacing alone (CRT-P) and in combination with defibrillation function (CRT-D) were demonstrated in several studies during the last years. The MUSTIC trial (the Multisite Stimulation in Cardiomyopathy) was the first multi-center, randomized trial which has demonstrated the clinical benefits of CRT therapy. Sixty-seven patients with impaired LV function (LVEF ≤ 35 %), NYHA class III HF, sinus rhythm and QRS duration>150 ms. Were involved in the trial. The initial programming of the devices was <40 bpm backup pacing for the first 3 months, which was later reprogrammed to the biventricular pacing. Biventricular pacing was associated with significant improvement in 6-min. Walking test and QOL (58 % of patients reported an improvement in QOL with CRT), peak oxygen uptake and decreased hospitalizations [48]. A similar parameters were evaluated in the MIRACLE trial (the Multicentre InSync Randomised Clinical Evaluation trial) which consistent with a larger population of included patients (n = 453). [49].

The comparison of biventricular pacing alone (CRT-P) with optimal medical therapy was performed in the CARE-HF trial (the Cardiac Resynchronization in Heart Failure). Eight hundred and thirteen consecutive patients with LVEF ≤ 35 %,

NYHA class III–IV heart failure, QRS duration ≥120 ms. And echocardiography evidence of a ventricular dyssynchrony were included in the trial and randomized into optimal medical therapy and CRT-P groups [50]. A composite primary endpoint of the trial was all-cause mortality or hospitalization for a major cardiac event, and a secondary endpoint was all-cause mortality. Biventricular pacing was associated with a 26 % significant reduction in the composite primary endpoint at 29 months of follow-up. CARE-HF was the first trial which has demonstrated a significant improvement in survival of HF patients even with a biventricular pacing alone, without an ICD-function.

The COMPANION trial (the Comparison of Medical Therapy, Pacing and Defibrillation trail) has included 1520 patients (ischemic or nonischemic cardiomyopathies) with NYHA class III-IV HF, LVEF ≤ 35 % and QRS duration>120 ms, who were randomized in a 1:2:2 ration to receive optimal medical therapy, medical therapy with a CRT-P, and medical therapy with a CRT-D [51]. The primary composite end point of the trial was the time to death from or hospitalization for any cause. The risk of the combined end point of death from or hospitalization for HF was reduced by 34 % in the CRT-P group ($p < 0.002$) and by 40 % in the CRT-D group ($p < 0.001$). The risk of the secondary end point of death from any cause was decreased by 24 % ($p = 0.059$) in the CRT-P group and by 36 % in the CRT-D group ($p = 0.003$). This trial has demonstrated that in patients with advanced HF and a prolonged QRS interval CRT-D was superior to CRT-P in reduction the combined risk of death from any cause or first hospitalization.

The average CRT implantation rate in western and central Europe in 2011 was 140/per million population (CRT-D – 107 units, CRT-P – 33 units) [20].

The Concept and Rational of the Subcutaneous Implantable Defibrillators

Recently, an entirely subcutaneous implantable defibrillator has been developed. One of the reasons to develop a S-ICD-system was the relatively high risk of complications associated with the implantation of transvenous ICD lead(s) (such as pneumothorax, cardiac perforation, dislodgement, pericardial effusion and cardiac tamponade) and chronic transvenous lead complications (such as systemic infections, insulation breaches, conductor breaks), which will be discussed below [52].

The investigational device exemption (IDE) trial has demonstrated the safety and effectiveness of the S-ICD system for treatment of ventricular arrhythmias [53]. The results of the European Regulatory trial, the US Investigational Device Exemption trial and the EFFORTLESS registry demonstrated the safety and efficacy of the subcutaneous implantable defibrillators as a viable alternative for primary and secondary prevention of SCD in selected patients without an indication for bradycardia, resynchronization therapy or the need for ATP [29, 52, 53, 54]. A limitation of the S-ICD system is the absence of cardiac pacing [52, 54].

Peri- and Post-procedural Complications of Implantable Cardioverter Defibrillators Implantation

As it was mentioned in the introduction of this chapter the design and programming of ICDs have been significantly improved to maximize therapeutic benefit and minimize patients' discomfort [55]. Despite the fact that the implantation procedure has been simplified since the initial experience the implantation of transvenous ICD systems is still associated with a certain risk of complications (up to 4–11 % of new ICD implantations are associated with complications [56–60]) both peri- and post-procedurally (such as mechanical complications, infections, lead damages, malfunctions, etc.).

Peri-procedural adverse outcomes associated with an ICD implantation can be categorized as major or minor [61]. Major complications are lead dislodgement, pneumothorax, cardiac arrest, coronary venous dissection, pericardial tamponade, device-related infection, cardiac perforation, transient ischemic attack or stroke, myocardial infarction, urgent cardiac surgery, hemothorax, peripheral embolus and valve injury. Minor complications are hematoma, drug reaction, conduction block, set screw problem, venous obstruction and peripheral nerve injury.

According to the data published by Dewland et al. dual-chamber ICD implantation was associated with increased periprocedural complications and in-hospital mortality as compared with single-chamber ICDs [62]. 104,049 consecutive patients who received either a single-chamber or a dual-chamber ICD from January 1, 2006 to December 31, 2007 were enrolled to the National cardiovascular data Registry ICD Registry. Sixty-two percent of patients were received a dual-chamber ICD, the rest underwent a single-chamber ICD implantation. The frequency of periprocedural adverse events as well as the rate of an in-hospital mortality were higher in the dual-chamber ICD group (3.17 % vs 2.11 %. $p < 0.001$; 0.40 % vs. 0.23 %, $p < 0.001$, respectively).

The frequency and the risk of post-procedural complications (such as systemic infections, insulation breaches, conductor breaks) are relatively high as well. Removal of infected or damaged transvenous leads is associated with a substantial morbidity and mortality [63, 64]. According to the study of Kleemann et al. published in 2007 ICD lead dysfunction appeared among nearly 40 % of patients, during the 8-year follow-up period [65]. The systematic review by Persson et al. in 2014 demonstrated 2.8–3.6 % of adverse events from 35 independent cohorts reported in 53 articles. Post-hospitalization device-related complications rate varies from <0.1 to 6.4 % (2–49 months), lead-related complications varies from <0.1 to 3.9 % (1.5–40 months), infections 0.2–3.7 % (1.5–49 months) and thrombosis 0.2–2.9 % (1.5–49 months) [66].

Therefore, nowadays a transevenous endocardial lead is considered as a weak chain of the whole ICD-system.

Although ICD implantation prolongs life in patients at risk, it does not improve the quality of life (QOL) or symptoms of HF [67]. Given the fact that 2/3 to 3/4 of patients underwent ICD implantation never receive a therapeutic defibrillation but

the implantation of ICD is associated with the above mentioned peri- and post-procedural complications potential benefits and harms of the implantation procedure, as well as at least 1 year life expectancy of the recipient have to be thorough investigated before implantation.

Future Developments

Future development of ICDs will refer to both the generator and lead(s). Current generators are still big and cause discomfort for the vast majority of patients. The evolution of the generators have to go toward smaller and thinner devices with improved shape, extended longevity and improved remote monitoring system. Improvement of the sensing and detection, diagnostic algorithm and antitachycardia pacing has to be performed to decrease the number of appropriate and inappropriate shocks. Recently, quadripolar ICD leads were represented with a better productivity, as well as leads with hemodynamic sensors are already present in the systems of some manufacturers. These sensors will allow to continuously monitor hemodynamic values, such as pressure, volume, intracardiac impedance and improve follow-up of patients. The number of long-term complications associated with ICD leads are still high, which has to be improved with the new generation of leads and possibly new techniques for implantation.

Overall, the effect of an implantable cardioverter defibrillator therapy on the reduction of sudden cardiac death among heart failure patients is indisputable. During the last decades and based on the substantial number of randomized clinical trials ICDs became one of the most powerful lifesaving therapies in cardiology.

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Chapter 14
Cardiac Resynchronization Therapy

Michael Glikson and Stefan Bogdan

Introduction

Since for the first case by Cazeau in 1994 showing the beneficial effects of four-chamber pacing in a 54-year old dilated cardiomyopathy patient [1], cardiac resynchronization therapy (CRT) has come a long way. Targeting cardiac dyssynchrony correction, it has become a well-established treatment for symptomatic heart failure patients with severe left ventricular systolic dysfunction and wide QRS (>120 ms). Evidence from large randomized trials have shown the clinical (symptoms improvement; mortality reduction) as well as structural (left ventricular reverse remodeling with ejection fraction increase and mitral regurgitation reduction) benefits of CRT and represent the basis for current guidelines [2]. Unfortunately, not all patients with LV dysfunction and wide QRS respond to CRT. Understanding nonresponse and predicting response has to do with understanding the interrelationship between electrical and mechanical dyssynchrony. Current efforts focus on better patient selection and improving CRT delivery using clinical, electrocardiographic and imaging techniques.

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M. Dorobanţu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_14

Pathophysiology of Cardiac Dyssynchrony. Dyssynchrony Assessment

Cardiac mechanical dyssynchrony refers to a difference in the contraction/relaxation timing (lack of synchrony) between different areas of the heart, that usually occurs in the setting of electrical conduction disease (electrical dyssynchrony). Large differences in contraction timing can result in reduced cardiac efficiency and are correlated to heart failure [3]. Cardiac imaging and advanced echocardiography in particular play an important role in mechanical dyssynchrony assessment. Other imaging techniques, including cardiac magnetic resonance and radionuclide imaging, are under development for cardiac dyssynchrony evaluation.

There are three main types of dyssynchrony that can be corrected by CRT: atrioventricular, interventricular and intraventricular (Table 14.1).

Atrioventricular dyssynchrony occurs because of a loss of timing between atrial and ventricular contractions, in the presence of prolonged PR interval, QRS widening or both [4]. The hemodynamic consequence is an impairment of the left ventricular (LV) filling secondary to a shortening of the diastole. Using pulsed-wave Doppler echocardiography, atrioventricular dyssynchrony can be evaluated by measuring the LV filling time from transmitral flow recordings. In the presence of prolonged atrioventricular interval, the early (E wave) and late (A wave) diastolic waves are fused with a shortening of the ventricular filling time. A ratio of the LV filling time (ms)/ RR interval (ms) <40 % indicates atrioventricular dyssynchrony [4]. An opposite type of AV dyssynchrony may occur following pacemaker implantation, after programming a too short AV delay so that the atrial systole is truncated (resulting into one wave) [5, 6].

Inter-ventricular dyssynchrony occurs because of a delay between right ventricular and left ventricular contractions, in the setting of wide QRS. This delay affects cardiac output by creating paradoxical septal motion that reduces contraction efficacy. One of the first indexes used to assess inter-ventricular dyssynchrony was the inter-ventricular mechanical delay (IVMD), obtained by calculating the difference between aortic and pulmonary pre-ejection intervals (time from QRS onset to flow onset) with pulsed-wave Doppler echocardiography [4]. Using a cut-off value >40 ms for defining inter-ventricular dyssynchrony, the CARE-HF trial showed a correlation between IVMD and response to CRT [7].

Table 14.1 Cardiac dyssynchrony: types, setting, consequence

Dyssynchrony	Electric disease	Consequence
Atrioventricular	Prolonged PR and/or wide QRS	Diastolic impairment
Inter-ventricular	Wide QRS	Systolic impairment
Intra-ventricular LV	Wide QRS	Systolic and diastolic impairment Mitral regurgitation

Wide QRS QRS duration >120 ms, *LV* left ventricle

Intra-ventricular dyssynchrony of the left ventricle (LV dyssynchrony) occurs because of delayed contraction of certain LV segments (usually the postero-lateral wall that is last to contract while the inter-ventricular septum contracts first). This phenomenon is associated but not limited to the setting of prolonged QRS duration – typically left bundle branch block (LBBB). The difference in activation timing results in contraction delay, loss of contraction efficiency and reduced stroke volume. In the setting of prolonged LV contraction, while the atria relax and atrial pressure falls, the LV pressure might exceed the atrial pressure resulting in diastolic mitral regurgitation. Dis-coordinated papillary muscle function can also cause or further aggravate the mitral regurgitation. These dyssynchrony related changes promote adverse LV remodeling [8].

Imaging in Cardiac Resynchronization Therapy

Imaging in CRT is crucial and serves several roles – to select patients with predicted response, to help define the location for the LV lead at the best area of LV in order to maximize response, and to follow the response. Lead location is the most complex element, which combines identification of the latest contracting segment as well as localization of scars that should be avoided as pacing in a scar area is associated with poor response [9].

It is mainly LV dyssynchrony that has been shown in several milestone studies to be an independent predictor of response to CRT in HF patients following CRT. Many years ago Pitzalis et al. introduced a reliable, easy-to-use and reproducible M-mode echocardiography parameter for LV dyssynchrony measurement [10]. Using parasternal short-axis LV view, the operator measures the time difference between the maximal systolic inward movement of the septum and posterior wall resulting in the septal-to-posterior-wall-motion-delay (SPWMD). A SPWMD $\geq$130 ms is correlated with significant LV dyssynchrony [10]. This initial approach was limited due to the non-uniform pattern of contraction in different segments of the LV, and the limited imaging by M-mode. Several other echocardiographic parameters have since been used for LV dyssynchrony evaluation besides M-mode, including tissue Doppler imaging, speckle tracking that is commonly used as it is considered superior to conventional echo Doppler techniques [11] and more recently 3D echocardiography (Table 14.2). It is conceivable that a technique that includes scar imaging in addition to dyssynchrony in the same test has an advantage in site selection of the LV lead.

Special attention has been given recently to the assessment of rotational dyssynchrony. Left ventricular fibers have a helical configuration: right-hand orientation from the base toward the apex in the endocardial layers and left-hand orientation in the epicardial layers [20]. This spiral architecture of the cardiac fibers causes the LV to make a wringing motion as a result of the opposite rotation of the LV apex and base (counterclockwise and clockwise, respectively, when viewed from the LV apex) [21]. Twist, that is the difference in rotation between apex and base, contributes

Table 14.2 Echocardiographic measurement of intra-ventricular LV dyssynchrony

Parameter	Echo technique	Cut-off
Septal to posterior wall motion delay [10]	M-mode	≥130 ms
Septal flash	M-mode	Non quantifiable[a]
Apical rocking	2D apical 4 chambers	Non quantifiable[b]
Basal septal to lateral Ts delay [12]	Tissue Dopple imaging	≥60 ms
Max delay in Ts in 4 basal LV segments [13]	Tissue Doppler imaging	>65 ms
SD of Ts of 6 basal LV segments [14]	Tissue Doppler imaging	≥34.4 ms
Max delay in Ts in 12 basal and mid LV segments [15]	Tissue Doppler imaging	≥100 ms
SD of Ts in 12 basal and mid LV segments (Dyssynchrony Index; Yu index) [16]	Tissue Doppler imaging	≥32.6 ms
SD of time-to peak longitudinal strain in 12 basal and mid LV segments [17]	Tissue Doppler imaging	>60 ms
Antero-septal to posterior time to peak strain difference (radial strain) [18]	2D speckle tracking	≥130 ms
SD of time to minimum systolic volume of 16 LV segments (systolic dyssynchrony index) [19]	3D echocardiography	>5.6 %

Ts time-to-peak systolic velocity, *SD* standard deviation, *LV* left ventricular, *2D* two dimensional, *3D* three dimensional

[a]Septal flash = early septal systolic thickening and thinning resulting in a short inward motion of the septum

[b]Apical rocking = the initial septal systolic thickening that causes the apex to move septally is followed by delayed activation of lateral wall that pulls the apex laterally while stretching the septum, resulting in a typical motion pattern of the apex defined as "apical rocking"

to LV systolic function [22] and in patients with heart failure it has been shown to be reduced [23]. Two-dimensional speckle tracking can assess the LV rotational motion and has demonstrated that twist can be affected by right ventricular pacing (the experimental model of LBBB) [24, 25]. While LV twist is the net difference at isochronal time points between apex and base in the rotation angle along LV longitudinal axis, LV torsion represents the LV twist indexed to the distance between the LV apex and the LV base (LV length) [20, 21]. LV torsion can be assessed in a standardized way by using three-dimensional speckle tracking echocardiography [26]. The use of two-dimensional speckle tracking echocardiography has proven its clinical utility in the field of CRT [27].

With the advent of cardiac magnetic resonance (CMR), several CMR derived dyssynchrony parameters [28] – such as regional vector variance (RVV), cross-correlation delay, uniformity of strain, time to maximum strain and standard deviation of time to maximum strain, have been analyzed in the setting of HF with low left ventricular ejection fraction (LVEF) and wide QRS. Some, such as RVV, may provide an additive value for the prediction of response to CRT [29]. Cardiac magnetic resonance has the potential to become an alternative to echocardiography for assessing cardiac dyssynchrony. Image acquisition is less operator dependent and it has the advantages of high spatial resolution, highly reproducible wall motion tracking and the capability to assess LV scar, volumes, systolic function, velocity,

strain, and torsion [30]. Current limitation is the fact that MRI derived dyssynchrony parameters have been investigated only in small sample size population and cutoff values for derived indices have yet to be established. Also its use in patients with existing devices is limited by safety issues as well as by the quality of imaging that may be distorted by the device.

Phase analysis of gated single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) has been used for evaluating LV dyssynchrony using radionuclide imaging [31]. Phase analysis is based on the partial volume effect, which indicates that LV regional maximal counts in SPECT MPI images are proportional to the regional wall thickness. Phase analysis approximates the variation of regional maximal counts over the cardiac cycle with the first Fourier harmonic function to measure the onset of mechanical contraction [31]. Quantitative gated SPECT-derived phased analysis on gated myocardial perfusion SPECT was able to detect left ventricular dyssynchrony (strong correlation with tissue Doppler imaging dyssynchrony parameters) and was able to accurately predict response to CRT [32]. Phase analysis of SPECT MPI has several advantages over other imaging techniques such as automated calculation, better reproducibility, and the ability to simultaneously assess myocardial scar location and severity for CRT optimization. The limitations include reduced availability and the small number of centers with clinical experience on relatively small sample size populations [30].

Clinical Evidence in Cardiac Resynchronization Therapy and Current Guidelines.

Randomized multi-center trials have provided solid evidence concerning the benefits of CRT in heart failure treatment.

The initial trials including limited numbers of severe HF failure patients (NYHA III-IV; QRS duration ≥150 ms; LVEF ≤35 %) only showed symptomatic benefit [33, 34]. In 2004, COMPANION was the first randomized trial to show a survival benefit following CRT in HF patients [35]. It included 1520 HF patients, NYHA class III-IV with QRS ≥ 120 ms and LVEF ≤35 %, that were randomized to either CRT or optimal medical treatment (OMT). Patients with pacemaker CRT (CRT-P) had the risk of combined end point of death or hospitalization for HF reduced by 34 % ($p < 0.002$), while in those with defibrillator CRT (CRT-D) the risk was reduced by 40 % ($p < 0.001$). These results were confirmed a year later by the CARE-HF trial [7].

The COMPANION and CARE-HF trials were followed by three cornerstone trials addressing less severe HF patients (NYHA class I-II), with low LVEF and wide QRS: the REVERSE [36], RAFT [37] and MADIT-CRT trials [38].

The REVERSE trial demonstrated in 610 patients with NYHA class I or II HF, wide QRS ≥ 120 ms and low LVEF ≤40 %, that CRT in combination with OMT (±defibrillator) reduces the risk for HF hospitalization and improves ventricular structure (LV end systolic volume reduction), with no effect however on mortality [36].

The RAFT trial randomized 1798 patients suffering from NYHA class II-III HF with wide or paced QRS and LVEF ≤30 %, to CRT with defibrillator (CRT-D) versus implantable cardioverter defibrillator alone (ICD). The trial showed a significant mortality reduction of 25 % ($p = 0.003$) and a reduction of 32 % for HF hospitalization ($p < 0.001$) in the CRT group, at the cost of more peri-procedural adverse events [37].

The MADIT-CRT trial included 1820 patients with NYHA class I-II HF, wide QRS ≥ 130 ms and reduced LVEF ≤ 30 %, that were randomized into CRT-D versus ICD alone. The initial results, published in 2009, showed, after an average follow-up of 2.4 years, a significant 41 % reduction in the risk of HF events ($p = 0.001$), a finding primarily evident in a pre-specified subgroup of patients with a QRS ≥ 150 ms. CRT was also associated with a significant reduction in LV volumes and LVEF improvement, with no influence however on mortality [38].

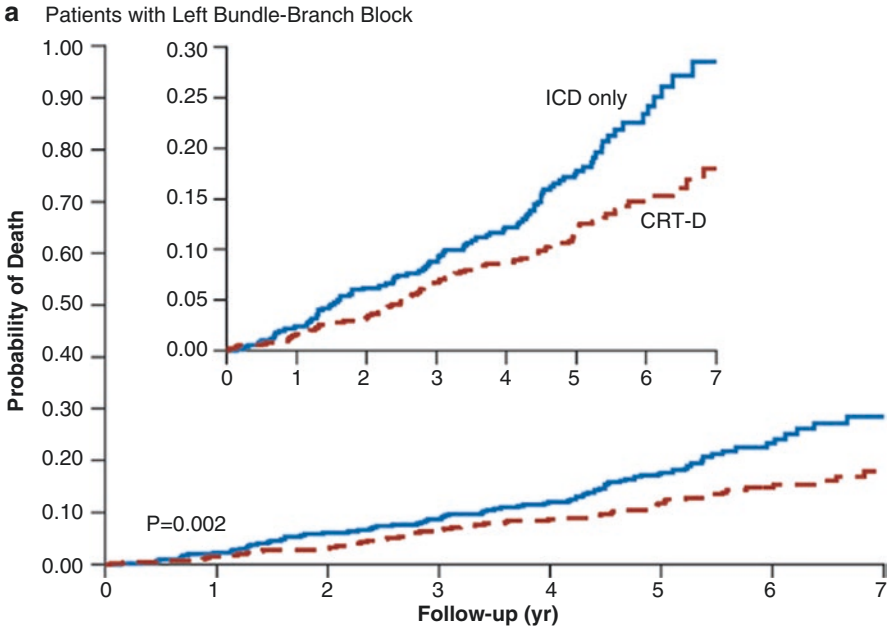
Recently, in 2014, the long-term follow-up of the MADIT-CRT trial has been published. At 7 years of follow-up, among the 1818 patients enrolled in the post-trial registries, CRT-D was associated with significant mortality reduction in LBBB patients (hazard ratio (HR): 0.59; 95 % confidence interval (CI) 0.43–0.80; $p < 0.001$). In contrast, CRT-D was not associated with any clinical benefit, and proved potentially harmful in patients without LBBB (HR: 1.57; 95% CI 1.03–2.39; $p = 0.04$) (Fig. 14.1) [39].

While all the main randomized trials addressed the issue of mechanical dyssynchrony correction in the presence of electrical dyssynchrony (defined mainly as wide QRS of at least 120 ms), the EchoCRT trial looked into the potential benefit of CRT in HF patients with narrow QRS. The trial enrolled 809 patients suffering for NYHA class III-IV HF, with narrow QRS <130 ms and low LVEF ≤ 35 %, in whom there was echocardiographic evidence of LV dyssynchrony (defined using color-coded tissue Doppler imaging as an opposing-wall delay in the peak systolic velocity of 80 ms or more in apical four-chamber or apical long-axis views, or by means of speckle-tracking radial strain as a delay in the anteroseptal-to-posterior wall of 130 ms or more in the mid-left ventricular short-axis view). All patients had a CRT device implanted and were randomized to have CRT capability turned on or off. After a mean follow-up of 19 months, the trial was prematurely stopped because of increased mortality in the CRT ON group (11.1 % vs. 6.4 %; HR: 1.81; 95 % CI 1.11–2.93; $p = 0.02$) [40].

The EchoCRT trial demonstrated that in HF patients with narrow QRS <130 ms, CRT does not reduce the rate of death or HF hospitalization and may increase mortality.

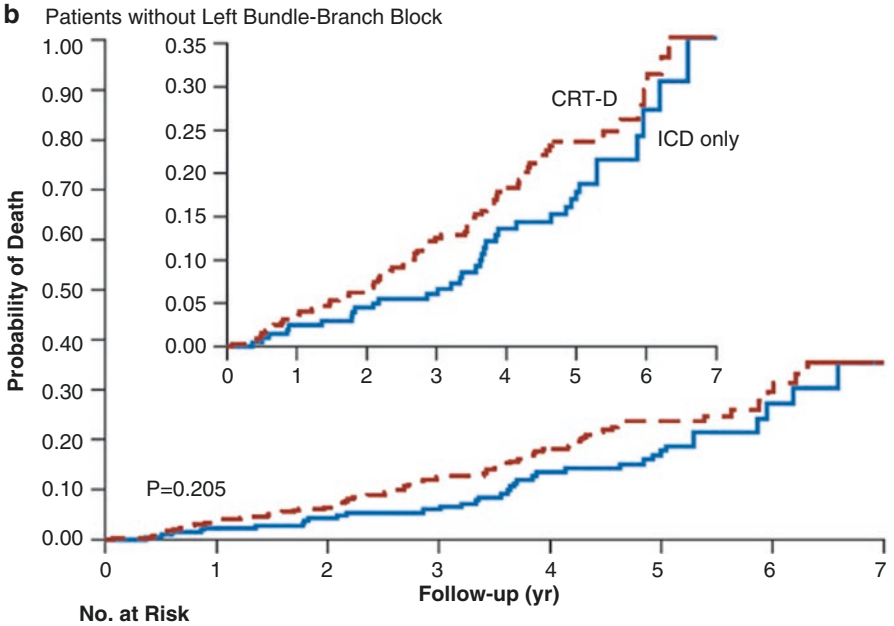
All the major evidence regarding CRT have been integrated into recently updated guidelines, where CRT is recommended in HF patients (NYHA class II-IV) with wide QRS ≥ 130 ms and reduced LVEF ≤ 35 % (Table 14.3) [41]. The American Guidelines dating 2012 are similar to the European ones from 2013, still retaining a

Fig. 14.1 Kaplan–Meier Estimates of the Cumulative Probability of Death from Any Cause among Patients with and Those without Left Bundle-Branch Block. *CRT-D* denotes cardiac-resynchronization therapy with defibrillator, *ICD* implantable cardioverter–defibrillator. The insets show the same data on an enlarged y axis (Goldenberg et al. from the long term follow-up of the MADIT-CRT trial [39])



No. at Risk

ICD only	520	488	463	40	326	254	94	41
CRT-D	761	734	714	636	527	425	157	70



No. at Risk

ICD only	209	197	189	156	115	95	24	10
CRT-D	328	312	292	240	182	136	39	13

CRT indication for QRS between 120 and 130 ms, with only a class IIa recommendation for LBBB 120–149 ms (as opposed to class I in the European guidelines) [2, 42].

Right ventricular apical pacing has been shown to have deleterious effects on LV systolic function, as it is associated with a delayed electrical LV activation, with consequences similar (but not identical) to that seen with LBBB (LV dyssynchrony with reduced LVEF and mitral regurgitation). Clinical consequences include increased risk for atrial fibrillation, HF hospitalization and death [43–45], especially in the setting of pre-existing HF and LV systolic dysfunction (below 40 %) [45].

The BLOCK-HF trial randomized 691 patients with NYHA class I – III HF, LVEF ≤ 50 % and an indication for bradycardia pacing to standard right ventricular pacing or biventricular pacing. The study has shown that patients receiving biventricular pacing had a lower incidence of primary outcome (urgent care visit for HF; death from any cause; progression of HF, defined as significant increase of left ventricular end-systolic volume index). The BLOCK-HF trial supports the use of CRT over standard right ventricular pacing in HF patients with LV systolic dysfunction and atrioventricular block requiring ventricular pacing [46].

Therefore, for patients with an indication for bradycardia pacing, in whom the percentage of ventricular pacing is expected to be high, in the presence of reduced LVEF (although debatable – usually below 40 %), de novo CRT implantation should be considered. In patients with ventricular pacing who develop HF and left ventricular systolic dysfunction (LVEF < 35 %), upgrade to CRT is indicated, as the benefit has been demonstrated by us and other studies [41, 47].

Table 14.3 The 2016 updated indications for cardiac resynchronization therapy in HF patients [41]

Patients characteristics	Rhythm	QRS morph.	QRS dur. (ms)	Class	Evid.
Ambulatory NYHA II-IV LVEF ≤ 35 %	Sinus	LBBB	>150 ms	I	A
			130–150 ms	I	B
		Non-LBBB	>150 ms	IIa	B
			130–150 ms	IIb	B
HF patients	Sinus	Regardless	<130 ms	III	A
HF patients (regardless NYHA) High degree AV block Reduced LVEF[a]	Sinus/AF	Regardless	Regardless	I	A
Worsening HF Previous PM/ICD High proportion of RV pacing Reduced LVEF[a]	Sinus/AF	RV pacing	(Wide)	IIb	B
NYHA III-IV LVEF≤35 %	AF	Regardless	≥130	IIa	B

AF atrial fibrillation, *HF* heart failure, *ICD* implantable cardioverter defibrillator, *LVEF* left ventricular ejection fraction, *LBBB* left bundle branch block, *NYHA* New York Heart Association heart failure class, *PM* pacemaker

[a]The 2016 guidelines do not define a clear cut-off for reduced LVEF in this scenario (usually considered <40 %)

Most patients included in large CRT randomized trials were in sinus rhythm. In one prospective study for HF patients with permanent AF, reduced LVEF ≤ 35 % and wide QRS > 120 ms, the per-protocol analysis including patients with biventricular pacing percentage >85 % showed a slight but significant symptomatic improvement at 6 months and 1 year follow-up [48]. A meta-analysis by Wilton et al. that included 7495 CRT recipients, 25 % with atrial fibrillation, from 23 observational studies, with a mean follow-up of 33 months, demonstrated an attenuated improvement of symptoms and LV end systolic volume, in the presence of AF, but not for the LVEF [49]. Current guidelines recommend CRT for AF patients with ambulatory NYHA class III-IV, wide QRS ≥ 130 ms and reduced LVEF ≤ 35 %, provided a high percentage a biventricular pacing (ideally 100 %) can be achieved – a target for which atrioventricular junction ablation should be taken into consideration [41].

Response to CRT: Patient Selection and Improving CRT Delivery

Response to CRT can be evaluated from a clinical and structural perspective (Table 14.4), using individual or composite parameters (such as "functional response" [50]).

Depending upon the definition of response, the rate of non-response to CRT varies between 20 and 40 % [51]. Patient's characteristics (underlying heart disease, comorbidities and arrhythmias; type and severity of conduction disorder; presence and degree of dyssynchrony; presence and extent of scar tissue; functional myocardial reserve) as well as CRT related aspects (electrical and anatomical positioning of LV lead; programming mode and percentage of effective bi-ventricular pacing) have been shown to influence the response to CRT [9, 51–54].

Diagnosing dyssynchrony is crucial for patient selection in view of successful cardiac resynchronization therapy. Despite remarkable cardiac imaging advancements in the evaluation and understanding of mechanical dyssynchrony, electrical dyssynchrony (i.e.: wide QRS) remains the guidelines criterion for CRT recommendation.

Table 14.4 Response to cardiac resynchronization therapy evaluation

Clinical		Structural	
Parameter	***Responder***	***Parameter***	***Responder***
NYHA	Reduction ≥1 class	LVEF	Absolute increase ≥5–6 %
6MWT	Increase ≥10–20 %	LVESV	Decrease ≥10–15 %
VO_2 max	Increase ≥10–15 %	Mitral regurgitation reduction	
Hospitalization rate	Decrease >25–30 %		
QOL	Decrease ≥8–10 points		

6MWT 6-minute walk test, *LVEF* left ventricular ejection fraction, *LVESV* left ventricular end-systolic volume, *NYHA* New York Heart Association heart failure class, *QOL* quality of life questionnaire, *VO_2 max* maximal oxygen consumption

The role of LV dyssynchrony assessment to predict response in CRT patients remains controversial to date. The PROSPECT trial investigated the predictive value of several echocardiographic dyssynchrony parameters (Doppler, M-mode, tissue Doppler imaging and delayed longitudinal contraction) on LV reverse remodeling and a composite clinical score. The conclusion was that given the modest sensitivity and specificity in this multicenter setting despite training and central analysis, no single echocardiographic measure of dyssynchrony may be recommended to improve patient selection for CRT beyond current guidelines [53]. More recently, the EchoCRT trial has shown that mechanical dyssynchrony detected by echocardiography is not a good target for CRT correction, in the absence of electrical dyssynchrony (i.e.: QRS < 130 ms) [40]. Still, other trials have shown that the amount of LV dyssynchrony at baseline and the remainder of LV dyssynchrony following CRT are correlated with clinical outcomes and response to CRT [10, 55].

Interestingly, the recently published PREDICT-CRT trial by Stankovic et al. has shown that the presence of apical rocking and septal flash – two subjectively measured echocardiographic dyssynchrony parameters (Table 14.2), is associated with more favorable long-term survival after CRT. Both apical rocking and septal flash were also indicators of an effective therapy [56]. Current guidelines recommend the use of echocardiography only for CRT optimization in case of non-response, but the results of PREDICT-CRT may impact the use of echo for patient selection in the future.

The type of electric disease is important for CRT response. LBBB morphology and a QRS duration >150 ms are associated with the best response following CRT. The question remains in patients with wide QRS of right bundle branch (RBBB) or intraventricular conduction delay (IVCD) morphology. The long-term MADIT-CRT follow-up has shown the absence of mortality benefit of CRT-D versus ICD alone in mild-to-moderate HF with reduced LVEF ≤ 30 %, who presented with RBBB or IVCD at baseline [39] (Fig. 14.1, Section B). Specific subgroup analysis from MADIT-CRT demonstrated that the use of CRT-D in non-LBBB patients with prolonged PR ≥230 ms was associated with a significant 73 % reduction in the risk of HF/death (HE: 0.27; 95 % CI 0.13–0.57; P < 0.001) and 81 % reduction in the risk of all-cause-mortality (HR: 0.19; 95 % CI 0.13–0.57; P < 0.001). At the same time, CRT-D use in non-LBBB patients with normal PR <230 ms was associated with increased risk of HF/death [57]. In the absence of prolonged PR, pure RBBB morphology should probably disqualify a patient for CRT. The Canadian Guidelines already consider RBBB with 120–150 ms duration not to be an indication for CRT [58], while European guidelines are more permissive, giving it a IIb recommendation [2].

The underlying heart condition and co-morbidities influence the overall prognostic and response to CRT. Although LV reverse remodeling after CRT is not affected by the duration of HF, clinical outcomes are better in patients implanted earlier in their disease course [59]. Atrial fibrillation, by comparison to sinus rhythm, is associated with increased risk of non-response to CRT (34.5 % vs 26.7 %; pooled relative risk 1.32; 95 % CI 1.12–1.55; P = 0.001), as demonstrated by Wilton's

meta-analysis [49]. In ischemic heart disease the benefit of CRT exists but is attenuated by comparison to non-ischemic heart disease, as shown in the MIRACLE trial [60]. Focal scar burden detected by late-Gadolinium enhancement on cardiac magnetic resonance was shown to correlate with poorer CRT response [61] as did lead localization in scar areas. Co-morbidities such as renal failure may also affect CRT. Interestingly, we have recently shown that functional response to CRT at 1 year did not differ significantly between patients with or without chronic kidney disease and was shown to be an independent predictor of improved long-term survival in patients with renal dysfunction (eGFR <60 ml/min/1.73m^2) [50]. Although data regarding CRT response in severe renal failure patients is scarce, we have recently shown that dialysis does not significantly modify the adverse outcomes associated with severe renal dysfunction (eGFR < 30 ml/min/1.73 m^2) following ICD/CRT-D implantation [62].

In order to ensure CRT response, *optimal LV lead placement is essential*. Ideally, it should be placed in the utmost late contracting segment of the left ventricle [63]. The area of delayed contraction can be previously detected by using echocardiography (tissue Doppler imaging and two-dimensional speckle tracking being considered the most sensitive) [63, 64]. Cardiac magnetic resonance and SPECT MPI may also detect it, with the advantage of offering supplemental information concerning its viability.

Reaching the target area for the LV lead is largely dependent upon the venous anatomy. Non-invasive pre-procedural visualization of the cardiac venous system can be performed using 64-slice computed tomography, which may offer important information concerning the existence of a potential target vein [65].

Hybrid methods for defining venous and myocardial anatomy are under development. Recently, a tool kit has been developed to reconstruct the three-dimensional LV venous anatomy from dual-view fluoroscopic venograms and to fuse it with LV epicardial surface on SPECT myocardial perfusion images. It is technically accurate for guiding LV lead placement by the 17-segment model and is feasible for clinical use in the catheterization laboratory [66].

Sometimes the target vein is difficult to access due to tortuosity or stenosis. For overcoming anatomical obstacles, the operator has now several tools and techniques, including telescopic delivering systems [67], performing venoplasty and the use of Lasso snaring techniques [68]. Once the target vein has been reached, electrical problems can arise such as local high pacing thresholds or phrenic capture. Currently, the introduction of quadripolar LV leads has significantly reduced these issues (Fig. 14.2) [69, 70]. Furthermore, the possibility to pace from multiple sites from the quadripolar LV lead has improved response to CRT [71]. When the target vein is unreachable or the patient has no target vein, the LV lead can still be implanted either using a transeptal approach [72] or surgically [73]. Finally, the LV lead should not be placed in an apical position but left in a basal or mid-ventricular segment [74].

Following implantation, in order to deliver optimal cardiac resynchronization therapy, the device has to be programmed in order to reach an ideal of 100 % biventricular pacing [75]. Further efforts should be performed in order to maxi-

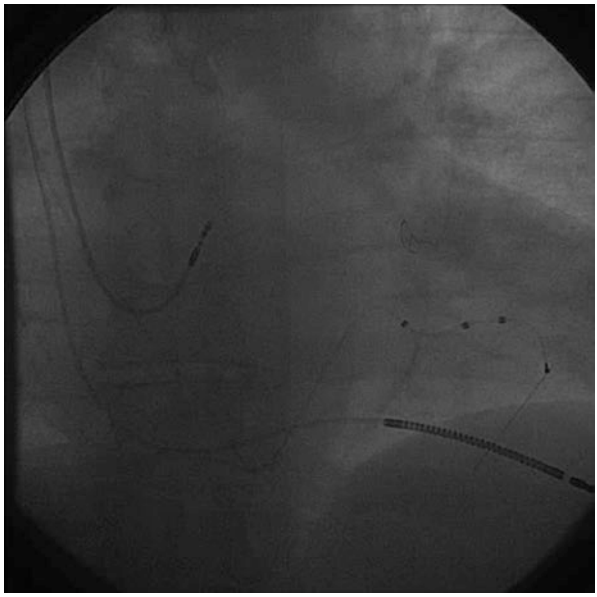


Fig. 14.2 A CRT-D system using a quadripolar LV lead

mize the percentage of biventricular pacing (very strict AF rate control – including atrio-ventricular node ablation if needed; ventricular premature beats elimination [76]).

Thus, preventing non-response should include:

- Prior dyssynchrony documentation and myocardial scar burden assessment
- Optimal LV lead positioning (preferably quadripolar lead)
- Obtaining consistent biventricular pacing (as close to 100 % of the time as possible)

In case of non-response, a protocol-driven approach for CRT optimization involving HF physician, electrophysiologist, and focused echocardiography has been shown to improve response rates [77].

Conclusion

Cardiac resynchronization therapy has become part of the standard of care for heart failure patients with reduced left ventricular ejection fraction and wide QRS. Despite its role in evaluating and understanding cardiac dyssynchrony, echocardiography was unable to top the classic ECG criteria (QRS morphology and duration) for patient selection. Future imaging techniques, such as cardiac magnetic resonance or SPECT myocardial perfusion imaging may provide better dyssynchrony assessment. Improved technology and better knowledge concerning therapy optimization will most likely improve CRT response in the near future.

Future Directions

- Improved dyssynchrony and myocardial scar assessment (3D echo; CMR; SPECT MPI)
- Better CRT delivery (quadripolar LV lead; multi-site LV pacing)
- Alternative biventricular pacing for non-responders (LV endocardial pacing)

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Chapter 15
Mechanical Circulatory Support

Liviu Klein and Lucian Dorobanțu

Introduction and Epidemiology

Heart failure incidence and prevalence are increasing at staggering levels, fueled by the success in treating acute myocardial infarction with primary angioplasty and by the overall marked increase in life expectancy, with a significant increase in the elderly population. In the United States, 5.8 million patients have heart failure, with a similar number in Western Europe [1, 2]. The incidence in the United States is 650,000 new cases annually, with more than 300,000 deaths/year being attributed to heart failure, and with an annual cost to manage these patients estimated at over $30 billion [1]. Close to 40 % of the heart failure patients have heart failure with reduced ejection fraction, and 10 % of these patients have advanced (end stage) disease, yielding an estimated cohort of approximately 200,000 patients who have a high 1-year mortality (over 30 %) and can benefit of advanced therapies such as heart transplantation or ventricular assist devices [1, 2].

The number of heart transplants performed worldwide is limited due to donor availability. This number has not increased in the past decade, with only about 2300 adult heart transplants being performed annually in the United States, and about 1200 in Europe [3–5]. Statistics from Eurotransplant have shown that the percentage of heart transplant candidates receiving a graft at the end of every year has decreased from 63 % in 2006 to 53 % in 2015, highlighting the lack of organs as main reason diminishing the clinical benefit of heart transplantation [5], and the need for mechanical alternatives for improving survival in this populations. As

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M. Dorobanțu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_15

result, the number of recipients bridged to transplant with ventricular assist devices has increased dramatically over the last decade; in 2013, 48 % of adult recipients in the United States were bridged with ventricular assist devices, compared to only 19 % in 2000 [4]. Moreover, the majority of these patients waited for over 2 years on mechanical support before receiving a heart transplant, with the waiting time poised to increase should the new heart allocation system be implemented [6].

The clinical profile of the advanced heart failure patients includes several of the following characteristics despite optimal medical and electrical therapies: (1) severe symptoms with New York Heart Association (NYHA) functional class III or IV, continuously for at least 2 months; (2) severe impairment of functional capacity demonstrated by either inability to exercise, a 6-min walk distance below 300 m, or a peak oxygen consumption below 12–14 ml/kg/min; (3) recurrent episodes of hospitalization with signs of fluid retention and/or peripheral hypoperfusion; (4) left ventricular ejection fraction below 25–30 %; (5) high left and/or right ventricular filling pressures with low cardiac output at cardiac catheterization; and (6) evidence of systemic organ injury, in particular renal and hepatic dysfunctions (elevated blood urea nitrogen, creatinine and bilirubin levels) [2, 7]. In our center we emphasize to the treating cardiologists that any two or more of these findings should prompt referral to our heart failure program for consideration of advanced therapies.

In order to further refine the prognosis and the risk of surgical intervention in advanced heart failure patients, the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) scale assigns patients into seven levels according to their hemodynamic profile and functional capacity (Table 15.1) [8]. Based on this risk profile, the time frame for intervention should be within hours (profile 1) or days (profile 2), or more elective such as weeks to months (profiles 3–6). During the first decade of modern circulatory support (2000–2010) the majority of patients implanted with durable ventricular assist devices were profiles 1 (40–50 % of patients) or 2 (25–35 % of patients) and, as consequence, the long-term survival was marginal [8]. Most of the mortality occurred during the initial hospitalization for assist device surgery, closely related to the degree of organ compromise and urgency at the time of implantation, which might have been associated with irreversible organ dysfunction.

These observations have led the heart failure community to begin using temporary (acute) mechanical circulatory support devices in order to stabilize high-risk patients (profiles 1–2) and downshift the risks of a durable assist devices implant into defined populations with lower post-operative morbidity (e.g. profiles 3–4) leading to better survival. Indeed, the most recent data from INTERMACS have shown that this strategy yields 80 % 1-year and 48 % 5-year survival in the current era [9], starting to approach the survival after heart transplantation in individuals older than 60 years of age (87 % 1-year and 69 % 5-year survival) [10]. Finally, the results from the recently completed Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients (ROADMAP) trial have shown that in carefully selected profile 4–7

Table 15.1 Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) clinical profiles

Profile 1	Critical Cardiogenic Shock ("crash and burn")	Patients with life-threatening hypotension despite rapidly escalating inotropic support, critical organ hypoperfusion, often confirmed by worsening acidosis and/or lactate levels
Profile 2	Progressive Decline ("sliding on inotropes")	Patient with declining function despite intravenous inotropic support; may be manifested by worsening renal function, nutritional depletion, or inability to restore volume balance. Also describes declining status in patients unable to tolerate inotropic therapy
Profile 3	Stable but Inotrope Dependent ("dependent stability")	Patient with stable blood pressure, organ function, nutrition, and symptoms on continuous intravenous inotropic support (or a temporary circulatory support device or both), but demonstrating repeated failure to wean from support because of recurrent symptomatic hypotension or renal dysfunction
Profile 4	Resting Symptoms ("frequent flyer")	Patient can be stabilized close to normal volume status but experiences daily symptoms of congestion at rest or during activities of daily living. Doses of diuretics generally fluctuate at very high levels. More intensive management and surveillance strategies should be considered, which may in some cases reveal poor compliance that would compromise outcomes with any therapy. Some patients may shuttle between profiles 4 and 5
Profile 5	Exertion Intolerant ("housebound")	Comfortable at rest and with activities of daily living but unable to engage in any other activity, living predominantly within the house. Patients are comfortable at rest without congestive symptoms, but may have underlying refractory elevated volume status, often with renal dysfunction. If underlying nutritional status and organ function are marginal, patient may be more at risk than in profile 4 and require definitive intervention
Profile 6	Exertion Limited ("walking wounded")	Patient without evidence of fluid overload is comfortable at rest, and with activities of daily living and minor activities outside the home, but fatigues after few minutes of any meaningful activity. Attribution to cardiac limitation requires careful measurement of peak VO2, in some cases with hemodynamic monitoring to confirm severity of cardiac impairment
Profile 7	Advanced New York Heart Association functional class III	A placeholder for more precise specification in future, this level includes patients who are without current or recent episodes of unstable fluid balance, living comfortably with meaningful activity limited to mild physical exertion

Adapted from Ref. [8]
Possible profile modifiers are: the need for temporary circulatory support (TCS) for profiles 1–3; arrhythmias (A) for profiles 1–7; and frequent flyer (FF) for profiles 3–6

patients, the 1 and 2 year survival were greater than continuing optimal medical therapy (80 % vs. 63 % for 1-year, and 70 % vs. 43 % for 2 year survival in the ventricular assist device and optimal medical therapy groups, respectively) [11].

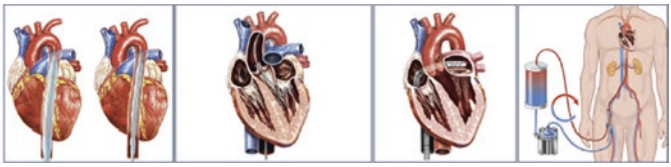
Acute (Temporary) Mechanical Circulatory Support Devices

These devices are used primarily in three patient populations including high-risk percutaneous coronary interventions, post-cardiotomy failure to wean from the cardiopulmonary bypass, and cardiogenic shock. Although the devices used are similar for all these indications, the current chapter will address only the setting of cardiogenic shock.

Cardiogenic shock occurs secondary to acute left or right ventricular systolic dysfunction, acute (on chronic) aortic or mitral valvular disease, and vasodilatory abnormalities in patients with acute myocardial infarction, out-of hospital cardiac arrest, and worsening chronic heart failure. In clinical practice, patients with cardiogenic shock represent a spectrum of disease that can be classified as early shock, shock, and severe shock, depending on the level of blood pressure, heart rate, intracardiac filling pressures, cardiac output, tissue perfusion (lactate, urine output) and need for vasoactive medications [12, 13]. Potential benefits of temporary mechanical circulatory support devices in this setting include the ability to provide circulatory support (thereby maintaining vital organ perfusion and preventing systemic shock syndrome); provide ventricular unloading (left, right, biventricular) in order to reduce intracardiac filling pressures (thereby reducing congestion and/or pulmonary edema), reduce ventricular volumes, wall stress, and myocardial oxygen consumption; and augment myocardial perfusion by increasing coronary blood flow (theoretically also limiting the infarct size in the setting of myocardial infarction). Each of the currently available devices (Fig. 15.1) is designed to tackle the entire equation (i.e. circulatory support, ventricular unloading, myocardial perfusion) but primarily address specific aspects of that equation.

The temporary mechanical circulatory support devices can be largely divided into pulsatile and non-pulsatile devices. The pulsatile device that has been used since 1960s is the intra-aortic balloon pump that primarily functions to augment the diastolic pressure and, as a result, increase coronary perfusion. The ventricular unloading aspect of the intra-aortic balloon pump (counter pulsation) relies on an intact ventricular-vascular coupling and may be diminished in patients with sicker left ventricles. The third part of the equation (i.e. circulatory support) relies on the augmented mean arterial pressure that is driven primarily by the augmented diastolic pressure. Its usefulness is limited to patients in the early shock phase or in patients with active ischemia or ischemic ventricular arrhythmias.

The continuous flow devices can be further divided into axial or centrifugal flow devices. The axial flow pumps that currently exist are the Impella axial flow catheters (2.5 L, CP and 5 L) and the St. Jude Thoratec percutaneous heart pump (currently in clinical trials). Both of these devices use a rotodynamic pump and work by taking blood from the left ventricle and directly ejecting it into the aorta. Axial flow devices will effectively increase mean arterial pressure and directly unload the left ventricle, thereby reducing ventricular pressure. As a result of the increased mean aortic pressure and lower ventricular pressure, the transmyocardial perfusion gradient changes and coronary perfusion will increase [12, 13].



	IABP	Impella	Tandemheart	VA-ECMO
Cardiac flow	0.3–0.5 L/ min	1–5 L/ min (Impella 2.5, Impella CP, Impella 5)	2.5–5 L/ min	3–7 L-min
Mechanism	Aorta	LV → AO	LV → AO	RA → AO
Maximum implant days	Weeks	7 days	14 days	Weeks
Sheath size	7–8 Fr	13–14 Fr Impella 5.0 - 21 Fr	15–17 Fr Arterial 21 Fr Venous	14–16 Fr Arterial 18–21 Fr Venous
Femoral artery size	>4 mm	Impella 2.5 & CP - 5-5.5 mm Impella 5 - 8 mm	8 mm	8 mm
Cardiac synchrony or stable rhythm	Yes	No	No	No
Afterload	↓	↓	↑	↑↑↑
Map	↑	↑↑	↑↑	↑↑
Cardiac flow	↑	↑↑	↑↑	↑↑
Cardiac power	↑	↑↑	↑↑	↑↑
LVEDP	↓	↓↓	↓↓	↔
PCWP	↓	↓↓	↓↓	↔
LV Preload	—	↓↓	↓↓	↓
Coronary perfusion	↑	↑	—	—
Myocardial oxygen demand	↓	↓↓	↔↓	↔

Fig. 15.1 Comparison of acute (temporary) mechanical circulatory support devices (Adapted from Ref. [12], with permission). *AO* aorta, *IABP* intra-aortic balloon pump, *LA* left atrium, *LV* left ventricle, *LVEDP* left ventricular end diastolic pressure, *MAP* mean arterial pressure, *PCWP* pulmonary capillary wedge pressure, *RA* right atrium, *VA-ECMO* veno-arterial extracorporeal membrane oxygenation

The centrifugal flow pumps are extracorporeal and include the TandemHeart device and veno-arterial extracorporeal membrane oxygenation (VA ECMO). In the TandemHeart configuration for left ventricular support, blood is taken out of the left atrium (via a trans-septal catheter) and delivered into the systemic circulation to the iliac artery. In the VA ECMO configuration, blood is taken from the right atrium, oxygenated, and delivered to the iliac artery into the systemic circulation. The hemodynamic effect between these two devices is very different. The TandemHeart will effectively address all three components of the equation by unloading the left ventricle, by reducing left atrial volume (reducing left ventricular preload), and by increasing mean arterial pressure, which leads to increase in the coronary perfusion pressure [12, 13]. The VA ECMO system is distinct from all the other devices by very effectively providing circulatory support (mean arterial pressure will increase). However, by directly transferring venous blood into the systemic circulation, afterload goes up and the left ventricle has to work harder. As such, VA ECMO in isolation will not unload the left ventricle and would need the addition of pharmacological (e.g. inotropes), mechanical (e.g. intra-aortic balloon pump, Impella) or surgical (e.g. direct left atrial or ventricular vent) unloading. In addition, there are limited data to understand the effect of VA ECMO on coronary perfusion pressure [12, 13].

A clear understanding of each device strengths and weakness [12–17] is crucial, since the complications are not trivial (Table 15.2). Patients are kept on support until end organ function has improved and a decision of weaning for recovery or proceeding to permanent support is achieved, or palliative withdrawal is instituted. In our center, we use preferentially the Maquet CardioHelp VA ECMO system for patients in cardiogenic shock, due to its ease of implantation (percutaneous, surgical), portability ("ECMO to go") and versatility, and we use a combination of pharmacological (i.e. dobutamine or epinephrine) and mechanical (i.e. intra-aortic balloon pump) unloading to achieve optimal hemodynamics. Our initial approach is to quickly achieve normal perfusion (mean arterial pressure above 65 mmHg, lactate level below 2 mmol/L), while maintaining the acid base equilibrium (pH 7.3–7.4), adequate tissue oxygenation (hematocrit above 30 %), and urine output (greater than 1.5–2 mL/kg/h). We anticoagulate all patients with intravenous heparin, targeting partial thromboplastin time of 45–60 s or unfractionated heparin level of 0.3–0.5 U/mL. When hemodynamics have improved (right atrial pressure below 10–12 mmHg, pulmonary capillary wedge pressures below 20 mmHg), we attempt echocardiography guided weaning of the VA ECMO. We gradually decrease the amount of support (from full support of 4–5 L to minimal support of 1–1.5 L), while paying attention to left ventricular size, severity of mitral regurgitation, right ventricular function (fractional area change, free wall s') and hemodynamics (mean arterial pressure, right atrial pressure and pulmonary capillary wedge pressures). If the weaning is successful, the VA ECMO is explanted and patients are bridged via inotropes to oral heart failure therapies. If the weaning is unsuccessful, the patients are then implanted with durable ventricular assist devices (on ECMO, rather than using cardiopulmonary bypass).

Durable (Permanent) Ventricular Assist Devices

Durable ventricular assist devices are evolving into an effective and reasonably cost-effective therapy for a growing population of patients with advanced heart failure. They provide significant left ventricular unloading and increased cardiac output and improve end-organ function. Patients supported with ventricular assist device enjoy a 1 and 5-year survival of 80 and 50 %, and marked improvement in symptoms and quality of life [9]. While the traditional indications for implantation were divided into bridge to transplantation, bridge to decision and destination therapy, the improved reliability of today's devices and the lack of available organs for transplantation has led to a paradigm shift where future device will be designed/ tested for short or long term use, without a transplant associated label [18, 19].

First generation positive displacement pulsatile devices (e.g. Thoratec HeartMate XVE, Novacor LVAS) used a diaphragm and unidirectional valves to mimic the pulsatile cardiac cycle through diastolic filling and systolic emptying of the pump. The use of HeartMate XVE in the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial [20] opened the door for mechanical circulatory support for long-term use in transplant ineligible

Table 15.2 Acute (temporary) mechanical circulatory support device contraindications and complications

	IABP	Impella	TandemHeart	VA-ECMO
Contraindications	Moderate to severe AI	Moderate to severe AI	Moderate to severe AI	Moderate to severe AI
	Severe PVD	Severe PVD	Severe PVD	Severe PVD
	Aortic disease (atherosclerosis, dissection)	Contraindication to anticoagulation	Contraindication to anticoagulation	Contraindication to anticoagulation
		LV thrombus	LA thrombus	
		Mechanical AV	HIT or DIC	
		AV area < 0.6 cm^2	VSD	
Complications	Limb ischemia	Limb ischemia	Limb ischemia	Limb ischemia
	Vascular trauma	Vascular trauma	Vascular trauma	Vascular trauma
	Infection	Infection	Infection	Infection
	Stroke	Stroke	Stroke	Stroke
	Acute kidney injury			Acute kidney injury
	Thrombocytopenia	Hemolysis	Hemolysis	Hemolysis
			Air embolism	Air embolism
			Thromboembolism	Thromboembolism
	IABP rupture	Device migration	Device dislodgement	Bleeding
		Device thrombosis		
	Bowel ischemia		Cardiac tamponade	Compartment syndrome
				Peripheral nerve injury
Bleeding/ Hemolysis	+	++	++	++
Peripheral vascular complications	+	++	+++	++++

AI aortic insufficiency, *AV* aortic valve, *DIC* disseminated intravascular coagulation, *HIT* heparin-induced thrombocytopenia, *IABP* intra-aortic balloon pump, *LA* left atrium, *LV* left ventricle, *PVD*: peripheral vascular disease, *VA-ECMO* veno-arterial extracorporeal membrane oxygenation, *VSD* ventricular septal defect

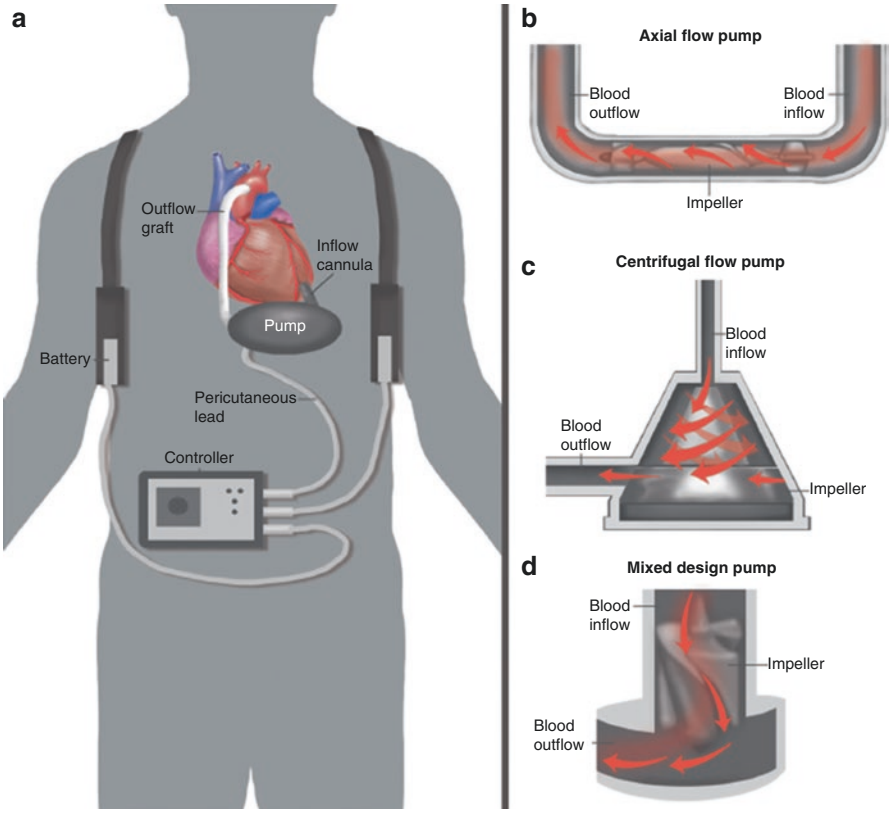


Fig. 15.2 Schematic of a left ventricular assist device system (From Ref. [19], with permission). Components include a surgically implanted pump that works in parallel with the native heart via an inflow cannula to the left ventricle and an outflow graft to the ascending aorta, a percutaneous driveline, a system controller and electrically powered batteries with a life span up to 12 h (**a**). Features of continuous-flow axial (**b**), centrifugal (**c**), and mixed design pumps (**d**), where the pump is axial but blood exits perpendicular to the inflow

patients ("destination therapy"). However, due to their size, adverse events and limited durability (18–24 months), their use was very limited and these pumps were eventually discontinued in mid to late 2000s.

Second and third generation continuous flow pumps are smaller, enjoy simpler implantation, and have more limited blood contacting area with fewer moving parts and without valves, air vents and compliance chambers, leading to longer durability and reduced risks for thromboembolism, infection, and malfunction. They use a permanent magnetic field designed to rapidly spin a single impeller supported by mechanical, hydrodynamic (using a layer of blood – blood bearing – to lift the rotor) or magnetic bearings (using magnetic bearings to levitate the rotor) [19]. Second-generation axial pumps have the impeller outflow directed parallel to the axis of rotation (Fig. 15.2) with the rotor spinning on mechanical (St. Jude Thoratec HeartMate II, Jarvik 2000, Reliant Heart HeartAssist 5) [21–23] or contact-free bearings (Berlin

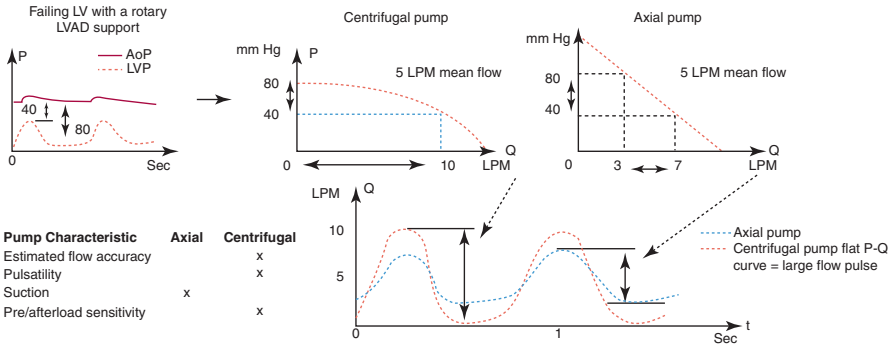


Fig. 15.3 Relationship between head pressure and pump flow in axial and centrifugal pumps and the effect on pulsatility (From Ref. [19], with permission). *AoP* mean aortic pressure, *LPM* liters per minute, *LV* left ventricle, *LVAD* left ventricular assist device, *LVP* left ventricular pressure, *P* pressure, *Q* flow

Heart Incor) [24]. Third-generation centrifugal pumps have the impeller outflow perpendicular to the axis of rotation (HeartWare Ventricular Assist Device [HVAD] and St. Jude Thoratec HeartMate III) [25, 26] or use a mixed design, where blood flows along the axis of rotation but exits perpendicular to the inflow (HeartWare miniature ventricular assist device [MVAD]) [27].

Underlying Physiologic Principles of Continuous Flow Devices

The pump blood flow is directly proportional to the rotor speed and inversely proportional to the pressure differential across the pump (i.e. head pressure, the pressure difference between the left ventricle and aorta). However, the axial and centrifugal pumps differ in their hydrodynamic performance, as characterized by the relation between flow rate and head pressure (Fig. 15.3) [28, 29]. Axial flow pumps have a steep and inverse linear relationship between flow and head pressure, while in centrifugal pumps this relationship is flatter and more susceptible to head pressure changes (i.e., more sensitive to pre-load and afterload). Due to these hydrodynamic characteristics, with the same change in pressure, centrifugal pumps generate larger changes in flow and yield more pulsatile waveforms, more accurate flow estimation, and have a lower risk of suction events (in setting of dehydration, arrhythmias, or right ventricular failure), but are more dependent on the loading conditions when compared with axial flow pumps (Fig. 15.3).

Patient Selection

As previously described in this chapter, the patients most likely to benefit from long-term use of ventricular assist devices are patients with advanced heart failure, preferably INTERMACS profiles 3–4, where the surgical risk of implantation is

fairly small (in-hospital mortality less than 3–5 %). Patients with INTERMACS profiles 1–2 should be bridged with temporary mechanical circulatory support devices and their end-organ function and nutritional status improved significantly or normalized in order to decrease the surgical mortality and morbidity associated with the durable ventricular assist devices implant.

Ideal candidates are patients with large left ventricles, relatively preserved right ventricular function, elevated left ventricular filling pressures and low cardiac output, with competent aortic valve, without history of gastrointestinal bleeding, compliant, with adequate social support, and with few extracardiac comorbidities that could limit the long-term benefit of ventricular assist devices [30, 31]. Carefully selected patients with restrictive cardiomyopathy [32], incessant ventricular tachycardia or congenital heart disease [33] could also benefit from ventricular assist device implantation.

In our center, the absolute medical contraindications to implantation include recent stroke (within 3 months), active systemic infection, uncorrectable peripheral vascular disease or aortic disease, severe irreversible lung disease (forced expiratory volume in first second less than 1 L or diffusing capacity of the lungs for carbon monoxide less than 35 % of predicted values), severe cardiac cachexia (body mass index below 19 kg/m^2, serum albumin level below 2.5 g/dL, or serum pre-albumin level below 15 mg/dL), end stage renal disease on dialysis or with high likelihood of needing dialysis post implant (e.g. creatinine above 3 mg/dL, unless the patient is considered as bridge to heart-kidney transplantation), biopsy proven liver cirrhosis, active or recent history (within 3 months) of heparin induced thrombocytopenia, irreversible cognitive dysfunction (as established by formal neurocognitive testing) and marked frailty [31]. Patients are also deemed to not be good candidates for implantation if they lack social support or have a recent or active history of significant alcohol or illicit substance use. Older patients (older than 80 years) or morbidly obese patients (body mass index above 45 kg/m^2) are evaluated on case-by-case basis.

Current Clinical Results with Continuous Flow Pumps

Several modern trials with ventricular assist devices have been presented in the last decade, with 1-year survival ranging from 68 % (in the initial St. Jude Thoratec HeartMate II bridge to transplant and destination therapy trials and HeartWare HVAD destination therapy trial) [34–36] to 86 % (HeartWare HVAD bridge to transplant trial, St. Jude Thoratec HeartMate II post approval studies) [37–39]. As discussed before, patients with INTERMACS profiles 3–7 had better survival, slightly greater than 90 % at 1 year [36–39].

The use of ventricular assist devices has been hampered by the relatively high probability of device related adverse events (rates per 100 patient-months): bleeding – mainly gastrointestinal (early [within first 90 days post implant] of 19.6 and late [90 days to 24 months post implant] of 3.25); infections – mainly driveline infections (early of 16.95 and late of 4.06), strokes (early of 4.64 and late of 1.21);

and pump thrombosis or mechanical failure (early of 2.79 and late of 1.53) [9, 40–42]. In addition, significant right heart failure can occur in up to 30 % of patients, and 5–10 % require insertion of a temporary or permanent right ventricular assist device [9, 43]. Over time, up to 30 % of patients will develop aortic insufficiency, which may be related to the degree of opening allowed by the ongoing assist device settings [44]. The hospitalization rates for device related complications are high, with reportedly up to 70 % of patients being hospitalized at least once during the first year on support [9]. However, as shown in the ROADMAP trial, the implantation of less sick patients, may lead to lower complication rates and allow for better hospital free survival [11].

In Hospital Management

Once the patient selection process has been completed and the patient has been determined to be a suitable candidate for ventricular assist device implantation, pre-operative optimization using a multi-systems approach prepares the patient for the best chance of a successful outcome. Although several risk scores have been proposed, there are currently no validated risk prediction models to identify patients at highest risk for perioperative complications for ventricular assist device implant. All efforts should be made to ensure that all patients go into surgery with optimal organ functions, irrespective of its baseline state.

Pre-operative Optimization The use of inotropes, vasopressors and temporary mechanical circulatory support devices can improve renal blood flow, while judicious decongestion with combination of intravenous diuretics, aquaretics or ultrafiltration will reduce the central and renal venous pressures. In our center, all attempts are made to improve renal function to pre-operative creatinine and blood urea nitrogen values of less than 2 mg/dL and 50 mg/dL, respectively. Hepatic dysfunction in heart failure is a result of circulatory shock from acute decompensation and persistently high right atrial pressures in the setting of venous congestion and poor right ventricular function.

Hepatic dysfunction can lead to coagulation abnormalities and increased risk of bleeding in patients undergoing ventricular assist device implantation. In our center, those with acute heart failure decompensation and elevations of transaminases or bilirubin receive aggressive therapy with diuresis, inotropes, and temporary mechanical circulatory support devices as necessary to improve hepatic function prior to implantation, to pre-operative transaminases and bilirubin values of less than 100 IU/L and 2 mg/dL, respectively.

Right ventricular dysfunction is common in advanced heart failure patients and is consequence of pulmonary venous hypertension from chronically elevated left ventricular filling pressures, valvular pathology, or a combination of these processes. In our center, all patients with right ventricular dysfunction (more than mild) are admitted to the hospital prior the implant surgery and are optimized by receiving inotropes (e.g. dobutamine or milrinone) and/or temporary mechanical circulatory

support devices in order to increase the cardiac index above 2.2 L/min/m^2. In addition, all patients receive intravenous diuretics or ultrafiltration in order to achieve a preoperative central venous pressure <10 mmHg. In patients with pulmonary vascular resistance above five Wood units and moderate to severe right ventricular dysfunction we use treatment with sildenafil or inhaled nitric oxide in order to decrease the pulmonary vascular resistance and enhance the right ventricular function preoperatively. Finally, we use low dose vasopressors (e.g. vasopressin, norepinephrine) to increase the perfusion pressure to the right coronary artery and minimize the risk for right ventricular ischemia if the mean arterial pressure is below 65–70 mmHg.

Poor nutritional state is associated with a high risk of post-operative complications, including infections, poor healing, poor functional recovery and prolonged length of stay. In our center, for patients with cardiac cachexia we use intensive nutritional optimization with high caloric oral supplements (e.g. Scandishake®), enteral feedings or parenteral nutrition in order to boost nutritional status on the short term (e.g. few days pre-op). We attempt to improve nutritional status to a pre-operative albumin and prealbumin values of above 3 mg/dL and 15 mg/dL, respectively.

Intra-operative Management The intraoperative period is the most critical time of the implant and proper anesthetic techniques, hemodynamic management and surgical techniques are key to a successful outcome. The right ventricle is particularly vulnerable during the implant procedure. Right coronary artery hypoperfusion from hypotension or air emboli should be avoided. Vasopressors (or vasodilators as needed) should be used to maintain a mean arterial pressure of 70–75 mmHg during the implant procedure. Inotropes should be used to maintain a good contractile function and intravenous diuretics or ultrafiltration should be used to maintain euvolemia. Judicious blood product and fluid management is key in order to prevent right ventricular volume overload and dysfunction. During surgical implantation, the ventricular assist device inflow cannula should be placed parallel to the septum directed towards the mitral valve, away from the free wall. This should be verified by transesophageal echocardiography. Correct inflow cannula placement will minimize the chance of suction events. For patients where lateral thoracotomy is used for implantation, sufficient surgical space should be available for a good visualization of the coring area and inflow cannula implantation. The outflow graft should be positioned to the right of sternal midline and avoid compression of right ventricle. Minimizing total cardiopulmonary bypass time may reduce the unfavorable extracorporeal-induced trauma of blood elements and the chance of bleeding. At the separation from cardiopulmonary bypass, pulmonary vasodilation therapy with inhaled nitric oxide should be initiated prior to separation from bypass in order to provide the most favorable conditions for the right heart. Inotropic therapy should be continued or initiated and volume management should be maintained. Sequential atrio-ventricular pacing can enhance right ventricular function and should be attempted if bradyarrhythmias exist.

Post-operative Management The primary objective of early post-operative management is to support organ recovery and to avoid multi-system organ failure

through optimization of organ perfusion. We use invasive monitoring of the patient for the first 48–72 h in order to ensure adequate optimization of hemodynamic support. Pump speed should be adjusted to maintain an output that provides the patient with adequate cardiac output while avoiding left ventricular suction and septum deviation to the left. A low pump output should trigger evaluation for hypovolemia (e.g. bleeding), tamponade, right heart failure, and in rare cases, inflow or outflow cannula obstruction. Surgical bleeding that occurs despite correction of coagulopathies will require that the patient be returned promptly to the operating room to identify the source. Uncontrolled bleeding should always be surgically evaluated.

Intravenous heparin is started after 24 h post-operatively if the surgical bleeding is controlled. We gradually increase the anticoagulation target (increasing partial thromboplastin time targets by 10–15 s every other day to a goal of 55–65 s), and start warfarin when the chest tubes have been removed. We start aspirin 81 mg when the platelet count has rebounded (usually 2–3 days post operatively).

The impact of the ventricular assist device on right ventricular function can be both beneficial and detrimental. The beneficial effects are realized through unloading the left ventricle and decreasing filling pressures, thereby reducing right ventricular afterload. The potential detrimental effects include an increase in right ventricular preload from the normalized cardiac support, and the septal shift observed with unloading the left ventricle. With lower left ventricular filling pressures, the septum will tend to shift to the left and decrease the septal contribution to right ventricular output. Pump speed should be maintained to achieve an optimal balance between an adequate cardiac output and avoidance of right ventricular dysfunction. Weaning of inotropic support should be initiated once the patient is euvolemic and is clinically guided by the physical examination with close monitoring of device parameters. As inotropes are weaned, the clinician should evaluate for evidence of right ventricular dysfunction including: increasing edema; elevation in jugular venous pressure above 12–15 mmHg; low cardiac output (mean arterial pressure below 60 mmHg, poor urine output, decrease central venous saturation); end organ dysfunction (renal or liver failure); and change in pump parameters (decrease in flows and loss of pulsatility). If needed, intravenous inotropes could be used for an extended period of time. All sustained atrial and ventricular arrhythmias should be treated with anti arrhythmic agents and synchronized cardioversion should be used in refractory cases.

We obtain a comprehensive transthoracic echocardiogram prior to discharge to evaluate ventricular size and function, cannula position and flow, aortic valve opening, tricuspid valve regurgitation and perform a ramp test to determine the best pump speed that unloads the left ventricle without inducing right ventricular dysfunction.

Using the above approach we have achieved superb outcomes with a survival to discharge of 98 % and a post-operatively median length of stay of 16 days.

Long-Term Management

After implantation of the ventricular assist device and discharge from the index hospitalization, the clinician is faced with the challenge of caring for the patient in the outpatient setting. This phase of care may last years and the clinical concerns may evolve (e.g. moving from rehabilitation in the early period to preventing or treating comorbid conditions over time). Patients can be followed at the implant center or in coordination with the referring cardiologist ("shared care"). If a shared care approach is used, management guidelines should be distributed to the referring cardiologist to ensure a uniform approach and long-term success [45].

In our center, patients are seen in the outpatient clinic weekly or biweekly for the first 30 days post discharge, then at 1 month and every 3 months afterwards. We obtain a panel of laboratory values (basic chemistry, complete blood count, lactate dehydrogenase, plasma free hemoglobin, international normalized ratio [INR], natriuretic peptide) with every clinic visit and monthly after the 1-month clinic visit. All patients receive home monitoring using the Alere® system to record daily weights, blood pressure, and pump parameters and biweekly INRs. Automatic thresholds are set in order to alert the clinic staff when patients' parameters deviate from desired values (e.g. weight gain, high pump power, sub- or supra- therapeutic INR, hypo- or hyper- tension) in order to promptly intervene and correct them. Using this approach our center has managed to drastically reduce the number of adverse events in these patients, well below those reported in the literature [9] (rates per 100 patient-months): bleeding (early of 10.4 and late of 0.9); infections (early of 5.5 and late of 1.7), strokes (early of 4.9 and late of 0.9); and pump thrombosis or mechanical failure (early of 2.1 and late of 0.3). In addition, our hospitalization rates during the first year post implant are 45 %, compared to the 70 % reported in the literature [9].

We maintain all patients on oral anticoagulation with a combination of warfarin (target INR 2–2.5) and aspirin 81 mg daily. The INR target is lowered to 1.8–2.2 for patients with evidence of gastrointestinal bleeding or individuals older than age 70 years at high risk for bleeding. All patients check their INRs biweekly using the Alere® system and in case of subtherapeutic values, patients use enoxaparin 40 mg daily subcutaneously until the INR returns to desired values.

Blood pressure control is key to preventing strokes in patients on ventricular assist devices [46]. In patients with pulsatile hemodynamics (pulse pressure more than 20 mmHg), we target a systolic blood pressure below 90–100 mmHg while in patients with non-pulsatile physiology we target mean arterial pressures of 70–80 mmHg. We use traditional neurohormonal antagonists (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, hydralazine) as first line therapy, and use beta-blockers only in patients without evidence of significant right ventricular failure.

Driveline management is an important part of the long-term care. We use a thoracic driveline exit site and driveline dressings are changed every third day using a standardized Centurion® driveline management tray. If trauma to driveline exists

site occurs (e.g. dropping the controller, pulling the driveline during physical activities), patients remotely send a picture of their exit site, and if erythema or early infection are identified, patients are promptly started on oral antibiotics. Using this approach we decreased our driveline infection rates to 5.7 % during the first year post implant, for an overall rate of 0.078 infections per patient-year [47].

All patients are optimized on neurohormonal antagonists for treatment of heart failure, to the highest tolerated doses. We use transthoracic echocardiography periodically (at 30 days, 3 months, then yearly) to optimize the ventricular assist device speed. In setting of recurrent heart failure, we use cardiac catheterization in conjunction with echocardiography to assess and optimize the device function.

Atrial and ventricular arrhythmias should be controlled, using specific antiarrhythmic drugs (e.g. dofetilide, amiodarone, mexiletine) or cardioversion. The cardiac implantable electric devices should be interrogated every 3 months, at the time of the clinic visit, in order to correlate potential ventricular assist device malfunction with concomitant arrhythmias.

Management of Ventricular Assist Device Long-Term Complications

Management of Gastrointestinal Bleeding

After hospital discharge, the most common cause of bleeding is the gastrointestinal tract. The reasons for this common complication are likely related to the use of antithrombotic therapy, acquired von Willebrand factor deficiency, acquired impaired platelet aggregation, and intestinal angiodysplasia related to continuous flow technology [48]. Our general approach to the first bleeding episode is to explore the gastrointestinal tract in detail (upper endoscopy, colonoscopy, capsule endoscopy and double balloon enteroscopy) and treat the identified lesions. If no lesions are identified or if the bleeding is recurrent, further investigations are not performed and we transfuse patients to a hematocrit above 30 %. We use intravenous or oral iron supplements, but do not use erythropoietin-stimulating agents, as they have been associated with thrombotic complications in patients with ventricular assist devices [49]. In patients with recurrent bleeding or significant need for transfusion, we have used octreotide (monthly injections of long acting octreotide) and/or oral thalidomide, with good results.

Management of Infections

The most common pathogens in ventricular assist device-related infections are Staphylococcus and Pseudomonas [50] and the most common site of infections if the percutaneous driveline exit site [51]. We have a low threshold for blood culture

collection to evaluate for an occult bloodstream infection and are aggressive with empiric antibiotics after blood cultures are obtained. We use empiric therapy with cephalexin 500 mg oral every 6 h for 10 days, or doxycycline 100 mg oral every 12 h for 10 days in patients with a history of/colonized with methicillin resistant *Staphylococcus Aureus*. The antibiotics are modified accordingly based on culture data. If the initial treatment has not led to resolution of the superficial driveline infection, we use a 48–72 h course of intravenous antibiotics, followed by longer oral antibiotic course (14–28 days). For recurrent superficial driveline infections, we use lifetime suppressive coverage. Deep driveline infections are treated with intravenous vancomycin 15–20 mg/kg mg every 8–12 h and piperacillin/tazobactam 4.5 g every 6 h for a minimum of 14 days. Consideration for surgical exploration, debridement and vacuum assisted closure system should be given early for deep driveline infections.

Management of Atrial and Ventricular Arrhythmias

In patients who develop symptomatic or sustained ventricular arrhythmias we optimize the hemodynamics with medical therapy and pump optimization. Additional medical therapy consists of beta-blockers (irrespective of the right ventricular function) and anti arrhythmic agents (including amiodarone, mexiletine, and sotalol). For patients with refractory ventricular tachycardia, catheter ablation is an option [52]. Atrial arrhythmias are common in patients on ventricular assist device support and persistent atrial fibrillation has been associated with worse right ventricular function and impaired functional capacity [53]. We attempt rhythm control strategies in these patients, and increase the INR goal to 2.5–3 in order to prevent microembolization. Rarely, if needed, catheter ablation can be used [54].

Management of de Novo Aortic Insufficiency

Postoperatively from device implantation, aortic valve insufficiency can develop de novo or underlying aortic valve pathology may be exacerbated. In order to prevent it, we replace at the time of implant all aortic valves with more than mild regurgitation. The de novo occurrence of aortic insufficiency is more common with continuous-flow pumps and occurs due to commissural fusion associated with reduced rates of aortic valve opening [44]. Medical management of aortic insufficiency includes aggressive blood pressure management to reduce the pressure gradient between the aorta and left ventricles. While percutaneous closure of the valve and transcatheter aortic valve replacement have been reported, we believe that the best long term solution is surgical replacement.

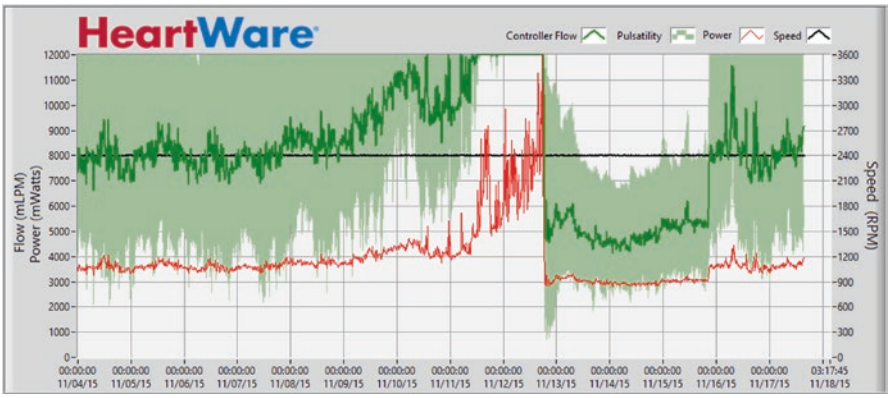


Fig. 15.4 Left ventricular assist device parameters and flow pulsatility in a patient with biochemical evidence of thrombosis. Clear increase in power (*solid red line*) starting in early November 2015, with a marked increase starting November 10, 2015, associated with marked increase in flow (*solid green line*). After administration of intravenous tissue plasminogen activator on November 13, 2015, the power returns to baseline (3 W). There is a subsequent power increase associated with a second episode of thrombosis on November 16, 2015 that responded to a second dose of intravenous tissue plasminogen activator (data not shown)

Management of Pump Thrombosis and Pump Malfunction

Continuous flow devices are more likely to fail due to pump thrombosis rather than mechanical pump failure. In the vast majority of cases, pump thrombosis is due to poor surgical pump or outflow graft positioning, and/or suboptimal long-term anticoagulation. Typical presentations for pump thrombosis range from asymptomatic rise in plasma free hemoglobin or lactate dehydrogenase, to hemolysis with hemoglobinuria, or to frank heart failure symptoms, associated with ventricular assist device flow and power elevations [55]. Initial management strategies focus on patient stabilization and consideration of emergent surgical interventions or thrombolytic agents, especially in HeartWare HVAD pumps, which seem to be more amenable to medical management [56]. For these patients, we use tissue plasminogen activator in a dose of 10 mg intravenous as bolus, followed by an infusion of 10 mg over an hour, with high dose unfractionated heparin (partial thromboplastin time of 70–80 s). If successful (normalization of pump power and a decrease of lactate dehydrogenase levels below 400 U/L), we then use aggressive antithrombotic therapy to prevent further thrombosis (INR 2.5–3) (Fig. 15.4). In patients with hemolysis refractory to intensification of antithrombotic therapy early device exchange should be considered in order to minimize the risk of stroke and death [57].

Management of Neurological Events

Neurological events (strokes) are relatively frequent in patients with ventricular assist devices, with a higher proportion of patients supported by HeartWare HVAD having hemorrhagic strokes compared to patients supported by St. Jude Thoratec HeartMate II devices (10 % vs. 5 %) [36]. Data from recent clinical trials have shown that these events are likely due to uncontrolled blood pressure [46]. Ischemic strokes are equally frequently seen in the two devices (5 %) and are due to suboptimal anticoagulation [36]. We hospitalize all patients presenting with a neurological event and withhold warfarin and antiplatelet agents in the setting of hemorrhagic stroke, intracranial hemorrhage, and subdural hemorrhage. We reverse anticoagulation immediately with prothrombin factor concentrates or fresh frozen plasma. Warfarin and antiplatelet agents typically continue to be withheld until the source of the hemorrhage has been addressed or, if a source has not been identified, until the bleeding subsides and the affected area is determined to be small enough to not bleed again. In the setting of ischemic stroke, we withhold antihypertensive medications to allow for a higher systemic pressure (mean arterial pressure of 80–90 mmHg or recovery of some pulsatility) to improve perfusion to the affected brain areas. In the setting of hemorrhagic stroke, intracranial hemorrhage, and subdural hemorrhage, the blood pressure targets are lower. If the patient recovers, warfarin and aspirin are reinstituted upon discharge. All patients are provided with intensive inpatient physical and occupational therapy with the goal of discharging the patient to a stroke rehabilitation center to maximize their functional recovery.

Total Artificial Heart

Compared to ventricular assist devices, the total artificial heart is implanted in a much smaller proportion of patients, such as patients with severe biventricular failure, fulminant myocarditis or primary heart transplant graft failure.

The Syncardia total artificial heart has a very simple design, delivering pulsatile flow by filling two artificial ventricles lined with polyurethane, and ejecting blood via a four-layer, pneumatically driven, moving diaphragm [58]. Four mechanical valves guarantee the unidirectional flow. The ventricles are connected to patient's circulatory system by cuffs sutured to the atria and vascular grafts sutured to the aorta and pulmonary artery. At maximal stroke volume (70 mL), the device can deliver a cardiac output of more than 9 L per min. The use of Syncardia total artificial heart has been associated with a 70 % survival to transplantation in a population of patients ineligible for left ventricular assist devices [59]. Patients are at risk of thrombotic or hemorrhagic stroke, which, alongside the high risk of infection due to the large percutaneous driveline and relatively heavy external power driver, limit the widespread use of this device.

The French Carmat total artificial heart was first implanted in December 2013 and it contains two ventricles, each with a blood compartment and a driving fluid compartment, separated by a flexible hybrid membrane. The hybrid membrane has a

polyurethane layer at the fluid-contacting surface and bovine pericardial tissue on the blood-contacting surface. The use of bioprosthetic valves and partial pericardium lining of the blood chambers are the most innovative features of this device [60].

The clinical utility of the total artificial hearts are likely to be expanded once appropriate technological improvements are made.

Conclusions

Mechanical circulatory support devices represent a significant advancement in the field of heart failure. Device technology continues to evolve rapidly and patient survival is improving, both for those with cardiogenic shock and for those with chronic advanced heart failure. Better patient selection, surgical techniques and post-operative and long-term management can minimize the device-related complications and allow more patients to benefit from this therapy. It is likely than within a decade advanced heart failure patients will benefit from a completely implantable assist device that will replace heart transplantation as the treatment of choice for advance heart failure. This device will provide full support, including physiologic optimization (i.e. during exercise), will be implanted via a minimally invasive surgery, will enjoy limited complications rate, will be remotely monitored and accessed, and will do so within cost effective parameters.

Future Directions

- Design of hemocompatible surfaces will alleviate the need for anticoagulation and minimize the risk of bleeding, pump thrombosis and stroke.
- Modulation of pulsatility in newer ventricular assist devices will likely decrease the complications related to gastrointestinal bleeding or aortic valve insufficiency.
- Pump speed modulation will be used for antithrombotic cycling to prevent pump thrombosis.
- In the future, speed modulation algorithms will respond to specific physiological demands, such as those related to exercise and remote monitoring will be able to control the pump [61].
- The advent of transcutaneous energy transfer will allow the development of completely implantable devices, with improved quality of life and marked decrease in the risk for infections.
- Newer devices will be miniaturized and will allow for smaller surgical or transcatheter implantation.
- Similarly to cardiac implantable electric devices, remote monitoring will allow for real time assessment of pump function. Currently the Reliant Heart HeartAssist carries a “cell phone system” within the controller and transmits direct flow, power, and speed data every 15 min.
- Ventricular assist devices will be used as platforms allowing concomitant administration of full dose neurohormonal blockade and intramyocardial injections of stem cells that will lead to myocardial recovery.

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Chapter 16
Gene and Cell Therapy in Heart Failure

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Introduction

The dramatic increase in the prevalence of heart failure (HF) [1] together with the limited effectiveness of currently available drugs due to side effects and reduced tolerability and efficacy, has lead to the study of the different molecular signalling pathways that are activated in this disease in order to identify new potential therapeutic targets [2]. In some cases, pharmacological agents are nor able to efficiently target specific genes and/or proteins making necessary the development of more sophisticated therapeutic strategies, such as gene and stem cell therapies, in order to overcome the complex pathophysiology of HF.

Gene Therapy

Gene therapy offers a unique opportunity to target the specific molecular disturbances in HF (Table 16.1). HF-associated changes in cardiac contractility and pressure overload, among others, induce the activation of different signalling pathways that lead to the activation of transcription factors, co-regulators and microRNAs in

Funding his work has been supported by grants from the Spanish Ministry of Economy and Competitiveness of Science [SAF2013-42962-R to L.B; SAF2015-71653-R to GV.]; and Institute of Health Carlos III, ISCIII [TERCEL RD12/0019/0026 and RIC RD12/0042/0027 to L.B.] Spain. We thank FIC-Fundacion Jesús Serra, Barcelona, Spain, for their continuous support.

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M. Dorobanțu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_16

Table 16.1 Pre-clinical studies for target genes for potential therapies of HF

Gene	Pre-clinical studies	
	Small animal model	Large animal model
Calcium homeostasis-related targets		
SERCA2a	Rat model of HF: aortic branding [10], post-infarction [14]	Pig models of HF: volume-overload [9], post-MI [11]
PLN	Hamster model of HF [12], rat model of HF post-MI [13], rat model of HF [16]	Sheep model of HF [15]
PP1/I-1	Mouse model of HF [17], mouse model post-MI [18]	Pig model of ischemic HF [19]
SUMO1	Mouse and rat model of HF [20]	Pig model of ischemic HF [21]
S100A1	Rat model of HF [22]	Pig model of HF post-IM [23]
Therapies targeting tachy- and bradyarrhythmias		
Gem	Guinea pig, analysis of isolated myocytes [26]	
L-type Ca^{2+} channel β	Aortic-banded rat model of LV hypertrophy [27]	
Kv4.3-I_{to}	Rat model of pressure overload [28]	
Cx43		Pig model of post-MI remodelling [30]
KCNH2 mutant		Pig model post-MI [32]
Therapies targeting adrenergic signalling		
$G\alpha_{i2}$		Porcine hearts *ex vivo* [34]
$G\alpha_{s}$		Pig model of β-adrenergic stimulation with isoproterenol [35]
βARKct	Rat model of HF [36]	Pig model of ischemic cardiomyopathy [37]
AC6	Mouse model of β-adrenergic stimulation [38]	Pacing pig model of HF [39]
Therapies targeting myofilaments		
R1R2	Mouse model [40]	
Cardiac regeneration and proliferation therapies		
SDF-1	Rat model of ischemic HF [46]	

the cell [3]. The identification of beneficial *versus* negative gene changes is crucial in order to target the specific genes that play a causative role in disease progression and that can afford a significant benefit in patient's evolution.

Calcium Homeostasis-Related Therapies

Among the different molecules that are known to be involved in calcium homeostasis, sarcoplasmic reticulum Ca^{2+} ATPase (SERCA2a) appears to play a critical role. More than two decades ago, Gwathmey et al. reported for the first time an abnormal calcium handling in the myocardium of patients with end-stage HF [4]. This result

has been consistently validated in different studies, both in animal models and in humans, showing that mRNA levels of SERCA2a and SERCA2a protein activity are reduced in the failing myocardium [5, 6]. These reduced levels of SERCA2a lead to an impaired calcium re-uptake by the sarcoplasmic reticulum during diastole that contributes to the HF-related impaired diastolic relaxation. This also induces a decrease in the calcium availability for systolic contraction further contributing to systolic impairment [7]. These evidences have been proved in experimental animal models in which SERCA2a gene knock-out induces the development of systolic and diastolic dysfunction [8]. Furthermore, pre-clinical studies in small and large animal models have demonstrated, not only an improved cardiac contractility after SERCA2a gene transfer, but also an enhanced energy utilization, decreased ventricular arrhythmias and improved blood flow [9–11].

Other explored approaches to target SERCA2a-mediated calcium homeostasis have been the manipulation of the regulators of SERCA2a activity such as phospholamban (PLN) and the small ubiquitin-like modifier type 1 (SUMO1).

The phosphorylation profile of PLN regulates SERCA2a function. Specifically, unphopshorylated PLN inhibits SERCA2a activity. Adenoassociated virus (AAV)-mediated overexpression of a mutant PLN form has shown to prevent cardiomyocyte deterioration and cardiac dysfunction in small animal models of HF [12] and post-MI remodelling [13, 14]. These results have been further validated in a sheep model of HF where treatment with an inhibitory PLN peptide has enhanced SERCA2a activity leading to an improved left ventricular (LV) function [15]. These data have been reproduced by the use of a RNA interference therapy in a rat model of HF where adenoviral and AAV vectors were used to silence PLN expression [16].

Besides, PLN phosphorylation is regulated by protein phosphatase-1 (PP1) and its inhibitor (I-1). Thus, PP1 inhibition or inhibitor I-1 overexpression in murine models have shown to improve cardiac function, preventing HF progression [17, 18]. In fact, transgenic mice expressing constitutively active inhibitor-1 (I-1c) show PP1 inhibition together with increased levels of phosphorylated PLN [17]. The relevance of a potential I-1 gene transfer therapeutic approach has been recently validated in a swine model of ischemic HF (IHF) where it has demonstrated to improve cardiac function [19].

SUMO1 protein regulates SERCA2a levels and activity through a post-translational modification known as SUMOylation. HF has been associated to a reduction in SERCA2a SUMOylation [20]. Gene therapy with an AAV-SUMO1 vector has shown to increase SUMO1 expression and to improve cardiac function in small and large animal models of HF in a comparable way to that obtained with SERCA2a gene therapy suggesting a potential additive effect of both gene-based therapies [20, 21].

Another protein involved in SERCA2a regulation in the heart is S100A1. This is a calcium regulated protein that enhances SERCA2a activity promoting cardiac contraction and relaxation. AAV-mediated long-term expression of S100A1 is able to revert LV dysfunction and adverse remodelling in a rat model of HF [22]. Similarly, AAV-mediated expression of S100A1 prevented and reversed these functional and structural changes in a pig model of post-ischemic HF [23].

Therapies for the Treatment of Tachy- and Brady-Arrhythmias

HF implies changes in the electrophysiological function that lead to the manifestation of a wide variety of arrhythmic disorders such as tachy- and brady- arrhythmias. This is crucial as, for example, bradyarrhythmias are associated to a worsening of HF and, if extreme, they can lead to sudden cardiac death. Moreover, the most prevalent tachyarrhythmic disorder associated to HF, atrial fibrillation (AF), dramatically increases the risk for stroke [24].

Because of the clinical relevance of arrhythmias in HF many efforts have been spent in the search for candidate targets for gene therapy [25]. In this context, adenoviral-mediated delivery of a ras-related small G-protein, Gem, in a guinea pig model, shortened the action potential duration (APD) which is an electrophysiological hallmark of the failing heart, and decreased the L-type calcium current ($I_{Ca\text{-}L}$) [26]. However, this approach blunted contractile function severely limiting its usefulness in the clinical scenario. Interestingly, *in vivo* knockdown of the L-type Ca^{2+} channel β-subunit in a rat model also reduced $I_{Ca\text{-}L}$ attenuating the hypertrophic response without affecting systolic performance [27]. Another strategy for shortening APD is increasing the activity of repolarizing K channels. Indeed, adenoviral-mediated overexpression of the gene encoding I_{to}, Kv4.3, is able to prevent pressure overload-induced APD prolongation diminishing the hypertrophic response [28].

The great importance of the cell-to-cell interactions and their potential implications on HF has lead to propose connexin 43 (Cx43) as a potential target for gene therapy [29]. Studies performed in a pig model of post-MI cardiac remodelling demonstrated that adenoviral-mediated delivery of Cx43 gene improved conduction velocity and reduced the susceptibility to ventricular tachyarrhythmias [30]. These results have to be taken cautiously due to the previously demonstrated positive association between Cx43 levels and infarct size [31]. Thus, more research is needed on Cx43 function in order to determine its potential usefulness in gene therapy in the context of HF.

An important advantage of gene therapy compared to pharmacological treatment is the possibility of performing targeted therapy in the tissue and/or cell type of interest. In line with this, Sasano et al. demonstrated that local transfer of a gene encoding a dominant-negative version of the KCNH2 potassium channel (KCNH2-G628S) to the scar border, eliminated all ventricular arrhythmias in a porcine model [32].

Therapies Targeting Adrenergic Signalling

Sympathetic nervous system hyperactivity is known to play a pivotal role in HF pathophysiology and progression. A key pathological event in HF is the hyperactivity of the sympathetic system that leads to a hyperadrenergic state of the heart. The chronic stimulation of β-adrenergic receptors (β-ARs) leads to their desensitization. These β-ARs are coupled to stimulatory G proteins (G_s) which regulate intracellular cAMP levels and are counterbalanced by inhibitory G proteins (G_i) [33]. Because of

their implication in HF pathophysiology, several groups have targeted G-proteins as a potential approach for gene therapy. In an *ex vivo* model, the infection of porcine hearts with an adenovirus carrying the $G\alpha_{i2}$-subunit suppressed baseline atrioventricular conduction and slowed the heart rate during AF [34]. Similarly, silencing $G\alpha_s$ with an adenovirus-small interfering RNA [35] in a pig model, reduced heart rates during normal sinus rhythm and prevented inappropriate rate increase after β-adrenergic stimulation [35].

The most abundantly expressed G protein-coupled receptor kinase (GRK) in the heart is GRK2. Several studies have demonstrated that the expression of a peptide inhibitor of GRK2 (βARKct) is able to improve the contractility of the failing heart [36, 37].

Another approach to target β-adrenergic stimulation is the modulation of cAMP expression. In this context, transgenic overexpression of adenylyl cyclase type 6 (AC6) in mice has shown to increase cAMP production and improve cardiac function [38]. This result has been validated in a pacing pig model of HF where adenovirus-mediated AC6 gene transfer also increased cAMP production improving LV function and remodelling [39].

Therapies Targeting Myofilaments

In muscle contractility myosin uses ATP hydrolysis energy to move along actin filaments. The overexpression of the enzyme ribonucleotide reductase (R1R2) in transgenic mice increases the production of 2-deoxyATP, significantly improving LV systolic function [40].

Cardiac Regeneration and Proliferation Therapies

Another potential approach for gene therapy would be to increase the amount of viable myocardium by targeting signalling pathways known to be determinant for embryonic and fetal cardiomyocyte proliferation [41]. The aim of such approaches would be to stimulate the intrinsic potential of differentiated cardiac cells to proliferate. In this context, two molecular pathways have shown to be crucial in cardiomyocyte proliferation, Notch and Hippo signalling. Indeed, adenovirus or AAV-mediated overexpression of the Notch Intra Cellular Domain (NICD) protects neonatal rat cardiomyocytes from apoptosis and promotes their expansion [42, 43]. Similarly, targeting the Hippo pathway by the miR-302/367 cluster induces cardiac regeneration after an MI [44].

Besides stimulating the intrinsic potential of differentiated cardiac cells to proliferate, an additional approach would be to favour stem cell (SC) homing into the failed heart. The stem cell-derived factor 1 (SDF-1) is a chemokine that binds to the G protein-coupled CXC chemokine receptor type 4 (CXCR4) that promotes the recruitment

of SCs into the injured myocardium [45]. Plasmid-mediated SDF-1 overexpression in a rat model of IHF promoted angiogenesis and improved cardiac function inducing a slight scar remodelling with a decreased myocardial fibrosis [46].

Cell-Based Therapies

One of the main challenges of cardiac medicine is the need to restore the cellular loss that occurs after a MI, which is the key trigger for adverse ventricular remodelling leading to HF development. In this scenario, cardiac regenerative therapies have emerged as an important tool with an enormous potential to overcome such challenge [47].

Since the regenerative era started, several types of cells have been included within the terminology of "stem cells". Each cell type has a different origin and is characterized by differential properties. In the early years, more heterogeneous cell populations were used, but with the improvement of the understanding of SC properties, plasticity and paracrine activity these first generation preparations have been replaced by more sophisticated SC-related therapies, the second generation SC [48].

Non-cardiac Origin SCs

One of the most investigated SC for cardiac regeneration is bone marrow-derived mesenchymal stem cells (BMCs) because of their ability to differentiate towards multiple tissue lineages and to secrete a wide range of factors [49].

Several studies on small animal models have reported an improved heart function after BMCs delivery [50–52]. Furthermore, similar results have been obtained in large animal models. As such, BMCs administration soon after acute MI in swine has shown to improve left ventricular ejection fraction (LVEF) and limit wall thickening in the remote non-infarcted myocardium [53]. These results have also been observed in a pig model of chronic ischemic cardiomyopathy where BMCs administration significantly improved heart function inducing both structural and functional reverse remodelling [54]. Although these pre-clinical evidence point out towards a potential key role of BMCs in the treatment of HF, some reports have obtained discouraging results [55, 56].

Adipose-derived stem cells (ASCs), is another mesenchymal SC type that contributes to tissue homeostasis, cell renewal and spontaneous repair. ASCs share many properties with BMCs such as their potential to differentiate towards multiple tissue lineages, their ability to secrete angiogenic and antiapoptotic cytokines, and their immunomodulatory properties. However, ASCs show clear

advantages in terms of accessibility and quantity of available sample and their easy *in vitro* expansion [57, 58]. One of the most important characteristics of ASCs is their ability to secrete angiogenic factors under hypoxic conditions. This key property, enable them to survive in an ischemic environment where they provide a reservoir of the necessary growth factors to promote angiogenesis, making ASCs an excellent target for cell-based therapies and especially in the context of ischemic heart disease (IHD). Indeed, several pre-clinical studies have demonstrated that ASCs administration improves cardiac function, perfusion and remodelling [59, 60].

The potential autologous use in the clinical setting of these cells is hampered by their loss of properties induced by the presence of factors that induced the pathology to be treated in the first place [61–65]. However, mesenchymal stem cells (MSCs) represent an excellent source for allogeneic therapy due to the possibility of obtaining cells from healthy donors and their low immunogenicity profile. In fact, preliminary pre-clinical studies have proven their safety and efficacy by showing their potential to differentiate into the three cardiac cell types and the improvement of cardiac function in large animal models of acute- [66] and chronic-IHD [67].

Despite the encouraging results obtained with both BMCs and ASCs, their potential use in the clinical setting is hampered by their lack of homogeneity [68] and more importantly their low retention rate in the target organ [69].

Second Generation SCs

Cardiac Origin SCs

The most logical way to target cardiac regeneration would be to stimulate the self-renewal ability of the tissue. However, it was not until the study of Beltrami et al. reporting the presence of mitotic cardiomyocytes and the existence of a multipotent population of cells able to differentiate into cardiomyocytes, smooth muscle cells and endothelial cells [70, 71], that the idea of a potential turnover of adult cardiomyocytes was plausible. These cardiac stem cells (CSCs) are rapidly activated after certain stimuli such as myocardial injury [72]. Indeed, in a pig model of chronic ischemic cardiomyopathy, CSCs administration seems to improve regional and global LV function and promote cardiac and vascular regeneration [73]. However, the amount of CSCs in adult hearts is too low, diminishing their potential usefulness in the clinical practice for the treatment of HF. In this scenario, the combination of CSCs with a more abundant and accessible SC type such as BMCs, has shown to enhance scar size reduction and restore diastolic and systolic function in a pig model of MI [74].

Another cardiac-related SC, are cardiospheres-derived cells (CDCs) which are a mixed cell population with clonogenic capacity that express SC markers (c-kit$^+$ and CD105$^+$) and show regenerative potential [75]. The isolation of this cell type allows obtaining a larger number of cells compared to CSCs. Importantly, CDCs have shown to afford equivalent effects on LVEF than CSCs in a pig model of ischemic cardiomyopathy but with higher benefits in improving hemodynamics and regional function, and in attenuating ventricular remodelling [76]. Furthermore, CDCs seem to be superior to other SC types providing the greatest functional benefit in a mouse model of MI [77].

Pluripotent SCs

The second generation of SC also includes what is known as pluripotent SC (PSCs) which include embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). ESCs are isolated from blastocysts and are able to generate functional cardiomyocytes. Indeed small and large experimental animal models have shown their ability to improve cardiac function after MI [78, 79]. iPSCs are generated by the introduction of certain transcription factors into terminally differentiated cells [80]. Both PSCs hold promise for the treatment of HF. However, there are many issues that have to be deeply investigated and resolved for these cells to be translated into the clinics, such as the ethical concerns regarding ESCs and the oncogenic risk of both cell types.

SC-Derived Products

One of the main unresolved issues regarding SC therapy in the context of cardiac regeneration is the fact that grafted cells are not retained in the tissue for long periods while their effects persist over time. This has led to the idea that SC-mediated beneficial effects can be driven by complex paracrine mechanisms that might stimulate endogenous repair signalling pathways [81]. Indeed, intracoronary administration of IGF-1 and hepatocyte growth factor reduced myocardial remodelling and induced regeneration leading to an improved cardiac function in a pig model of MI [82].

However, due to the high complexity of cardiac regeneration it seems implausible that the administration of single growth factors could fully regenerate the mass of the myocardium that is damaged after an MI and that can afterwards evolve into adverse cardiac remodelling and HF. In this scenario, some authors have proposed that exosomes and microparticles released from SCs could be responsible for their beneficial effects. In line with this hypothesis, a recent study performed in a mouse

model of HF has shown that extracellular vesicles derived from human ESCs exert the same beneficial effects on adverse remodelling and cardiac function as their parent cells [83].

Additionally, gene engineering and SC therapy can be combined to improve the properties and enhance the regenerative potential of SC by the up-regulation of specific transcription factors in order to: favour their differentiation into a cardiac phenotype (e.g. TBX5, MEF2C and GATA-4); enhance their pro-survival properties (e.g. Akt, ERK1/2 and HIF-1α); favour their electromechanical integration (e.g. N-cadherin and connexin-43); promote angiogenesis (e.g. VEGF and SDF-1); revert cell senescence (e.g. Pim-1 kinase and Notch-1); or promote cardiomyocyte regeneration (e.g. by regulating the Hippo pathway) [84–88].

Clinical Evidences

The promising results obtained in pre-clinical studies with both gene and SC-based therapies,have led to a quick translation into clinical studies in order to test their potential benefit in humans.

Regarding gene therapy (Table 16.2), clinical trials targeting SERCA2a (CUPID) reported encouraging results with a trend towards reduction of clinical events [89] that was further confirmed after follow-up [90]. Unfortunately, the larger CUPID2 study failed to demonstrate efficacy [91]. Due to the key role of SERCA2a in the development of HF, two other clinical trials were initiated to test the effect of AVV1.SERCA2a gene transfer, AGENT-HF (AAV1-CMV-Serca2a GENe Therapy Trial in Heart Failure) and SERCA-LVAD (Safety and Feasibility of AAV1/SERCA2a Gene Transfer in Patients With Chronic Heart Failure) (https://clinicaltrials.gov). However, both studies were terminated due to the neutral results obtained in the CUPID2. The STOP-HF (SafeTy and efficacy Of JVS-100 administered to adults with ischemic heart failure) trial targeting SDF-1 demonstrated a significant improvement in LVEF in those patients who where in the lowest quartile at inclusion but failed to demonstrated other benefits [92].

Another trial to test the overexpression of AC6 is currently ongoing.

In the SC area, the clear advantages and benefits shown in several pre-clinical studies have driven a quick translation of SC-based therapies into clinical studies in order to test their potential usefulness in the context of IHD and HF (Table 16.3). However, contradictory findings have been described with some clinical studies showing improved cardiac function after SC therapy [93–96], other showing modest changes [97–99] and others even showing a lack of benefit [100, 101]. What is true is that, for most of these SC-based therapies, we still do not know if they are able to induce clinically meaningful reverse cardiac remodelling having an impact in the clinical evolution of patients.

Table 16.2 Gene-therapy based clinical trials for HF treatment

Name/clinical trial registration	Gene	Design	Vector administration	Patients	Outcome (or current status)
CUPID [89, 90]	SERCA2a	Randomized, double-blind, placebo-controlled	AAV1 Intracoronary	Advanced HF; N=39	Reduction in CV events including death. No safety concerns
CUPID2 [91]	SERCA2a	Multinational, randomized, double-blind, placebo-controlled	AAV1 Intracoronary	HF LVEF ≤ 35 %; N = 250	Lack of improvement in recurrence or death. No safety concerns
AGENT-HF	SERCA2a	Randomized, double-blind, placebo-controlled	AAV1-CMV ntracoronary	HF LVEF ≤ 35 %	Terminated
SERCA-LVAD	SERCA2a	Randomized, double-blind, placebo-controlled	AAV1 Intracoronary	HF with LV assistance device	Early terminated
NCT00787059	AC6	Randomized, double-blind, placebo-controlled	Adenovirus Intracoronary	Congestive HF	Ongoing but not recruiting patients
STOP-HF [92]	SDF-1	Randomized, double-blind, placebo-controlled	Plasmid Endomyocardial	IHF LVEF ≤ 40 %; N = 93	Improved LVEF. Trend to improved LVESV and stroke volume. No safety concerns

AAV1 Adenoassociated virus, *CMV* Cytomegalovirus promoter, *CV* Cardiovascular, *IHF* Ischemic heart failure, *LVEF* Left ventricular ejection fraction, *LVESV* Left ventricular end-systolic volume

Table 16.3 SC therapy based clinical trials for the treatment of HF

Name/cinical trial registration	SC type	Design	Rout of administration	Patients	Outcome (or current status)
REVIVE [93]	Bone marrow aspirate concentrate	Multinational, prospective, randomized, open-label	Retrograde into coronary sinus	IHF and NIHF; N = 60	Safe procedure. LVEF improved. LVESD and BNP improved only in NIHF patients
REGENERATE-IHD [97]	Bone marrow derived-SCs	Randomized, controlled, pilot study	Intramyocardial vs. intracoronary	IHF; N = 58	Safe and feasible procedures. Trend towards improved symptoms
NCT00418418 [100]	Bone marrow derived-SCs	Randomized, double blind	Intramyocardial in the border area	IHF LVEF ≤ 45 %; N = 39	Reduced scar size. LV systolic function not improved
CARDIO133 [101]	$CD133^+$ bone marrow derived-SCs	Randomized, double blind, placebo-controlled	Intramyocardial	Chronic IHD and LVEF < 35 %; N = 60	Scar size and regional perfusion improved. No effect in global LV function
STAR-heart [98]	Bone marrow derived-SCs	Not randomized	Intracoronary	Chronic HF LVEF ≤ 35 %; N = 191	Safe procedure. Improved ventricular performance, quality of life and survival
FOCUS-HF [103]	Bone marrow mononuclear cells	Prospective	Transendocardial	Chronic HF; N = 30	Safe procedure. Quality of life scores improved
TAC-HFT [99]	MSCs vs. Bone marrow mononuclear cells	Randomized, blinded, placebo-controlled	Transendocardial	Ischemic cardiomyopathy and LVEF < 50 %; N = 65	Safe procedures. Regional myocardial function improved only with MSCs

(continued)

Table 16.3 (continued)

Name/cinical trial registration	SC type	Design	Rout of administration	Patients	Outcome (or current status)
MSC-HF [94, 95]	BMCs	Randomized, double blind, placebo-controlled	Intramyocardial	Chronic IHF and LVEF < 45 %; N = 60	Safe procedure. Reduced LVESV. Improved LVEF, stroke volume and myocardial mass
C-CURE [96]	BMCs	Multinational, prospective, randomized	Endomyocardial	IHF; N = 47	Safe and feasible procedure. LVEF improved and LVESV reduced. Improved clinical scoring
POSEIDON [104]	BMCs (allogenic vs. autologous)	Randomized, without placebo-control group	Transendocardial	Ischemic cardiomyopathy with LV dysfunction; N = 30	Low rates of immunologic reactions and clinical complications
NCT01350310 [105]	$CD34^+$ SCs	Randomized, control group without placebo	Intracoronary	Dilated cardiomyopathy; N = 110	Increased LVEF and 6-min walk distance. Decreased NT-proBNP. Lower total mortality and pump failure, but not sudden cardiac death
CHART-1 [106]	Bone marrow-derived and lineage-directed autologous cardiopoietic	Multicenter, randomized, sham-controlled	Intramyocardial	Chronic HF LVEF < 35 % at high risk of recurrent events; N = 240	Ongoing trial

PRECISE [107]	ASCs	Randomized, double blind, placebo-controlled	Transendocardial	Ischemic cardiomyopathy; N = 27	Safe procedure. Improved ventricular function, myocardial perfusion and exercise capacity
SCIPIO [108]	CSCs	Randomized, open-label	Intracoronary	Ischemic cardiomyopathy; N = 33	Improved global and regional LV function. Reduced infarct size and increased viable tissue
CADUCEUS [109]	CDCs	Prospective, randomized, two centers	Intracoronary	LV dysfunction after MI; N = 25	Safe procedure. Reduced scar mass. Increased viable myocardium, regional contractility and regional systolic wall thickening. No changes in LVEF and LVESV at 6 months

BNP B-type natriuretic peptide, *IHD* Ischemic heart disease, *IHF* Ischemic heart failure, *LVEF* Left ventricular ejection fraction, *LVESD* Left ventricular end-systolic diameter, *LVESV* Left ventricular end-systolic volume, *MI* Myocardial infarction, *NIHF* Non-ischemic heart failure, *NT-proBNP* N-terminal B-type natriuretic peptide

Future Directions
Despite the encouraging results obtained in pre-clinical models, gene therapy has not yet demonstrated benefits in HF patients in Phase II clinical trials. This fact highlights the need to deeply analyze the optimal genes, cardiac specific vectors, delivery methods, and experimental models to target this complex disease, in order to obtain reproducible results that would warrant their translation into the clinics.

Regarding SC therapy, the discrepancy between promising pre-clinical animal research and the uncertain efficacy of human clinical trials has revealed the need to improve our understanding of the mechanisms of SCs-mediated protection, delineate their paracrine effects, and develop therapies which maximize their effects [102]. Although, clinical trials have proven the safety of SC-based therapies, further research is needed before this strategy can be translated into standard clinical therapy. Specifically, three main key issues need to be addressed: (1) the search for the ideal cell type for each specific situation; (2) the standardization of protocols for SC preparation; and (3) the identification of the correct subsets of patients and control groups to be tested in clinical trials in order to obtain reliable results.

Conflict of Interest/Disclosures None

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Chapter 17
Valvular Surgery in Heart Failure

Jean Porterie, Bertrand Marcheix, and Yves Glock

Introduction

Heart failure (HF) may be the current trend of many heart diseases. Although most cases of HF observed in Western countries are due to coronary artery disease (CAD), high blood pressure (HBP) or alcoholic etiology, valvular heart diseases (VHD) are still the source of nearly 10 % of HF cases [1, 2]. The occurrence of HF in a patient with valvular stenosis or insufficiency is usually an evolutionary turning point of the disease and requires (in the absence of contraindication) to consider a correction of this valve disease. Indeed, when valvular disease is managed correctly and pre-emptively, its adverse consequences on ventricular function can be ameliorated. Thus, surgical therapies and percutaneous interventions commonly integrated in HF management include aortic valve replacement and mitral valve repair or replacement. However, even if VHD may cause or aggravate HF, the issue of liability of the valve disease in heart dysfunction is sometimes difficult to determine, particularly when left ventricular (LV) dysfunction is associated with mitral or aortic insufficiency.

Aortic Regurgitation

Aortic regurgitation (AR) can be caused by primary disease of the aortic valve leaflets and/or abnormalities of the aortic root geometry. Congenital abnormalities, especially bicuspidy, are the second most frequent aetiology. Generally, AR increases LV pre-load and afterload, with subsequent increases in LV diastolic pressures, dilatation and eventual systolic dysfunction.

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M. Dorobanțu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_17

Natural History

Patients with acute severe AR (most frequently caused by infective endocarditis or aortic dissection) have a poor prognosis without intervention due to their haemodynamic instability. Symptomatic patients with chronic severe AR also have a poor long-term prognosis, with a mortality up to 10–20 % per year. In asymptomatic patients with severe chronic AR and normal LV function, the likelihood of developing HF is close to 50 % in some series. LV ejection fraction (LVEF) or LV end-systolic diameter (LVESD) are reported among main predictors of occurrence of death, symptoms or LV dysfunction [3].

Evaluation

Echocardiography has a key role in the diagnosis and evaluation of AR severity: vena contracta width >6 mm, effective regurgitant orifice area (EROA) ≥30 mm^2, regurgitant volume (RVol) ≥60 ml. Echocardiography also permits to evaluate regurgitation mechanisms, describe valve and aortic root anatomy, and determine the feasibility of valve repair [4]. Determining LV function and dimensions is essential, with indexing for body surface area (BSA), especially in patients of small body size (BSA ≤ 1.68 m^2) [5, 6]. Special attention should be given not to confuse mild to moderate aortic incompetence secondary to LV dilatation with LV dilatation and systolic dysfunction due to primary severe aortic regurgitation.

Indications for Surgery

In symptomatic acute severe AR, urgent or emergent surgical intervention is indicated.

In chronic severe AR, surgery must be performed in all symptomatic patients and in asymptomatic patients with LV dysfunction (EF < 50 %) [7]. HF, LV function and symptoms usually improve after early aortic valve replacement or repair. Surgery should also be performed in asymptomatic patients with severe aortic regurgitation and marked LV dilatation: LV end-diastolic diameter (LVEDD) >70 mm or LVESD >50 mm (>25 mm/m^2 BSA). Indeed, the likelihood of developing irreversible myocardial dysfunction is higher if intervention is delayed [4, 8]. Likewise, surgery should be considered in case of rapid worsening of ventricular parameters on serial testing. A management algorithm of AR is proposed in Fig. 17.1.

Surgery

Valve replacement remains the most widely used technique for the treatment of isolated AR. In the past 20 years, repair strategies have been developed and are increasingly used in experienced centres, especially in young patients [9, 10].

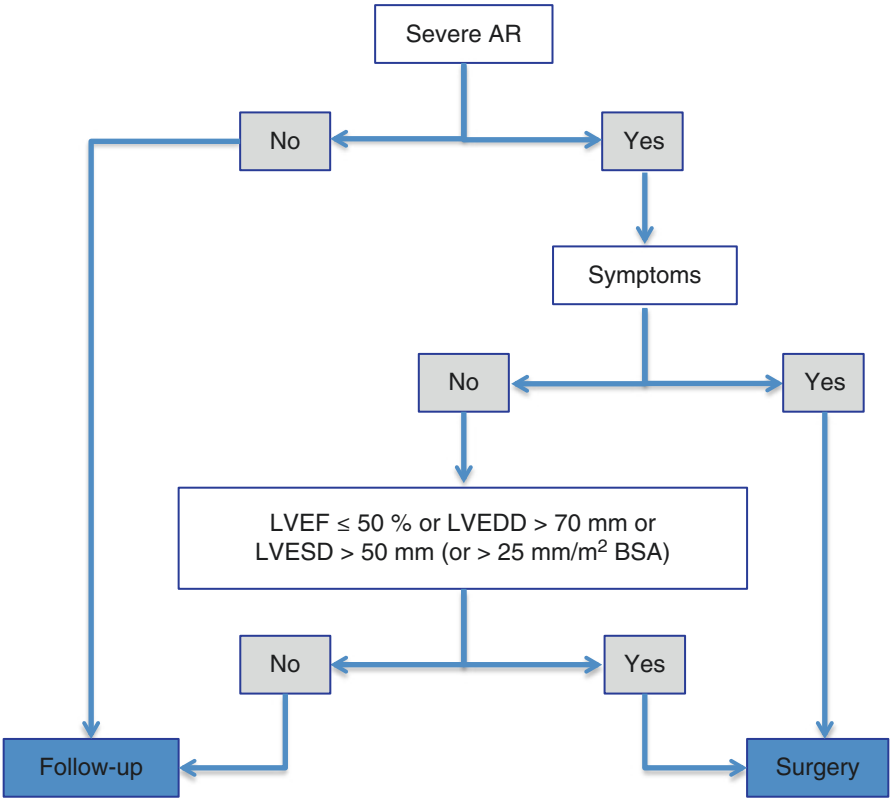

Fig. 17.1 Management algorithm of aortic regurgitation. *AR* aortic regurgitation, *BSA* body surface area, *LVEDD* left ventricular end-diastolic diameter, *LVEF* left ventricular ejection fraction, *LVESD* left ventricular end-systolic diameter

Intraoperative trans-oesophageal echocardiography (TOE) is mandatory in aortic valve repair or valve-sparing intervention, to assess the functional results and identify high-risk patients for early recurrence of AR [11].

Operative mortality is low (1–4 %) in isolated aortic valve surgery, both for replacement and repair [12]. Mortality increases with advanced age, higher preoperative functional class, impaired LV function (LVEF < 50 %; LVESD > 50 mm), and the need for concomitant coronary artery bypass grafting (CABG).

Medical Therapy

Vasodilators, angiotensin receptor blockers (ARBs) and inotropic agents may be used for short-term therapy to improve the condition of patients with severe HF before aortic valve surgery, or when surgery is contraindicated or LV dysfunction persists postoperatively.

Aortic Stenosis

Aortic stenosis (AS) has become the most frequent type of VHD in western countries, especially calcific AS in elderly. The second most frequent aetiology is congenital, more frequently involved in younger patients.

Natural History

AS is a chronic, progressive disease. During a long latent period, patients remain asymptomatic, with a reported average event-free survival at 2 years ranged from 20 to 50 %. Risk factors of symptom development and adverse outcomes are: older age, peak aortic jet velocity, abnormal parameters of systolic and diastolic LV function [13], increase in gradient with exercise [14], excessive LV hypertrophy [15], clinical symptoms and ST-segment depression during exercise testing, elevated plasma levels of B-type natriuretic peptides (BNP) [16].

As soon as symptoms occur, the prognosis of severe AS is dismal, with survival rates of only 15–50 % at 5 years. Sudden cardiac death is frequent in symptomatic patients but appears to be rare in the asymptomatic. That highlights the importance of follow-up and screening of symptoms as soon as they occur.

Evaluation

A careful clinical evaluation is essential, including research of symptoms of HF.

Echocardiography confirms the presence of AS, assesses LV function, size and wall thickness, detects the presence of other associated valve disease or aortic pathology, and provides prognostic information. Although AS with a valve area <1.0 cm^2 is considered as severe, critical AS is most likely with a valve area <0.8 cm^2 [17] and a mean pressure gradient >40 mmHg (with normal cardiac output and transvalvular flow). Valve area should be indexed to BSA, with a cut-off value of 0.6 cm^2/m^2.

The main concern in patients with LV systolic dysfunction is the entity of « low-flow, low-gradient » AS (valve area <1 cm^2, EF <40 %, mean gradient <40 mmHg) because some may have severe aortic stenosis and others “pseudo-severe AS” (low flow across the aortic valve not caused by a severe fixed obstruction but by low stroke volume). Low-dose dobutamine stress echocardiography may be helpful to distinguish these two types of patients. In the first case, only small increases in valve area (<0.2 cm^2 and remaining <1 cm^2) are observed, with increasing flow rate, but a significant increase in gradients (mean gradient > 40 mmHg). In the second case, a marked increase in valve area but only minor changes in gradients are observed. In addition, this test provides information about contractile reserve, which is of prognostic importance. Individuals with flow reserve (increase > 20 % of stroke volume) have a lower operative mortality and better long-term prognosis [18, 19]. Stress echocardiography

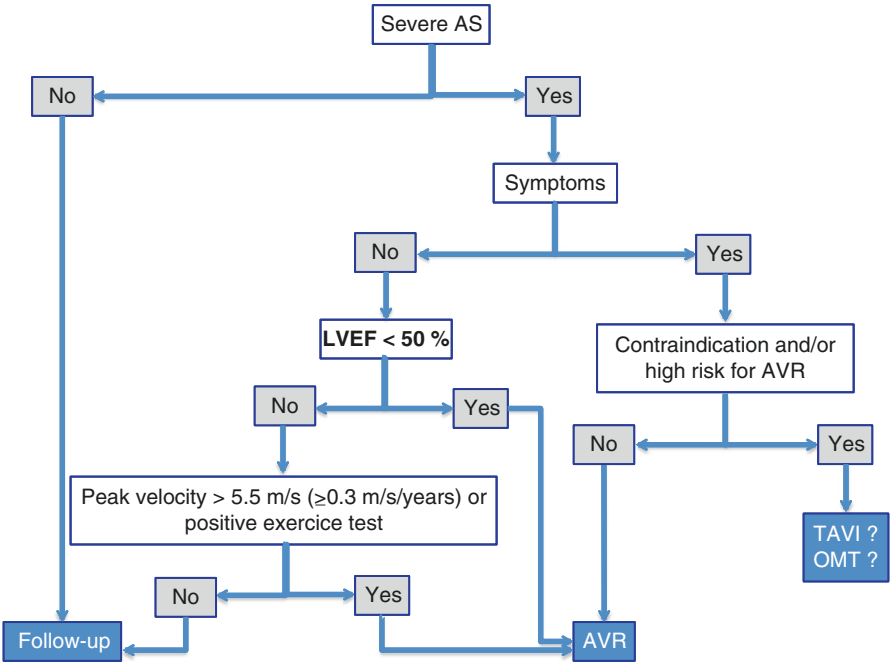

Fig. 17.2 Management algorithm of severe aortic stenosis. *AS* aortic stenosis, *AVR* aortic valve replacement, *LVEF* left ventricular ejection fraction, *OMT* optimal medical therapy, *TAVI* transcatheter aortic valve implantation

may provide prognostic information in asymptomatic severe AS, by assessing the increase in mean pressure gradient and change in LV function [14, 21–23].

Computed tomography (CT) and magnetic resonance (MR) provide additional assessment of the ascending aorta when it is enlarged. Moreover, CT has become an important diagnostic and assessment tool before undertaking transcatheter aortic valve implantation (TAVI).

Intervention

A management algorithm of AS is proposed in Fig. 17.2.

Aortic Valve Replacement (AVR)

LV function usually improves after AVR if reduced EF is predominantly caused by excessive afterload [20]. Conversely, if the primary cause is scarring due to extensive myocardial infarction or cardiomyopathy, improvement in LV function is uncertain. Early AVR is recommended in all symptomatic patients with severe AS, regardless of

LVEF. The management of patients with « low-flow, low-gradient » AS is more difficult. In patients with low gradients and evidence of flow reserve, surgery improves long-term outcome in most patients, through an acceptable risk. Although the outcome of patients without flow-reserve is compromised by a higher operative mortality, AVR has been shown to improve EF and clinical status in such patients [24]. Final decision-making should take into account the patient's comorbidities, the degree of valve calcification, the extent of potential CAD and the feasibility of revascularization.

Management of asymptomatic severe AS remains controversial [13, 25]. Early elective AVR is indicated in the very rare asymptomatic patients with depressed LV function (not due to other causes) or with an abnormal exercise test [23]. Surgery may also be considered in patients at low operative risk with elevated BNP levels without other explanation [15, 16].

In contemporary series, operative mortality of isolated AVR for AS is 1–3 % in patients younger than 70 years and 4–8 % in older adults [12, 26, 27]. Higher functional class and LV dysfunction are identified among main predictors of operative mortality (emergency intervention, pulmonary hypertension, coexisting CAD and previous heart surgery). Although combined AVR and CABG carries a higher risk than isolated AVR [12], late AVR after CABG is also associated with significantly increased risk. Thus, decision-making is based on individual judgement [28]. After successful AVR, symptoms and quality of life are in general improved [26, 27]. Risk factors for late death and morbidity include severe symptoms, LV dysfunction, ventricular arrhythmias, untreated co-existing CAD, prosthesis-related complications and suboptimal haemodynamic performance.

Balloon Valvuloplasty

Balloon valvuloplasty may be considered as a bridge to surgery or TAVI in haemodynamically unstable patients who are at high risk for surgery, or in patients with symptomatic severe AS who require urgent major non-cardiac surgery. Valvuloplasty may also be considered as a palliative treatment when surgery and TAVI are contraindicated.

Transcatheter Aortic Valve Implantation

TAVI is recommended in patients with severe symptomatic AS who are, according to a "heart team", considered contra-indicated or at high risk for conventional surgery because of severe comorbidities.

Medical Therapy

No medical therapy is able to improve outcome, compared with the natural history. Thus, symptomatic AS require early intervention and optimization of treatment should not delay surgical decision-making. Management of HF symptoms

or co-existing hypertension may involve vasodilators, diuretics, angiotensin-converting enzyme (ACE) inhibitors, or ARBs. These treatments may cause substantial hypotension in patients with severe AS and should only be used with great caution.

Mitral Regurgitation

Mitral regurgitation (MR) is the second most frequent valve disease requiring surgery in Europe [29]. Assessment of MR is complex, particularly in patients with systolic dysfunction. Moreover, assessment of systolic function is complicated in the presence of significant MR, because EF may be preserved and stroke volume reduced. Differentiating between primary and secondary mitral regurgitation is crucial.

Primary (Organic) Mitral Regurgitation

Primary MR covers all aetiologies in which intrinsic lesions affect one or several components of the mitral valve apparatus: degenerative MR is now the most common aetiology in western countries, followed by endocarditis. Incidence of rheumatic fever decreased significantly [30].

Several echocardiographic criteria can be used to define severe primary MR: width of the vena contracta ≥7 mm, proximal isovelocity surface area (PISA), EROA ≥40 mm^2, RVol ≥60 ml. The final assessment of severity requires integration of such data with the effects on left atrial (LA) volume, LV size and EF, systolic pulmonary arterial pressure (SPAP), and right ventricular (RV) function.

Acute Mitral Regurgitation

Acute MR due to papillary muscle rupture should be considered in patients presenting with acute pulmonary oedema or shock, following myocardial infarction, infective endocarditis or trauma. The diagnosis is suggested by the demonstration of hyperdynamic function in the presence of acute HF [31]. Acute MR is poorly tolerated, but may stabilize after an initial symptomatic period. However, left unoperated, it carries a poor spontaneous prognosis due to development of pulmonary hypertension.

Urgent surgery is indicated in patients with acute severe MR, if necessary after stabilization of haemodynamic status using intra-aortic balloon pump (IABP), positive inotropic agents or vasodilators. Valve surgery consists of valve replacement in most cases or in repair, depending on valve anatomy and lesions, surgical expertise, and the patient's condition [31].

Chronic Mitral Regurgitation

Surgery is indicated in symptomatic patients with chronic MR, LVEF >30 % and LVESD <55 mm, and no contraindication to surgery. Intervention should also be considered in patients with severe LV dysfunction (LVEF < 30 % and/or LVESD > 55 mm), refractory to medical therapy, with low comorbidity and high likelihood of durable repair, as assessed by echocardiography providing precise definition of the different anatomical lesions (according to the Carpentier classification). Mitral annular dimensions should also be assessed. Exercise echocardiography is useful to quantify exercise-induced changes in MR, in systolic pulmonary artery pressure, and in LV function. Exercise-induced changes in LV volumes, EF and global strain may predict postoperative LV dysfunction [32].

Several studies suggest the value of elevated BNP level as a risk factor of developing HF, LV dysfunction or death on mid-term follow-up, making it potentially helpful in the follow-up of asymptomatic patients [33, 34].

The management of asymptomatic severe chronic MR is controversial. In these patients, the estimated 5-year rates of death from any cause, death from cardiac causes, and cardiac events (death from cardiac causes, HF, or new atrial fibrillation (AF)) have been reported to be 22 %, 14 %, and 33 %, respectively. In addition to symptoms, the predictors of poor outcome are: age, AF, severity of MR, pulmonary hypertension, LA dilatation, increased LVESD, and low LVEF [35–40]. Surgery is indicated in patients with signs of LV dysfunction (LVEF ≤60 % and/or LVESD ≥45 mm). Surgery should also be considered in asymptomatic patients with new onset of AF [41] or pulmonary hypertension (SPAP >50 mmHg at rest), and a high likelihood of durable valve repair [40, 42]. Finally, surgery may be considered in patients with SPAP >60 mmHg at exercise [43] or with severe LA dilatation (≥60 ml/cm^2 BSA) [38]. In other asymptomatic patients, severe MR requires careful and regular follow-up until symptoms supervene or previously recommended cut-off values (LV dysfunction) are reached.

When indicated, early surgery (within 2 months) is associated with better outcomes, since the development of even mild symptoms by the time of surgery is associated with deleterious changes in cardiac function after surgery [41–44]. A management algorithm of primary MR is proposed in Fig. 17.3.

Surgery

It is widely accepted that, when feasible, valve repair is the optimal surgical treatment of severe MR, involving a lower perioperative mortality, improved survival, better preservation of postoperative LV function, and lower long-term morbidity, compared with valve replacement.

Degenerative MR due to segmental valve prolapse can usually be repaired with a low risk of reoperation. Conversely, rheumatic lesions, extensive valve prolapse, and MR with leaflet or extensive annulus calcifications are less accessible to repair [45]. The results of mitral valve repair must be assessed intraoperatively by TOE to

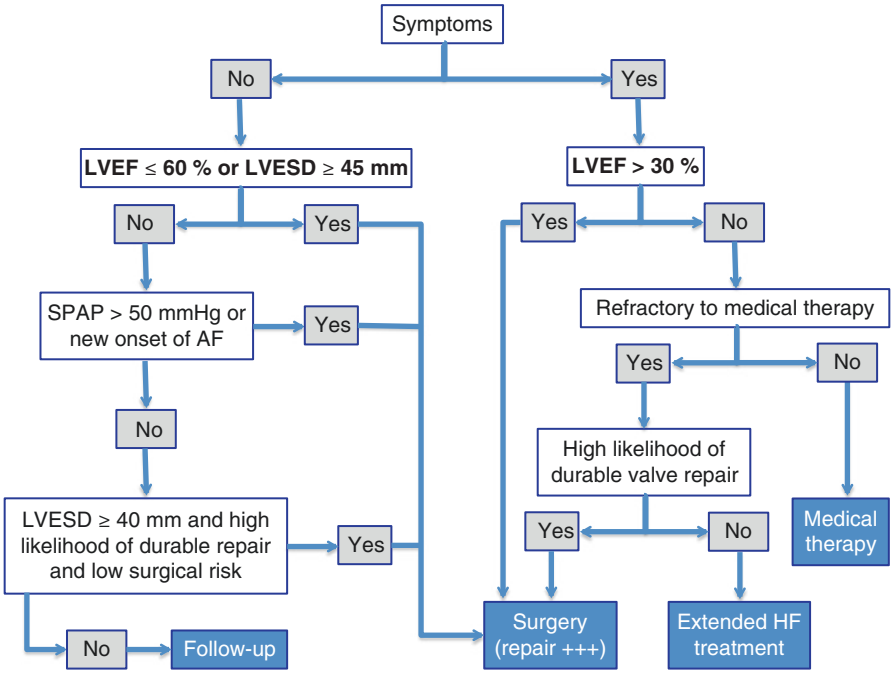

Fig. 17.3 Management algorithm of severe chronic primary mitral regurgitation. *AF* atrial fibrillation, *HF* heart failure, *LVEF* left ventricular ejection fraction, *LVESD* left ventricular end-systolic diameter, *SPAP* systolic pulmonary arterial pressure

enable immediate further surgical correction if necessary. When repair is not feasible or suboptimal, mitral valve replacement with preservation of the subvalvular apparatus is performed.

Beside symptoms, the most important predictors of post-operative outcome are: age, AF, preoperative LV function (the best results are observed in patients with a preoperative EF >60 %, LVESD <40 mm (22 mm/m^2 BSA)) and pulmonary hypertension [40].

Percutaneous Intervention

Percutaneous interventions have been developed to correct MR, and may be proposed in patients with symptomatic severe primary MR, considered inoperable or at high surgical risk by a "heart team", and have a life expectancy greater than 1 year [46, 47].

Medical Therapy

In acute MR, reduction of filling pressures can be obtained with nitrates and diuretics, reducing afterload and regurgitant fraction (as does an IABP). Inotropic agents and IABP should be added in case of HF. In chronic MR with HF symptoms, ACE inhibitors, beta-blockers and spironolactone can be beneficial [48].

Secondary Mitral Regurgitation

In secondary MR or "functional MR", valve leaflets and chordae are structurally normal and MR results from geometrical distortion of the subvalvular apparatus (apical and lateral papillary muscle displacement, annular dilatation), secondary to LV dysfunction, enlargement and remodelling (due to idiopathic cardiomyopathy or CAD), leading to reduced leaflet closing [49].

Natural History

Patients with chronic ischaemic MR have a poor prognosis. The presence of severe CAD and LV dysfunction have prognostic importance. Likewise, severity of MR is associated with worse outcome. In patients with secondary MR due to non-ischaemic aetiology, a precise analysis is more difficult [35].

Evaluation

In secondary MR, because of their prognostic value, lower thresholds of severity have been proposed (20 mm^2 for EROA and 30 ml for RVol) [35, 49]. Ischaemic MR is a dynamic condition and its severity may vary, depending upon changes in loading conditions, with potential increase in pulmonary vascular pressure and acute pulmonary oedema. The dynamic component can be assessed and quantified by exercise echocardiography [50]. The assessment of coronary status is necessary to complete the diagnosis and allows evaluation of revascularization options. In patients with low LVEF, it is also mandatory to assess the presence and extent of myocardial viability, which is a predictor of good outcome after repair combined with CABG [51, 52].

Indications for Intervention

Severe ischemic MR should be corrected at the time of bypass surgery. Valve repair should be discussed for moderate ischaemic MR, in patients undergoing CABG. Mitral valve surgery should also be considered in symptomatic patients with LV systolic dysfunction (LVEF <30 %), CAD suitable for revascularization and evidence of viability. Exercise-induced dyspnoea and a large increase in MR severity and SPAP favour combined surgery. The role of isolated mitral valve surgery in patients with severe functional MR and LV systolic dysfunction who cannot be revascularized or have non-ischaemiccardiomyopathy is uncertain. Repair may be considered in selected patients with low comorbidity, in order to avoid or postpone transplantation, in case of failure of optimal medical therapy (OMT), including cardiac resynchronization therapy (CRT) and ventricular assist devices.

Surgery

Surgery for secondary MR remains a challenge. Operative mortality is higher than in primary MR and the long-term prognosis is worse, particularly due to comorbidities. When surgery is indicated, there is a trend favouring valve repair using only an undersized, rigid ring annuloplasty, which confers a low operative risk although it carries a high risk of MR recurrence [53, 54]. Predictors of late failure of valve repair and recurrent secondary MR are associated with a worse prognosis: LVEDD >65 mm, systolic tenting area >2.5 cm^2, coaptation distance >10 mm, end-systolic interpapillary muscle distance >20 mm, among others [54]. In these patients, mitral valve replacement may be advisable. A recent meta-analysis of retrospective studies suggests better short-term and long-term survival after repair than after replacement [55].

Ischaemic MR should be more suitable for surgical repair [56]. Most studies show that severe ischaemic MR is not usually improved by revascularization alone, and that persistence of residual MR carries an increased mortality risk; however the impact of valve surgery on survival remains unclear [57, 58], even if valve repair is considered to improve functional class, EF, and LV diameter [59].

Percutaneous Intervention

Experience from a limited number of patients in the EVEREST trials and from observational studies suggests that percutaneous edge-to-edge mitral valve repair is feasible (at low procedural risk) in patients with severe secondary MR despite OMT and may provide short-term improvement in functional condition and LV function.

Medical Treatment

OMT is mandatory: it should be the first step in the management of all patients with secondary MR, according to the guidelines on the management of HF. Reverse remodelling of the LV may reduce functional MR. This includes ACE inhibitors, beta-blockers and aldosterone antagonists. A diuretic is required in the presence of fluid overload. Nitrates may be useful for treating acute dyspnoea. CRT should be indicated in accordance with related guidelines [60, 61].

Mitral Stenosis

If mitral stenosis (MS) can lead to signs of left heart failure, it doesn't involve left ventricular failure. Rheumatic fever, predominant aetiology of MS, decreased significantly in industrialized countries. Nevertheless, MS still results in significant morbidity and mortality worldwide [29]. Survival in asymptomatic patients is

usually good up to 10 years, progression being highly variable with sudden deterioration, usually precipitated by pregnancy or complications such as AF. Symptomatic patients have a poor prognosis without intervention.

Echocardiography is the main method used to assess MS, considered as severe when valve area is <1.0 cm^2 and mean gradient is >10 mmHg [62, 63]. Mean transvalvular gradient, is highly rate- and flow-dependent, but is useful to check consistency in the assessment of severity. Echocardiography also evaluates pulmonary artery pressures, associated MR and LA size. A comprehensive evaluation of the aortic and tricuspid valves is mandatory, due to the frequent association of MS with other valve diseases. In asymptomatic patients or in case of discordant symptoms with the severity of MS, stress testing (dobutamine or exercise echocardiography) may provide additional information by assessing changes in mitral gradient and pulmonary pressures [22].

Intervention should be performed in symptomatic patients with significant MS (valve area $\leq$ 1.5 cm^2). Surgery for MS is mostly valve replacement, as a result of unfavourable valve characteristics for valve repair. Operative mortality (3–10 %) and long-term survival are related to functional class, pulmonary hypertension and preoperative LV/RV function, among other factors. Percutaneous mitral commissurotomy provides good initial results (defined as valve area >1.5 cm^2 with no MR >2/4) in over 80 % of cases. Major complications include procedural mortality, haemopericardium, embolism, and severe regurgitation. Emergency surgery is seldom needed (<1 %) [64]. Event-free survival ranges from 30 to 70 % after 10 to 20 years [62]. When functional deterioration occurs, it is late and mainly related to restenosis [65].

Tricuspid Regurgitation (TR)

Pathological TR is more often secondary, rather than due to a primary valve lesion. Secondary TR is due to annular dilatation and increased tricuspid leaflet tethering in relation to right ventricular (RV) pressure overload (pulmonary hypertension resulting from left-sided heart disease, idiopathic pulmonary arterial hypertension, chronic corpulmonale) and/or volume overload (atrial septal defects or intrinsic disease of the RV).

Natural History

The limited available data on the natural history of primary TR suggest that severe TR has a poor prognosis, even if it may be well-tolerated functionally for years [4, 66]. As for left-sided valvular regurgitation, prolonged volume overload may result in ventricular dysfunction and irreversible myocardial damage, associated with increased risk of HF and decreased survival [67]. Secondary TR may improve or

disappear as RV failure improves, following the treatment of its cause. However, TR may persist even after successful correction of left-sided lesions, with risk factors such as pulmonary hypertension, increased RV pressure and dimension, reduced RV function, AF and severity of tricuspid valve deformation [68, 69].

Evaluation

Predominant symptoms are those of associated valve diseases. Although they are load-dependent, clinical signs of right HF are of value in evaluating the severity of TR.

Echocardiography is a key tool in assessment of severe TR, defined by an EROA ≥40 mm^2 and/or a RVol ≥45 ml. Annular dilatation should also be assessed and is considered as significant if diastolic diameter is ≥40 mm or ≥21 mm/m^2 [4, 68]. RV dysfunction could be revealed by a tricuspid annular plane systolic excursion (TAPSE) <15 mm or a RV end-systolic area >20 cm^2 [69]. When available, CMR is the preferred method for evaluating RV size and function. In primary TR, the aetiology can usually be identified from specific structural lesions such as vegetations in endocarditis [70], leaflet thickening and retraction in rheumatic and carcinoid disease, prolapsing leaflet in myxomatous disease and dysplastic tricuspid valve in congenital diseases such as Ebstein's anomaly [71]. In secondary TR, a coaptation distance >8 mm characterizes significant tethering [72]. The presence of left-sided associated valve lesions and LV function have to be assessed.

Indications for Surgery

Surgery should be performed early enough to avoid irreversible RV dysfunction and poor results of late surgical intervention; careful follow-up of asymptomatic patients is needed to detect progressive RV enlargement and development of early RV dysfunction. Surgery limited to the tricuspid valve is recommended in symptomatic patients with severe primary TR. Correction of TR is also considered at the time of surgery for left-sided valve lesions, in patients with severe TR, as well as in patients with mild or moderate TR and significant dilatation of the annulus (≥40 mm) [68].

Surgery

When indicated, valve repair is preferred to valve replacement. Ring annuloplasty is key to surgery for TR, especially in case of isolated tricuspid annular dilatation. Better long-term results are observed with prosthetic rings than with the suture annuloplasty [68, 73, 74]. When the tricuspid valve is significantly deformed, complementary tricuspid valve procedures may be useful in order to reduce residual

postoperative TR [75]. In more advanced forms of tethering and RV dilatation, valve replacement should be considered. Bioprostheses are currently favoured, because of their satisfactory long-term durability in the tricuspid position and the higher risk of thrombosis carried by mechanical valves [76, 77].

Adding a tricuspid repair, if indicated during left-sided surgery, does not increase operative risks, main predictors being preoperative functional class, LV and RV function, and prosthetic complications [73–76]. Reoperation on the tricuspid valve in cases of persistent TR after mitral valve surgery carries a high risk, mostly due to the clinical condition of the patient (including age and the number of previous cardiac interventions) and may well have poor long-term results related to the presence of irreversible RV dysfunction before reoperation, or LV myocardial or valvular dysfunction.

Tricuspid Stenosis

Tricuspid stenosis (TS), which is mostly of rheumatic origin, is rarely observed in developed countries.

Evaluation

Clinical signs are often masked by those of the left-sided associated valvular lesions, especially MS [77]. Echocardiography provides the most useful information. A mean gradient ≥5 mmHg at normal heart rate is considered indicative of clinically significant TS [63]. Echocardiography should also examine the presence of commissural fusion and the degree of concomitant TR.

Interventions

Intervention is usually carried out at the time of intervention on the other valves in patients who are symptomatic despite medical therapy. Conservative surgery or valve replacement (according to anatomy and surgical expertise) is preferred to balloon commissurotomy (frequently inducing significant regurgitation), which can only be considered as a first approach in the rare cases of isolated TS.

Combined and Multiple Valve Diseases

There is a lack of data on mixed and multiple valve diseases [77]. Besides the separate assessment of each valve lesion, it is necessary to take into account the interaction between these different valve lesions. Indications for intervention are

based on global assessment of the consequences of the different valve lesions, such as symptoms or presence of LV dilatation or dysfunction. As an illustration, associated MR may lead to underestimation of the severity of AS, since decreased stroke volume due to MR lowers the flow across the aortic valve and the aortic gradient. Conversely, MR severity may be overestimated in such patients. As long as there are no morphological leaflet abnormalities, mitral annulus dilatation or marked abnormalities of LV geometry, surgical intervention on the mitral valve is usually not necessary and non-severe secondary MR usually improves after aortic valve treatment. Intervention can be considered for non-severe multiple lesions associated with symptoms or leading to LV impairment, and should take into account the extra surgical risk of combined procedures. The choice of surgical technique should take into account the presence of the other VHD. Although repair remains the ideal option, the desire to repair one valve may be decreased if prosthetic valve replacement is needed on another.

Future Directions

VHD is not an infrequent cause of HF. However, when valvular disease is managed correctly and pre-emptively, its adverse consequences on ventricular mechanics can be ameliorated.

Stress echocardiography should be considered as part of the follow-up of all asymptomatic patients with VHD, providing the clinician with diagnostic and prognostic information (assessment of dynamic changes in valve and ventricular functions, hemodynamics) that may contribute to subsequent clinical decisions. Nevertheless, convincing evidence is still lacking and prospective large-scale and randomized studies are needed to support evidence-based strategies in patients with VHD.

Surgical therapies and percutaneous interventions commonly integrated in HF management include AVR and mitral valve replacement or repair. Repair strategies are increasingly used in experienced centres, especially in young patients. It is widely accepted that, when feasible, valve repair is the optimal surgical treatment of severe MR, involving a lower perioperative and long-term mortality, better preservation of postoperative LV function and lower long-term morbidity. Intraoperative TOE is mandatory to assess the functional results and identify high-risk patients for early recurrence of VHD.

The advent of effective transcatheter approaches to both mitral and aortic disease creates the need for greater considerations of structural interventions for patients with LV systolic dysfunction and VHD. AVR or TAVI for critical AS is an effective strategy with reasonable outcomes noted even in patients with advanced age (>80 years). To date, the surgical or transcatheter management of functional MR has not been proven superior to medical therapy, and consideration should be given to participation in clinical trials and/or databases.

Disclosures All the authors have nothing to disclose with regard to commercial support

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Chapter 18
Percutaneous Valvular Therapies in Heart Failure

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Transcatheter Aortic Valve Intervention for Patients with HF

According to the wide definition of heart failure (HF), a clinical syndrome resulting from any structural or functional cardiac disorder that impairs the pumping function of the heart, this condition accounts from most of patients with symptomatic aortic stenosis (AS) [1]. The onset of symptoms of HF is linked to the worst prognosis in these patients, with a predicted survival of 1–2 years [2]. And, although survival is dramatically improved by the aortic valve replacement, the presence of HF is an independent predictor of mortality after surgery [3]. The prevalence of left ventricular dysfunction (LVD) among patients with severe AS ranges between 6 and 11 %, considering a cut-off value of LV ejection fraction (LVEF) of ≤30 %, and between 27 and 46 %, if LVEF is 30–50 % [4–6]. The small proportion of patients with severe LVD represents a particular high-risk subgroup with specific therapeutic and prognostic issues [7, 8]. It has been previously reported that the presence of LVD, defined as LVEF <50 %, is associated with an increased mortality even in asymptomatic patients [9]. However, although LVD does not contraindicate aortic valve

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M. Dorobanțu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_18

surgery [10], its association with an increased perioperative mortality makes this feature one of the main reasons for denying surgery in elderly patients with AS [11]. In this situation the management with less invasive transcatheter techniques is an appealing alternative.

Pathophysiologic and Diagnostic Considerations

The LV afterload produced by the LV outflow obstruction, the occurrence of ischemia owing to an impairment of coronary blood flow reserve and neuro-hormonal factors involving the renin-angiotensin system have been associated with the occurrence of myocites apoptosis and fibrosis, which have been proposed as the responsible mechanisms for the transition from LV hypertrophy to LV systolic dysfunction [12, 13]. The presence of LVD in patients with AS can be caused by other coexisting conditions independent form the outflow obstruction such as coronary artery disease or primary myocardial affection.

Severity of AS is defined by an aortic valve area (AVA) <0.8–1.0 cm^2 (<0.6 cm^2/m^2) with a maximum peak velocity >4.0 m/s and a mean gradient >40 mmHg [14]. However the occurrence of low flow in patients with LVD secondary to LV outflow obstruction may lead to a lower mean transaortic gradient despite the presence of a truly severe AS. This condition is so-called low-flow low-gradient AS and is defined by an AVA <1.0 cm^2, a LVEF <40 % and a mean transaortic gradient <40 mmHg. This entity may account for 5–10 % of patients with severe AS and is poses a challenging management owing to the difficulty of being differentiated from the "pseudo-severe AS", in which the low gradient is produced by a primary myocardial disease. The differentiation of both entities is essential since aortic valve replacement in patients with low-flow low-gradient AS is associated with improved survival, but not in patients with "pseudo severe AS" [15, 16]. The performance of a low dose dobutamine stress echo is helpful to distinguish between both conditions by assessing the AVA, mean gradients and LVEF during the test [14]. Other potential diagnostic tool is the aortic valve calcium evaluation by computed tomography (CT). It has been proposed that in the subgroup of patients with LVD a cut-off of 1651 Agatston Units may help to differentiate those with severe AS [17]. And finally, BNP and NT-pro-BNP levels are useful in the management of patients with AS. It has been reported that BNP levels indicates a heart failure status in patients referred to transcatheter aortic valve implantation (TAVI) and higher levels predicted the presence of lower LVEF and stroke volume [18]. In the TOPAS study levels of BNP were higher in patients with true AS compared to those with pseudo-severe AS and were predictors of mortality regardless the treatment strategy [19]. Likewise, BNP has been proved to be predictive of survival in patients undergoing TAVI [20, 21] and its levels should be included in the management of such patients.

Transcatheter Treatment

Percutaneous Balloon Aortic Valvuloplasty (PBAV)

The procedure is performed by the use of a single or dual balloon that is inflated in the aortic annulus under rapid pacing. The PBVA produces an immediate decrease in transaortic mean gradient and increase in AVA of 0.2–0.4 cm^2, which translates into symptomatic improvement and LV performance recovery [22, 23]. This acute effect is counterbalanced by a high rate of restenosis (50 % at 6 month), a finding linked into an increase in the rate of hospitalizations, HF symptom recurrence and lack of survival benefit [22, 24–26] even in those patients with a successful procedure. This finding was recently corroborated in the PARTNER trial (cohort B) [27] where patients randomized to medical therapy (with 60 % of PBAV) presented a 51 % rate of mortality during first year. Furthermore, the procedure is associated with a significant number of complications [26]. Both facts are responsible that this technique has been restrained to palliative treatment.

However, in spite of the poor results of the technique there are two scenarios where PBAV still may have a role. The first one is the use of PBAV as a bridge to surgical aortic valve replacement (SAVR) or TAVI [26, 28–31] in patients presenting with severe HF or cardiogenic shock or severe LVD [32]. In these situations, PBAV allows to perform the intervention in better clinical and hemodynamic conditions reducing the risk of complications [26]. Likewise, in patients with LVD the PBAV allows the recovery of LV performance, favorable LV remodeling and decrease of BNP levels [23, 33]. Nonetheless, the definite therapy should be performed soon after the PBAV, since the high probability of restenosis may lead to further complications [29, 34]. The second scenario is the use of PBAV as a diagnostic tool in patients whose symptoms are not clearly related to AS and in patients with decompensated HF and/or severe LVD. The acute reduction in LV overload would led to a better LV performance and reduction in symptoms, thus identifying those who will benefit from a definite therapy [28, 35].

Transcatheter Aortic Valve Implantation (TAVI)

Since the first TAVI implantation in 2002 [36] this technology has spread along the world becoming a routine therapy for patients with symptomatic AS. TAVI has been proved to be superior to medical management [27] and non-inferior to SAVR in high-risk patients in the events death or death and stroke [37, 38], and this was maintained at 5-year follow-up [39, 40]. Furthermore, it has been recently reported that TAVI was non-inferior to surgery in an intermediate risk population [41].

More than 90 % of patients included in main trials and registries were highly symptomatic (NYHA functional class III or IV) but in a compensated stable HF status. However, data on patients with acute pulmonary edema, cardiogenic shock or severe LVD are scarce. A few case series have reported the feasibility of

performing TAVI in those patients with acceptable results, suggesting that TAVI may be used in well-selected cases, as a bailout strategy, in patients with cardiogenic shock or pulmonary edema [42, 43].

More interest is focused in those patients with significant LVD. In this subset a controversy exists regarding the effect of LVD in the results of TAVI: whereas several publications raised the awareness that is linked to an increased mortality [6, 8, 44, 45], other find no association with worse outcome [46, 47]. In the PARTNER 1 trial the presence of low flow rather than LVD was associated with impaired prognosis [48]. In addition, patients with low flow low gradient AS were at an increase risk for acute and late mortality. Notwithstanding, TAVI in these patients was associated with a significant symptom improvement, hemodynamic benefit and recovery in LV function and, therefore, it is recommended in this subset [47–49]. No differences in mortality have been observed between TAVI and SAVR in patients with LVD, however, patients referred to TAVI are associated with greater LV recovery, and this difference is more evident in those patients undergoing transfemoral TAVI [50]. There is little information regarding factors associated with LV recovery in patients with LVD. Although several factors have been proposed only the use of TAVI and the increase in AVA have been independently associated with an improvement in LVEF [50]. Also, the presence of conduction disturbances and the necessity for permanent pacemaker have been associated with lack of improvement or even deterioration in LV function [51, 52]. And, finally, the presence of coronary disease and its management may influence as well the LV recovery. Revascularization in patients undergoing TAVI has not proved to increase survival and thus, the effect of this therapy in patients with LVD and AS is yet to be determined [53].

In Fig. 18.1 a proposed algorithm for management of this patients is pointed out.

Transcatheter Mitral Valve Intervention (TMVI) for Patients with HF

Why Do We Need TMVI?

Mitral regurgitation (MR) is the second most common symptomatic valvular disease worldwide [54]. Functional MR (FMR), also known as secondary MR, is secondary to LV remodeling with otherwise structurally preserved mitral leaflets. Moderate-to-severe MR may be present in up to 50 % of patients with congestive HF [55] and the presence of MR after myocardial infarction or with dilated cardiomyopathy is associated with an increased risk of cardiac insufficiency and death [56–59]. This negative effect is observed as well in patients with MR after an acute myocardial infarction treated with primary angioplasty [60]. And, although the optimal management for FMR has still to be defined, a long series form Duke University has proved that medical management alone in patients with ischemic MR is associated with the highest rates of death after 20 years of follow-up [61]. Mitral valve (MV) surgery is the

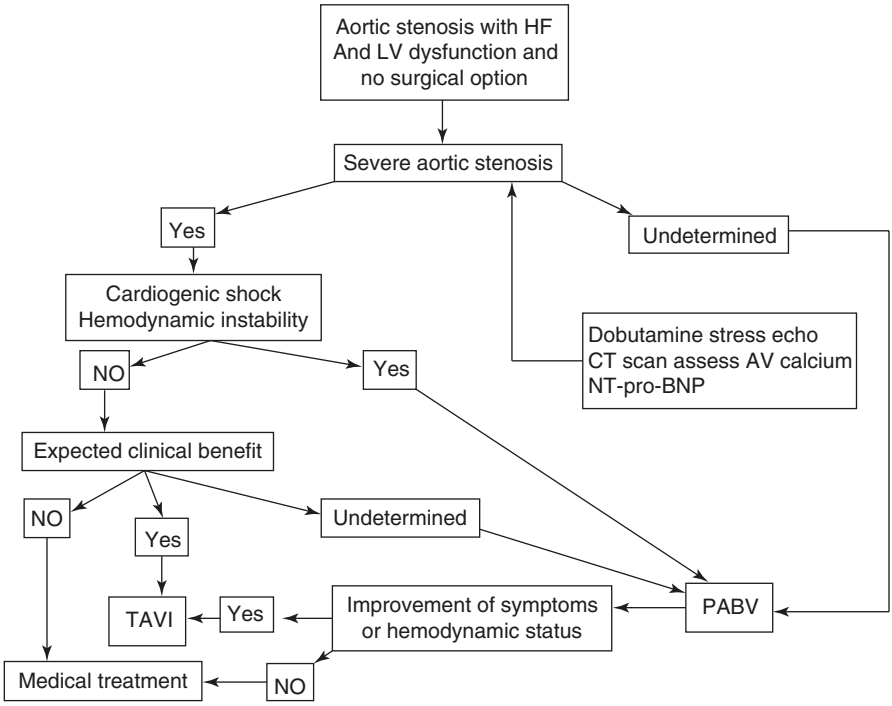

Fig. 18.1 Algorithm proposed for the management of AS and LVD

treatment of choice for patients with severe MR that fulfill guidelines' criteria [14]. However, 50 % of patients [62, 63] referred for MV surgery are not operated on, predominantly due to comorbidities, LV dysfunction or advanced age [64]. And the proportion of patients with FMR undergoing surgical treatment is even lower [65]. The reason for this finding is not only related to the high-risk population but also to the fact that surgical interventions for FMR have yielded conflicting results. This is due to the lack of clear survival benefit and the high recurrence rate of significant MR 1 year after surgery, even with modern annuloplasty techniques [66–69]. Patients with FMR managed medically represent a high-risk population with high rates of death and readmission due to HF [70]. And readmissions are the main reason for the progressive increase in the costs of HF patients [71]. In this population catheter-based interventions have emerged to fill a large unmet need.

Which Device Should We Use for TMVI?

Mitral valve is a complex apparatus with several structures that, if affected, may lead to the presence of MR [72]. That is the reason why in the last few years we have witnessed a large innovation in this field with several devices under

Table 18.1 Devices in pipeline for transcatheter mitral valve interventions

Anatomic Target					
Leaflet/ Chordae	Indirect annuloplasty	Direct or LV annuloplasty	Hybrid surgical	LV remodeling	Replacement
MitraClip	Carillon XE2 Mitral Contour System	Mitralign	Adjustable Annuloplasty Ring	The Basal Annuloplasty of the Cardia Externally (BACE)	CardiaQ
Neochord DS1000 System	Kardium MR	GDS Accucinch system	EnCor Dinaplasty ring	Tendyne repair	Fortis
Mitra-Spacer	Cerclage annuloplasty	Cardioband	Cardinal ring		Tendyne
Mitra-Flex		Milipede			Tiara
Middle Peak Medical		TASRA			Medtronic valve
V-Chordal					M-Valve
					Cephea
					Sinomed
					Twelve
					Endovalve

investigation [73]. These devices aim to correct one or several mechanisms that led to MR. A summary of these devices is shown in Table 18.1. Some of them have gained approval for human use and have been tested in small clinical trials [74, 75]. Among all, only MitraClip (Abbott Vascular, Abbott Park, IL) has gained wide clinical use. The device consists of two 8-mm clip arms and opposing grippers, which can be opened and closed against each other in order to grasp and gain coaptation at the origin of the regurgitant jet. Under general anesthesia and using fluoroscopic and two- and three-dimensional transesophageal echo guidance, the device is advanced via the transseptal route across the MV into the left ventricle. With the two arms of the clip extended, the device is retracted to capture, and subsequently closed to coapt the MV leaflets (Fig. 18.2). Repositioning before release is feasible and a second or more clips can be placed as needed for optimal MR reduction. Feasibility of MitraClip was first demonstrated in the Endovascular Valve Edge-to-Edge Repair Study (EVEREST) I trial and subsequently compared with surgery in the randomized EVEREST II trial [76, 77]. In these studies stringent echo criteria were used to guide the feasibility of device insertion and deployment. However, with increasing experience more complex valve pathologies can be treated with excellent results [78]. The vast majority of clinical evidence in TMVI derives from MitraClip studies and patient selection and the potential benefits of the therapy mentioned in this chapter are related to this device.

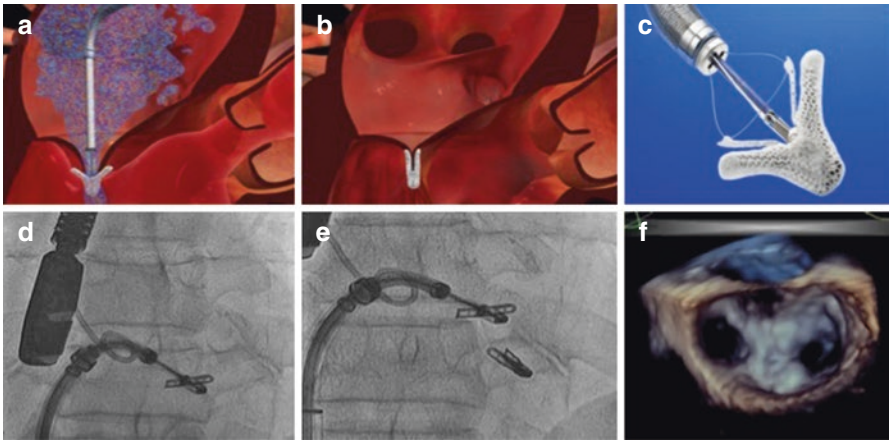

Fig. 18.2 Panel (**a**) MitraClip opened and with leaflet insertion prior to grasp. Panel (**b**) Grasping performed and reduction in regurgitant jet is observed. Panel (**c**) MitraClip device with arms and grippers. Panel (**d**, **e**) Fluoroscopic vision of MitraClip implantation. Panel (**f**) Final double-orifice mitral valve morphology

Patient Selection for TMVI

In the randomized EVEREST II trial, 184 patients were designated (2:1) to receive MitraClip therapy and 95 patients to undergo surgical repair or replacement. Baseline characteristics of the study population revealed a mean age of 67 years, almost a decade older than usual surgical series of repair, as well as more comorbidities. Major adverse events at 30 days were significantly less frequent with MitraClip therapy (9.6 % versus 57 % with surgery, $P < 0.0001$), although much of this difference was attributable to the greater need for blood transfusion with surgery. The primary end point of freedom from death, mitral valve surgery, and MR severity >2+ at 12 months in patients with initial clinical success was similar, but by intent to treat analysis was lower with MitraClip (55 %) as compared with surgery (73 %, $P = 0.0007$) [77]. Results of this trial at 5 years confirmed the initial results of the study. In those patients with an initial successful repair showed no differences in mortality or reoperation compared to surgery. And, the proportion of patients with MR 3+ to 4+ at 5-year follow-up was 19 %, the same figure that the observed at 1 year, reassuring the durability of the percutaneous repair [79]. Most patients included in this trial had degenerative MR. Interestingly, in those patients with LVD or FMR, no differences were observed between MV surgery and MitraClip, opening a new niche for TMVI.

The prototype of patient candidate for TMVI can be derived from the patients included in the main European registries of MitraClip [80–83]. Summary of the characteristics of those patients are depicted in Table 18.2 and Fig. 18.3. In brief, the typical MitraClip patient has advanced age, high-surgical risk, FMR, frequent ischemic history, LVD and a significant proportion of carriers of defibrillators and/or resynchronization devices.

Table 18.2 Clinical profile in main registries of MitraClip implantation

	ACCESS-EU	TVT SENTINEL	TRAMI
n	567	628	1064
Age (years)	74	74	75
logES, %	23	20	STS 9.2
FMR, %	77	72	79
Previous MI, %	32	31	28
NYHA III/IV, %	85	86	87
LVD	52 % EF < 40 %	33 % EF < 30 %	33 % EF < 30 %
DCI/CRT, %	27 %	NA	21 %

EF ejection fractio, *FMR* functional mitral regurgitation, *logES* logistic EuroScore, *LVD* left ventricular dysfunction, *MI* myocardial infarction, *ICD* implantable cardiverter-defibrillator, *CRT* cardiac resynchronization therapy

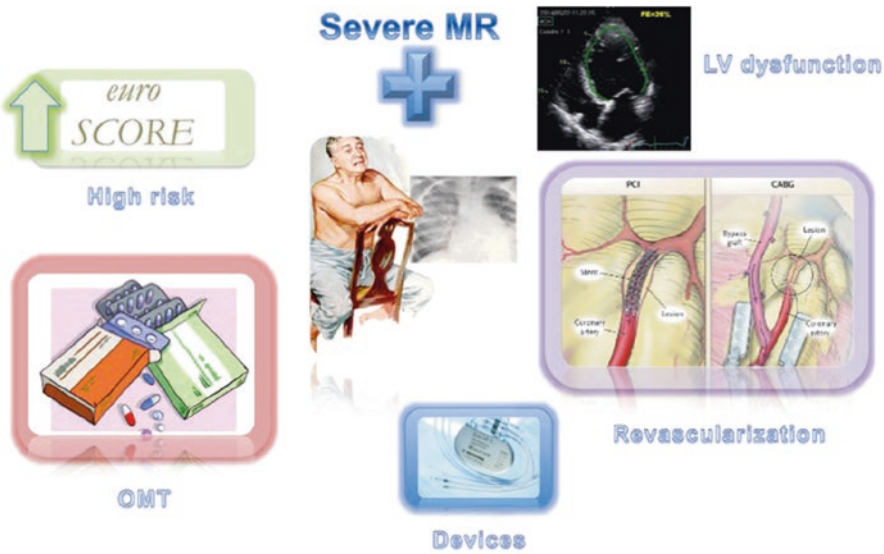

Fig. 18.3 Summary of MitraClip patient prototype

CRT Non-responders

MitraClip has also been proved to be a useful tool for those patients with HF not responding to CRT therapy [84]. The authors published their experience with 51 patients who were severely symptomatic despite CRT therapy. They showed that MitraClip implantation was associated with significant reduction in MR that was progressive during a median follow-up of 14 month, with clinical improvement and favorable remodeling parameters on echocardiographic follow-up.

End-Stage Heart Failure

Franzen et al. reported the effect of MitraClip in patients with end-stage heart failure [85] analyzing the treatment of 50 patients in 7 European centers with LVEF ≤25 %, MR ≥ 3+ and advanced functional class (NYHA III or IV). The authors reported an acute procedural success (APS) of 94 %, and 92 % of patients were discharged with MR ≤ 2+. The 30-day mortality was 6 % in this high-risk group (mean Euro Score 34 %). At 6-month follow-up of 32 patients, 72 % patients were in functional class I or II, there was reverse remodeling on echo follow-up and a significant reduction in BNP levels. The beneficial effects in this subgroup of patients may be related to the positive hemodynamic changes observed after the device implantation including significant reductions in pulmonary pressure, capillary wedge pressure, increase in cardiac output (and avoiding the low cardiac output post MV surgery) and favoring a positive remodeling in left ventricle [86–88]. However, patients with very poor LV function are at high risk of mortality even with MitraClip treatment. Careful selection of these candidates based on operators experience, probability of success and expected benefits is strongly recommended [82].

Acute MR Following Acute Myocardial Infarction

Acute ischemic MR is a life threatening complication associated with high rates of morbidity and mortality even when surgically corrected [89]. Small series have proved that MitraClip is a safe and effective alternative to surgical intervention in these unstable patients [90, 91]. Potential advantages of this therapy are, first, the rapid decrease in LV, left atrium and pulmonary artery pressures and the increase of cardiac output observed after a successful correction of the MR [86]. Second, the avoidance of LV damage induced by the systemic inflammatory response, free radical injury and myocardial oxidative stress associated with cardiopulmonary bypass [92]. Acute MR usually develops in a previously normal mitral valve and the characteristics of leaflet tissue and coaptation measurements are optimal for MitraClip therapy. An example is shown in Fig. 18.4.

Failing Annuloplasty Rings

Patients treated with annuloplasty rings suffering from FMR (mainly ischemic MR) are at high risk for recurrence, even more than 50 % at 2 years [93]. Frequently these patients are symptomatic, with an increase in the number of hospitalizations, present significant LVD and reoperation may carry an unacceptable risk [93]. Series from Italy and Spain have proved that the use of the device is safe and produces a persistent reduction in MR, hemodynamic improvement and symptom relief [94, 95], and MitraClip must be taken into consideration in such cases.

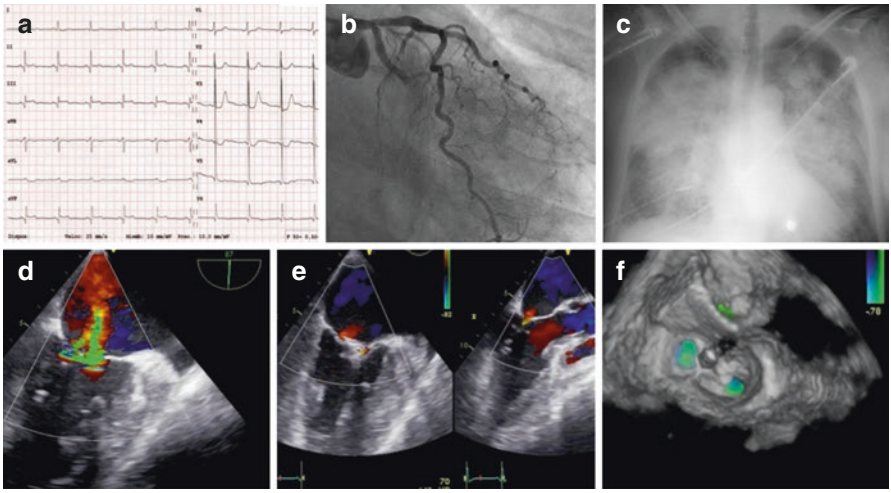

Fig. 18.4 MitraClip therapy in acute MR following inferior-wall myocardial infarction. Panel (**a**) ECG showing ST segment elevation in inferior leads. Panel (**b**) Occluded left circumflex artery. Panel (**c**) Chest X ray showing acute pulmonary edema. Panel (**d**) Severe MR. Panel (**e**) After two clips significant reduction in MR was obtained. Panel (**f**) Double-orifice imaging on mitral valve after procedure

Expected Benefits from TMVI

Persistent MR Reduction

Persistent MR reduction is on of the main goals of this therapy. The goal proposed since the EVEREST trials is to maintain a MR $\leq$ 2+ and this is what is considered a procedural success (PS) and an acceptable result during follow-up [76]. Interestingly, the study that settled the basis for the take off of the therapy was the one with the lower PS presented, 77 % [77]. This fact was responsible for the significant lower efficacy of the device compared to surgery and the main reason for this was the use of a single clip in most patients and that the trial was conducted in the beginning of the learning curve of most centers. With increasing experience PS has raised to a > 95 % [80, 81, 83, 85]. A persistent MR reduction is linked to better outcomes and "the less MR possible" should be used as a rule of thumb [96]. Conversely, acute failure to reduce MR is an independent marker of poor prognosis [81, 82]. The mechanisms supporting this observation are likely to be related to the positive hemodynamic changes that are observed after MR correction, with reduction of pulmonary and capillary pressures and increase in cardiac output [86]. Recurrence of significant MR is observed in 6–21.1 % of cases at one year [80, 81], similar figures to those observed at one year with surgical repair for ischemic FMR [97].

Symptom Improvement

Symptomatic improvement is one of the most reported benefits of this therapy. Pre-procedure patients are usually highly symptomatic with proportions of NYHA functional class III–IV ≥85 %. After treatment with MitraClip there is a significant recovery in the functional capacity with patients presenting on NYHA functional class I–II in a range of 63.3–86 % [80–82, 98, 99]. Beyond this variable, patients as well experience improvement in 6MWT [80], quality of life [98, 100] and reduced the BNP levels [85]. And, notably, there is a significant reduction in re-hospitalizations for HF, which probably will turn into an improved prognosis and will reduce costs of patients' care [98].

Survival Advantage

Survival of patients with FMR treated with MitraClip is in the range of 15.3–20.3 % in the first year [80–82]. More relevant than the reported mortality is to know if the use of the device is capable of reducing mortality compared to optimal medical. For this reason there are four randomized controlled trials ongoing that will address this question: COAPT, RESHAPE2HF, MATTERHORN and MITRA-HF. The evidence to date regarding this issue relies on four retrospective studies. The first published was the EVEREST high-risk study [101] where 78 patients at high surgical risk (STS ≥ 12 %), most of them with FMR, were treated with MitraClip (96 % PS) and compared with a cohort of 36 patients managed medically. At one year MitraClip patients had significant higher survival rates (76 % MitraClip vs. 55 % medical therapy, $p = 0.045$). MitraClip patients exhibited as well inverse LV remodeling, improved their quality of life and decreased the number of rehospitalizations. In a study by Swaans et al. [102] 139 patients treated with MitraClip were compared to 59 patients medically treated. At one year transcatheter repaired patients showed better prognosis than those treated only medically (survival MitraClip 85.8 % vs medical therapy 67.7 %, $p < 0.05$). After controlling by the propensity score MitraClip was associated with relative reduction in the risk of mortality of 59 % compared to medical therapy alone. In a recent paper, Velazquez et al. [103] compared the outcomes of 351 patients included in the EVEREST high-risk registry and historic comparator cohort from the Duke Echocardiography Laboratory Database medically managed. After propensity matching 239 patients in each group were analyzed and MitraClip was associated with a 1 year improved survival (mortality 22.4 % MitraClip vs. 32 % stand-alone medical therapy, $p = 0.043$). The relative risk reduction in mortality for the device was 34 % and the number needed to treat to save one life at one year was only 10. And finally, a recent report by Giannini [104] included 60

patients treated with MitraClip and propensity matched with 60 patients conservatively managed. All patients presented FMR. After a median follow-up of 515 days, patients treated with TMVI showed less mortality, less cardiac mortality and less readmissions due to HF (log-rank test p = 0.007, p = 0.002, and p = 0.04, respectively).

Effect on Heart Remodeling: Annulus and LV

Reverse LV remodeling is one of the most expected effects of TMVI. This feature has been reported in surgical series of primary MR and has been linked to an improved prognosis [105]. Data derived from EVEREST trial have demonstrated that there is an inverse remodeling after a successful MitraClip procedure in patients with FMR [106] that affects both LV and left atrium (LA). And, interestingly, the magnitude of the remodeling is greater with greater reduction in MR. This positive effect is maintained at 5 years follow-up [79]. And this finding is true as well for patients in the EVEREST high-risk cohort [98, 101]. Notably, in these series patients with very poor LV function (<25 %) and severe LV dilation (LV end-systolic diameter >55 mm) were excluded. By contrast, real world FMR patients treated with MitraClip tend to exhibit poor or no remodeling at all [81].

MitraClip offers not only a heart chamber remodeling effect but also an annulus effect. That is the reason why MitraClip is not considered an Alfieri procedure but something else. Recent studies have demonstrated that in secondary MR annulus size (posteroanterior diameter), annulus area and tenting area significantly decrease after device implantation [107]. And interestingly this reduction is associated with an improved functional status at 6 month after the procedure [108]. Conversely, in primary MR annulus parameters remain stable after clipping.

When Is the Right Time for TMVI?

We have learnt from conventional surgery in primary MR that when surgical correction is performed in a timely manner and before LV dysfunction or pulmonary hypertension develops, life expectancy can be returned to normal [14]. Taking into account that FMR patients usually present in a pretty advanced stage of the disease, an enormous change in prognosis is unlikely to be seen. For this reason is difficult to establish the perfect time-point for TMVI.

Several factors have been associated with an impaired prognosis after MitraClip implantation, such as, NYHA functional class IV, advanced age, NT-pro-BNP >10,000 pg/ml, right ventricular dysfunction, significant tricuspid regurgitation, significant pulmonary hypertension, ischemic MR, severely dilated LV or severe renal dysfunction [85, 109–112]. Most of these markers are signs of advanced LV disease and occur in the late phase of this condition. Therefore, if a prolonged survival and inverse remodeling are the targets of our treatment, TMVI should be accomplished in early stages, since duration of heart failure is one of the main reasons for a worse prognosis [113].

Transcatheter Tricuspid Valve Intervention for Patients with HF

Tricuspid regurgitation (TR) is most commonly produced after right ventricle (RV) annular dilatation secondary to chronic pressure or volume overload. Progressive RV dysfunction may lead to an irreversible RV damage, which is thought to be the reason for the poor outcomes of late surgery in this scenario. Several studies have reported that significant TR is linked to increase mortality during follow up, and this is independent form the RV function [114, 115]. Despite this association few patients undergo TR surgery and the vast majority are managed medically. Furthermore, mortality of those patients surgically managed ranges between 2 and nearly 10 %, depending on the presence of a prior left-side valve surgery [116, 117]. In recent years, several transcatheter techniques have been developed to treat TR. The main candidates are those with symptomatic severe TR and prior open-heart surgery at high risk of reoperation and patients with significant TR and progressive RV dysfunction with RV failure despite optimal medical therapy if an isolated surgical TR repair is not indicated. Interestingly, prior to any indication a right heart catheteterization is mandatory to rule out precapillary pulmonary hypertension (PH) or severe PH, since correcting TR in these scenarios may lead to negative clinical effects due to RV failure.

Transcatheter devices that are under investigation and have been implanted in clinical cases are shown in Table 18.3. There are very few patients treated and, although some of the results are encouraging, we need further trials with a relevant number of patients to prove their efficacy [118, 119].

Table 18.3 Description of devices for TR treatment

Device	Description	Pros	Cons
Mitralign	Two pair of pledgets delivered in the annulus. Plication system reduces distance between pledgets, thus bicuspidizing the TV	Surgical background supports the technique High safety profile	Risk of leaflet or RCA injury Technically demanding
TriCinch device	Corckscrew implanted in the proximity of the mid part of the anterior tricuspid annulus. System tensioned to produce annular cinching. Stent deployed in IVC to secure system	Surgical background supports the technique High safety profile Fully retrievable and technically not demanding	Risk of leaflet or RCA injury
TRAIPTA concept	Circumferential annuloplasty device implanted in the pericardial space	Preclinical experience documented safety of implants	Absence of surgical background Limited clinical applicability
Millipede system	Ring that can be implanted surgically or transcatheter in the atrial side of the native tricuspid annulus to restore its shape and diameter	Retrievable and repositionable	Risk of AV block
CAVI concept (Caval Valve Implantation)	Implant a transcatheter prosthesis in the IVC (single) or in SVC (dual) as well to prevent damage in liver and other organs. Reasonable experience with Edwards XT	Technically easy RV improvement documented	No surgical background Palliative
FORMA	A valve spacer which is positioned in the regurgitant orifice in order to improve leaflet coaptation	Preliminary results in 7 patients showed successful device implantation with at least one degree reduction in TR	Very large devices needed Absence of surgical background
MitraClip	Same device for mitral valve but with modified technique to clip the TV leaflets	Huge experience in MV Friendly to operators	No annular treatment Three-leaflet configuration of the valve
Transcatheter TV replacement	Standard TAVI devices implanted in a valve-in-valve or valve-in-ring fashion	Good outcomes on valve in valve registry Fast	Only valve in valve application Transfemoral approach limited by the narrow angle between IVC and TV

AV atrio-ventricular, *MV* mitral valve, *RCA* right coronary artery, *TV* tricuspid valve

Future Direction Box

- TAVI will probably become the therapy of choice in patients with AS and LVD
- TMVI should be performed in an early phase, as soon as the diagnosis is performed and symptoms develop
- Today MitraClip is the device that has proved to be associated with the best balance on safety/efficacy
- New devices such as direct or indirect annuloplasty rings and transcatheter mitral valves will share the mitral space with MitraClip in the forthcoming years
- The development of percutaneous approaches to TR will extend the treatment of this valve usually associated with advance right HF symptoms

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Chapter 19
Pre-transplant Evaluation

Maria G. Crespo-Leiro and Gonzalo Barge-Caballero

Introduction

Heart transplantation (HT) is the treatment of choice for carefully selected patients with end-stage or "Stage D" heart failure (HF). Stage D HF defines those patients who continue to progress and develop refractory or persistently severe symptoms despite maximum guideline-directed medical therapy (GDMT), devices or surgical management [1]. According the European Society of Cardiology (ESC) guidelines on HF, although controlled trials have never been conducted, there is a consensus that HT, −provided that proper selection criteria are applied-, significantly increases survival, exercise capacity, quality of life and return to work compared with conventional treatment [2].

Since the first successful HT was performed in 1967 [3], survival after HT has been constantly improved as a consequence of developments in careful recipient and donor selection, immunosuppression and management of infectious complications. That is why HT is now considered the gold standard therapy for refractory HF. Data from the International Society for Heart and Lung Transplantation (ISHLT) Registry with 112,521 HT performed between 1982 and 2013 showed 1-year survival of 82 % and 5-year survival of 69 % with a median survival of 11 years for all and 13 years for those surviving the first year [4]. Compared with advanced heart disease before HT, there is a dramatic benefit not only in survival but also in functional status and quality of life. At years 1–3 post-HT the proportion of survivors capable of normal activity (Karnofsky score 80–100 % as rated by the physician) is 90 % [4].

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M. Dorobanțu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_19

Table 19.1 ESC definition of advanced heart failure

	Objective clinical criteria
1	Severe symptoms of HF with dyspnea and/or fatigue at rest or with minimal exertion (NYHA class III or IV)
2	Episodes of fluid retention /pulmonary and/or systemic congestion, peripheral edema) and/or reduced cardiac output at rest (peripheral hypoperfusion)
3	Objective evidence of severe cardiac dysfunction shown by at least one of the following: (a) LVEF < 30 % (b) Pseudonormal or restrictive mitral inflow pattern (c) Mean PCWP > 16 mmHg and/or RAP > 12 mmHg by PA catheterization (d) High BNP or NT-proBNP plasma levels in the absence of non cardiac causes
4	Severe impairment of functional capacity shown by 1 of the following (a) Inability to exercise (b) 6-min walk distance < 300 m (c) Peak VO2 < 12–14 ml/kg/min
5	History of ≥HF hospitalization in the past 6 months
6	Presence of all the previous features despite "attempts to optimize" therapy including diuretics, GDMT, unless these are poorly tolerated or contraindicated, and CRT when indicated

Adapted from Metra [7] and Yancy [1]
BNP B-type natriuretic peptide, *CRT* cardiac resinchronization therapy, *ESC* European Sociaty of Cardiology, *GDMT* Guideline-directed medical therapy, *HF* heart failure, *LVEF* left ventricular ejection fraction, *NT-proBNP* N-terminal pro-type natriuretic peptide, *NYHA* New York Heart Association, *PA* pulmonary artery, *PWCP* pulmonary capillary wedge pressure, *RAP* right atrial pressure

The main challenges in HT are shortage of donors and, after transplant, the consequences of both, the limited effectiveness and complications of immunosuppressive therapy (including antibody mediated rejection, cardiac allograft vasculopathy, malignancy, renal dysfunction, hypertension and diabetes among others) [4].

There are three main considerations in the pre-HT evaluation. First is determining if the patient is in truly refractory HF i.e. to make sure that the diagnosis is correct and there are no other treatable etiologies or alternative explanations for advanced symptoms. This is important to guarantee the candidacy for HT and reserve organs (always scarce) for the more needed patients. Secondly, it is estimation of prognosis, the most important component of the selection process. The greatest survival benefit is seen in those patients who are at highest risk of dying from advanced HF [5]. Some useful clinical criteria to define advanced HF are showed in Tables 19.1 and 19.2. Table 19.3 shows the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles, defined in the setting of a multi-institutional registry of ventricular assist devices [6] to improve risk stratification and selection of target populations for advanced HF therapies. And, finally, the third important consideration in the pre-HT evaluation is to assess comorbidities that may contraindicate HT.

The recommendations on pre-HT evaluation discussed in this chapter are mainly based on the ISHLT listing criteria for heart transplantation, published in 2006 [8] and updated in 2016 [9].

Table 19.2 Clinical events and findings useful for identifying patients with advanced heart failure

Repeated (≥2) hospitalizations or ED visits for HF in the past year
Progressive deterioration in renal function (e.g. rise in BUN and creatinine)
Weight loss without other cause (e.g. cardiac caquexia)
Intolerance to ACE inhibitors due to hypotension and/or worsening renal function
Intolerance to beta blockers due to worsening HF or hypotension
Frequent systolic blood pressure <90 mmHg
Persistent dyspnea with dressing or bathing requiring rest
Inability to walk 1 block on the level ground due to dyspnea or fatigue
Recent need to escalate diuretics to maintain volume status, often reaching daily furosemide equivalent dose over 160 mg/d and/or use of supplemental metolazone therapy
Progressive decline in serum sodium, usually to <133 mEq/l
Frequent ICD shocks

Adapted from Yancy [1]
ACE angiotensin-converting enzyme, *BUN* blood urea nitrogen, *ED* emergency department, *HF* heart failure, and *ICD* implantable cardioverter-defibrillator

Indications for Heart Transplantation

In Table 19.4 are shown the indications for HT considered in the ACC/AHA guidelines on HF [10], including three etiologies of heart disease (heart failure, ischemic heart disease and intractable arrhythmias) and differentiating the indications as absolute, relative or inappropriate. Table 19.5 shows the indications and contraindications according the latest ESC heart failure guidelines, published in 2016 [2].

Patients on Stable Condition

Cardiopulmonary Stress Testing

Cardiopulmonary stress testing (CPST): CPST is routinely used in determining the candidacy for cardiac transplantation. Mancini et al. [11]first demonstrated the prognosis utility of CPST. In general, the peak VO_2 (Vo_2max) provides an objective assessment of functional capacity in patients with HF and is one of the best predictors of when to list an individual patient for cardiac transplantation. ISHLT 2016 listing criteria for HT [9] regarding CPST are as follows:

- A maximal CPST is defined as one with a respiratory exchange ratio (RER) > 1.05 and achievement of an anaerobic threshold on optimal pharmacologic therapy (Class I, level of evidence B)
- The presence of a CRT device does not alter the current peak VO2 cutoff recommendations (Class I, level of evidence B)
- In patients intolerant of a β-blocker, a cutoff for peak VO2 of ≤14 ml/kg/min should be used to guide listing (Class I level of evidence B)

Table 19.3 INTERMACS profiles

INTERMACS level	Short description	NYHA Class	Description
1	Critical cardiogenic shock ("Crash and burn")	IV	Life-threatening hypotension and rapidly escalating inotropic/pressor support, with critical organ hypoperfusion often confirmed by worsening acidosis and lactate levels
2	Progressive decline ("Sliding fast" on inotropes)	IV	Intravenous inotropic support with acceptable blood pressure but rapid deterioration of renal function, nutritional state or signs of congestion
3	Stable but inotrope dependent ("dependent stability")	IV	Clinically stable on mild-moderate doses of intravenous inotropes (or has a temporary circulatory support device) after repeated documentation of failure to wean without symptomatic hypotension, worsening symptoms, or progressive organ dysfunction (usually renal)
4	Resting symptoms on oral therapy a home	IV ambulatory	Temporary cessation of inotropic treatment is possible, but patients presents with frequent symptom recurrences and typically with fluid overload
5	Exertion intolerant ("housebound")	IV ambulatory	Complete cessation of physical activity, stable at rest, living predominantly within the house or housebound
6	Exertion limited ("walking wounded")	III	Minor limitation on physical activity and absence of congestion while at rest. Easily fatigued by light activity
7	Advanced NYHA class III ("placeholder")	III	Clinically stable with a reasonable level of comfortable activity, despite a history of previous decompensation that is not recent.

Modified from Stevenson et al. [6] and Ponikowski et al. [2]

Modifier options: Profiles 3–6 can be modified with the designation of "frequent flyer" (FF) for patients with recurrent decompensations leading to frequent (generally at least two in the last 3 months or three in the last 6 months) emergency department visits or hospitalizations for intravenous diuretics, ultrafiltration, or brief inotropic therapy. Other modifier options include A (arrhythmia), which should be used in the presence of recurrent ventricular tachyarrhythmia contributing to the overall clinical course (eg. Frequent ICD shocks or requirement of external defibrillation, usually more than twice weekly); or TCS (temporary circulatory support) for hospitalized patients profiles 1–3

Table 19.4 Indications for Heart Transplantation. ACC/AHA Guidelines

1. Absolute indications in appropriate patients:
For hemodynamic compromise due to HF
Refractory cardiogenic shock
Documented dependence on intravenous inotropic support to maintain adequate organ perfusion
Peak Vo_2 less than 10 mL/kg per min with achievement of anaerobic metabolism
Severe symptoms of ischemia that consistently limit routine activity and are not amenable to coronary artery bypass surgery or percutaneous coronary intervention.
Recurrent symptomatic ventricular arrhythmias refractory to all therapeutic modalities
2. Relative indications:
Peak Vo_2 of 11–14 mL/kg per minute (or 55 % predicted) and major limitation of the patient's daily activities.
Recurrent unstable ischemia not amenable to other intervention
Recurrent instability of fluid balance/renal function not due to patient noncompliance with medical regimen
3. Insufficient indications:
Low left ventricular ejection fraction
History of functional class II or IV symptoms of HF
Peak Vo_2 greater than 15 mL/kg per min (or greater than 55 % predicted) without other indications.

Adapted from Hunt S et al. [10]

Table 19.5 Heart Transplantation: Indications and Contraindications. 2016 ESC Guidelines on Heart Failure

Patients to Consider	1. End-stage HF with severe symptoms, a por prognosis, and no remaining alternative treatment options. 2. Motivated, well informed, and emotionally stable 3. Capable of complying with the intensive treatment required postoperatively
Contraindications	1. Active infection 2. Severe peripheral arterial or cerebrovascular disease 3. Pharmacological irreversible pulmonary hypertension (LVAD should be considered with a subsequent reevaluation to establish candidacy) 4. Cancer (a collaboration with oncology specialists should occur to stratify each patient as to their risk of tumor recurrence) 5. Irreversible renal dysfunction (e.g. creatinine clearance <30 ml/min) 6. Systemic disease with multi-organ involvement 7. Other serious co-morbidity with poor prognosis 8. Pre-transplant BMI > 35 kg/m^2 (weight loss is recommended to achieve a BMI < 35 kg/m^2) 9. Current alcohol or drug abuse 10. Any patient for whom social supports are deemed insufficient to achieve compliant care in the outpatient setting.

From: Ponikowski et al. [2] and Mehra M et al. [9]

- In the presence of a β-blocker, a cutoff for peak VO2 of ≤12 ml/kg/min should be used to guide listing (Class I, level of evidence B)
- In young patients (<50 years) and women, it is reasonable to consider using alternate standards in conjunction with peak VO2 to guide listing, including percent of predicted (≤50 %) peak VO2 (Class IIa, level of evidence B)
- In the presence of a sub-maximal CPST (RER < 1.05), use of ventilation equivalent of carbon dioxide (VE/VCO2) slope of >35 as a determinant in listing for transplantation may be considered (Class IIb, level of evidence C).
- In obese (body mass index [BMI] > 30 kg/m^2) patients, adjusting peak VO2 to lean body mass may be considered. A lean body mass-adjusted peak VO2 of <19 ml/kg/min can serve as an optimal threshold to guide prognosis (Class IIb, level of evidence B)
- Listing patients based solely on the criterion of peak VO2 measurement should not be performed (Class III, level of evidence C)

Use of Heart Failure Prognostic Scores

Apart from VO2, several risk models have been developed to establish a risk score for prognosis in HF patients. The two more relevant are the Heart Failure Survival Score (HFSS) [12] and the Seattle Heart Failure Model (SHFM) [13].

The predictors of survival in the HFSS include: (1) presence or absence of coronary artery disease, (2) resting heart rate, (3) left ventricular ejection fraction, (4) mean arterial blood pressure, (5) presence or absence of an intraventricular conduction delay on ECG, (6) serum sodium and (7) peak VO2. The HFSS stratifies patients into low- (HFSS ≥ 8,10), medium- (HFSS 7.20–8.09), and high-risk (HFSS ≤ 7.10) categories, based upon a sum of the aforementioned variables multiplied by defined coefficients [12]. The SHFM which is available online at www.SeattleHeartFailureModel.org, has incorporated the impact of other HF therapies on survival including ICDs and CRT and estimate 1, 2 and 3 year survival.

HF prognosis scores should be performed along with CPST to determine prognosis and guide listing for transplantation for ambulatory patients. An estimated 1-year survival as calculated by the Seattle HF Model (SHFM) of <80 % or a Heart Failure Survival Score (HFSS) in the high/medium risk range should be considered as a reasonable cut points for listing (Class IIb, level of evidence C). Listing patients solely on the criteria of HF survival prognostics scores should not be performed (Class III, level of evidence C) [9].

Role of Diagnostic Right-Heart Catheterization (RHC)

Patients with an elevated pulmonary vascular resistance (PVR) or a transpulmonary gradient (mean pulmonary artery pressure minus mean pulmonary capillary wedge pressure) above 15 mmHg have an increased risk of right ventricular failure in the

Table 19.6 Poor prognostic Markers for survival in Restrictive Cardiomyopathy

Pulmonary congestion at diagnosis
Angina or ischemic electrocardiographic findings
Left atrial dimension >60 mm
Male gender
Reactive pulmonary hypertension
Reduced left ventricular fractional shortening
Increased end-diastolic posterior wall thickness

Adapted from Mehra et al. [9]

immediate post-heart transplant period, when the normal donor right ventricle is acutely subjected to a marked increase in workload. Patients whose PVR can be substantially acutely reduced are usually considered acceptable candidates for transplantation [14, 15].

RHC should be performed on all adult candidates in preparation for listing for cardiac transplantation and periodically until transplantation (Class I, level of evidence C). Periodic RHC is not advocated for routine surveillance in children (Class III, level of evidence C) [9].

When an acute vasodilator challenge is unsuccessful, hospitalization with continuous hemodynamic monitoring should be performed, as often the PVR will decline after 24–48 h- of treatment consisting of diuretics, inotropes and vasoactive agents such as inhaled nitric oxide (Class I, level of evidence C). [9].

If medical therapy fails to achieve acceptable hemodynamics and if the left ventricle cannot be affectively unloaded with mechanical devices, it is reasonable to conclude that the pulmonary hypertension is irreversible (Class IIb, level of evidence C) [9].

Restrictive and Infiltrative Cardiomyopathies

Some patients with advanced HF are affected by diseases not characterized by left ventricle dilation and reduced ejection fraction and are usually unresponsive to guidelines directed medical therapies or device therapies. In this group are included, hypertrophic cardiomyopathy, restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular dysplasia and infiltrative cardiomyopathies. Prognosis and therapeutic strategies require specific considerations.

RCM patients with severe HF symptoms (NYHA III-IV) should be referred for HT evaluation. Table 19.6 shows poor prognostic markers for survival in RCM, which can help in the decision to list a RCM HF patient.

Amyloidoses are a family of diseases accumulating misfolded or misassembled proteins in the extracellular matrix of several organs including the heart, leading to a RCM phenotype with progressive diastolic and systolic dysfunction, HF and death. The two most common types that infiltrate the heart are immunoglobulin AL amyloid and TTR amyloid (familial or genetic), which have different approaches. Table 19.7 shows criteria for prognostic stratification of cardiac involvement in AL.

Table 19.7 Criteria for prognostic stratification of cardiac involvement in amyloid light-chain amyloidosis

Stages	Criteria
Stage I	NT-proBNP < 332 ng/L **and** troponin T < 0.035 μg/L
Stage II	NT-proBNP > 332 ng/L **or** troponin T > 0.035 μg/L
Stage III	NT-proBNP > 332 ng/L **and** troponin T > 0.035 μg/L
Low risk stage III	NT-proBNP 332–8500 ng/L **and** SBP > 100 mmHg
Intermediate risk stage III	NT-proBNP > 8500 ng/L **or** SBP < 100 mmHg
High risk stage III	NT-proBNP > 8500 ng/L **and** SBP < 100 mmHg

Adapted from Mehra et al. [9]
NT-pro BNP N-terminal prohormone brain natriuretic peptide, *SPB* systolic blood pressure

Recommendations from 2016 ISHLT [9] on amyloidosis guidelines are as follows:

- Selected patients with AL who are not candidates for disease-specific therapies due to cardiovascular compromise may be considered for HT in experienced centers with established collaborations between cardiovascular and hematologist teams. Autologous stem cell transplantations (ASCT) should be planned as soon as clinically feasible after recovery from HT (Class IIa, level of evidence B)
- Patients with ATTR involving the heart may be considered for HT. Patients with familial ATTR should be considered for combined heart and liver transplantation in experienced centers with established collaboration between cardiology, hepathology and neurology teams (Class IIa, level of evidence B)
- Amyloid involvement of extracardiac organs must be carefully evaluated when considering AL patients for sequential HT/ASCT (AL patients) or ATTR patients for HT or combined HT with liver transplantation. Severe extracardiac amyloid organ dysfunction should be a contraindication to proceed with HT (Class IIa level of evidence B). In Table 19.8 is shown evaluation of extracardiac organ AL amyloid involvement.

Patients on Unstable Conditions

Pre-operative clinical stability is a strong predictor of early post-transplant outcomes. Ventricular assist devices (VADs) can provide mechanical support to "bridge" selected patients to transplantation who are extremely ill and have a high-expected mortality while being on the waiting list. VADs can also bridge patients with end-organ damage in order to make an ineligible patient eligible for HT and the use of short-term devices can be useful for patients in cardiogenic shock until hemodynamic and end-organ perfusion are stabilized, contraindications for HT excluded (example brain damage after resuscitation) and HT therapy can be evaluated [2]. Although there is a possibility in many countries of urgent HT listing, this strategy is now being discussed. Among patients listed for emergent heart transplantation in the Spanish National Heart Transplant Registry database, recipients meeting the INTERMACS profile 1 criteria (cardiogenic shock) and profile 2 criteria (progressive clinical decline despite treatment with inotropes) had the highest risk of primary graft failure, dialysis requirement, and in-hospital mortality following HT

Table 19.8 Evaluation of extracardiac organ amyloid light-chain amyloid involvement

Organ system	Screening test
Pulmonary	Pulmonary function testing, including arterial oximetry, diffusion capacity Chest X-ray imaging and computed tomography to assess for interstitial disease, effusions Thoracocentesis may be necessary to differentiate manifestations of amyloidosis from heart failure
Gastrointestinal	Nutritional assessment, including plasma pre-albumin, albumin Assessment for bleeding by esophagogastroduodenoscopy, colonoscopy Assessment of amyloid deposition by random biopsy Assessment of intestinal motility with gastric-emptying studies
Hepatic	Serum alkaline phosphatase, bilirubin An alkaline phosphatase >1.5 × upper limit of normal in the absence of congestion should prompt liver biopsy to assess for portal and parenchymal amyloid deposition. The presence of solitary vascular deposition should not be considered a contraindication to HT/ASCT
Renal	Measured creatinine clearance or eGFR 24-h urinary protein excretion A eGRF or measured creatinine clearance <50 ml/min/1.73 m^2 in the absence of decompensated heart failure or urinary protein excretion >0.5 g/24 h should prompt renal biopsy to assess the renal amyloid burden.
Coagulation	Factor X and thrombin time Patients with a severe (<25 %) factor X functional deficiency have <50 % survival after ASCT.

Adapted from Mehra et al. [9]
ASCT autologous stem cells transplantation, *eGFR* estimated glomerular filtration rate, *HT* heart transplantation

[16] Therefore in these critically patients a VAD implantation might constitute a more reasonable initial strategy than an urgent HT.

Comorbidities and Their Implications as Contraindications for Heart Transplantation

Evaluation and management of comorbidities is crucial to improve outcomes after transplantation [4]. In the past there were absolute and relative contraindications, but eventually the absolute have been reduced and nowadays, in general, comorbidities need to be considered in the context of the severity of the heart disease. Contraindications can be grouped in medical conditions and social/psychological (mainly adequate compliance and caregiver support).

Age

Older age has been a classical contraindication for HT. However the upper limit of age for HT is unknown. Most centers now focus on the patient's physiological age, with emphasis on the functional integrity of major organ systems and

the absence of relevant comorbid diseases. Age older than 70 is a relative contraindication depending of the associated comorbidities, therefore carefully selected patients >70 years of age may be considered for HT (Class IIb, level of evidence C) [9].

Local policies to define the upper limit for eligibility should be placed in the context of local organ availability and quality in order to maintain acceptable transplant outcomes and a reasonable chance to transplant all listed patients.

Obesity

A pre-transplant body mass index (BMI) > 35 kg/m^2 is associated with a worse outcome after HT. For such obese patients, it is reasonable to recommend weight loss to achieve a BMI of ≤35 kg/m^2 before listing for HT (class IIa, level of evidence C) [9]. Patients with severe obesity have greater difficulty in finding a suitable donor and longer waiting times on the transplant list.

Diabetes Mellitus

Diabetes with end-organ damage (other than non-proliferative retinopathy like neuropathy or nephropathy) or persistent poor glycemic control (glycosylated hemoglobin HbA1c > 7.5 % or 58 mmol/l), despite optimal effort, is a relative contraindication for HT (Class IIa, level of evidence C) [9].

Renal Function

Renal function should be assessed using the estimated glomerular filtration rate (eGFR) or creatinine clearance under optimal medical therapy. If abnormal renal function should prompt further investigation including renal ultrasonography, estimation of proteinuria and evaluation for renal arterial disease, to exclude renal intrinsic disease. It is reasonable consider the presence of irreversible renal dysfunction (eGFR < 30 ml/min/1.73 m^2) as a relative contraindication for HT alone (Class IIa, level of evidence C) [9]. In case or irreversible renal dysfunction, combined heart and kidney transplantation can be an option [17, 18].

Cancer

An active malignancy of any kind, which can be worsened by the immunosuppressive therapy, is considered a contraindication for HT. However, pre-existent neoplasms are diverse and many treatable with surgery, radiotherapy, or chemotherapy

to induce remission. Collaboration with oncologists is crucial to stratify each patient as to their risk of tumor recurrence. Heart Transplantation should be considered when the risk of tumor recurrence is low based on tumor type, response to therapy and negative metastatic work-up. The specific period of time to wait to transplant after neoplasm remission depend on the previous factors and no arbitrary time period for observation should be used [9].

Cerebral and Peripheral Vascular Disease

Clinically severe symptomatic cerebrovascular disease (CVD) may be considered a contraindication to transplantation. Peripheral vascular disease may be considered a relative contraindication when its presence limits rehabilitation and revascularization is not a viable option (Class IIb, level of evidence C) [9].

Assessment of Frailty

The role of frailty in heart failure has recently been introduced. However, the absence of standardized measures to study it hinders their clinical use. In fact the latest ISHLT Guidelines were unable to assign a high level of recommendation. What is recommended is that assessment of frailty (3 of 5 possible symptoms, including unintentional weight loss of ≥10 pounds within the past year, muscle loss, fatigue, slow walking speed, and low levels of physical activity) could be considered when assessing candidacy (Class IIb, level of evidence C) [9].

Mechanical Circulatory Support (MCS) for Bridge to Candidacy

Use of MCS should be considered for patients with potentially reversible or treatable comorbidities, such as cancer, obesity, renal failure, tobacco use, and pharmacologically irreversible pulmonary hypertension, with subsequent evaluation to establish candidacy (Class IIb level of evidence C) [9].

Tobacco Use, Substance Abuse

Education on the importance of tobacco cessation and reduction in environmental or second-hand exposure should be performed before the transplant and continue after HT. It is reasonable consider active tobacco smoking as a relative contraindication to transplantation (Class IIa, level of evidence C) [9].

Patients must be screened for the use and abuse of alcohol and other recreational drugs. Active substance abuses (including alcohol) should be considered an absolute contraindication for transplantation (Class III, level of evidence C). [9].

Psychosocial Evaluation

All heart transplants candidates should undergone a complete psychosocial evaluation during the initial screening process to identify social and behavioral factors that may cause difficulty during the waiting period, convalescence, and long-term follow-up, in special adherence to therapy [19]. The patient must understand that full cooperation and compliance are critical to the safe and effective use of immunosuppressive medications.

Neurocognitive and social assessments concentrates on four areas: compliance (the capacity to adhere to a complex lifelong regime of drug therapy, life style changes and regular follow-up), comprehension (the ability to understand explanations of relative complex procedures and instructions on transplantation and give informed consent), quality-of-life assessments (patient's perception of happiness and wellbeing and desire for long-term survival) and social evaluation (family or friends able to give support and who are willing to make long-term commitments for the patient's welfare) [8].

According the 2016 ISHLT guidelines any patient for whom social supports are deemed insufficient to achieve compliant care in the outpatient setting may be regarded as having a relative contraindication to transplant. The benefit of HT in patients with severe cognitive-behavioral disabilities or dementia (e.g. self-injurious behavior, inability to ever understand and cooperate with medical care) has not been established, has the potential for harm, and therefore, HT cannot be recommended for this subgroup of patients [9].

Retransplantation

Retransplantation (re-HT) remains a small percentage of HT, usually <3 % of all HT patients [4]. The prognosis is acceptable when re-HT is for cardiac allograft vasculopathy (CAV) but poor when is due to acute rejection [20]. The ISHLT 2016 guidelines consider that reHT is indicated for those patients who develop significant CAV with refractory cardiac allograft dysfunction, without evidence of ongoing rejection (Class IIa, level of evidence C). [9].

Human Immunodeficiency Virus (HIV)

HIV infection has been in the past considered an absolute contraindication, however the availability of antiretroviral (ARV) therapy has changed the prognosis of HIV and now is not sufficient reason to refuse transplantation [21, 22]. The 2016 ISHLT Guidelines recommend that selected HIV-positive patients may be consider for HT if they have no active or prior opportunistic infections (progressive multifocal leukoencephalopathy or chronic intestinal cryptosporidiosis >1 month), are clinically stable and compliant on combination ART for >3 months, have undetectable HIV RNA and have CD4 counts >200 cells/μl for >3 months (class IIa, level of evidence C). [9].

Chagas Disease

Chagas disease is a growing indication for HT in special in those countries where this disease is endemic. A major concern is the risk of reactivation of *Trypanosoma cruzi* (T cruzi) after HT. All HT candidates born in Latin America, those who have spent significant time in Latin America, those with a Latin America mother or those who have received unscreened blood products should undergo universal screening for *T cruzi. (Class I level of evidence C).*

Serologic testing should be done using 2 serologic assays and an initial positive test should be followed-up with a confirmatory test. Detection of *T cruzi* infection should prompt treatment with benznidazole (first-line) or nifurtimox (second-line). (Class I level of evidence C). [9].

Hepatitis C and Hepatitis B

Heart transplantation in patients with acute or fulminant hepatitis C or B is considered contraindicated. However patients with chronic or resolved hepatitis B or C infections can be accepted for HT in most centers.

Resolved hepatitis C virus infection is defined by a clinical phenotype of HCV antibody (Ab) positive, HCV RNA PCR negative and normal synthetic liver function test with a low risk of reactivation. Chronic HCV infection is defined by HCV RNA PCR (+) or active use of HCV anti-viral drugs.

Prior HBV infection that is no longer active is characterized by HBV core Ab (HBcAb) positive, and/or HBV surface Ab (HBsAb) positive but who remains HBV-surface antigen (HBsAg) negative, (HBcAb positive and/or HBsAb positive but HBsAg negative). Chronic HBV are defined as HBsAg positive or who are on HBV anti-viral drugs. [9].

Evaluation of these patients includes assessment for the level of active viremia, serology and often also liver biopsy to assess for the presence of cirrhosis.

Vaccinations

Assessment of vaccination history and serologic protection is recommended during the transplant evaluation. Table 19.9 shows a vaccination protocol suggested for HT candidates. [9].

Recommended Tests for Heart Transplant Evaluation

Each center has its own protocol for pretransplant evaluation. In general should include the following assessments: (1) Complete medical history and physical exam; (2) Immunocompatibility, (3) Assessment of HF severity, (4) evaluation of

Table 19.9 Vaccination protocol for heart transplant candidates

Vaccine	Pre-transplant serology	Pre-transplant vaccination	Confirm response pre-transplant	Special circumstances
Hepatitis A	Yes	Yes	Yes	Recommended for those with increased risk travel or residence in high-risk areas, occupational, or lifestyle exposure risk.
Hepatitis B	Yes	Yes	Yes	
Pneumococcus (conjugated or polysaccharide)	Consider	Yes	Consider	Recommendation for conjugate vaccine, followed 8 weeks later by polysaccharide vaccine
Tetanus (dT)	Yes	Yes	No	Administer Tdap
Pertussis (Tdap)	No	Yes	No	Administer Tdap to all who have not previously received Tdap
Influenza	No	Yes	No	Seasonally, vaccination also recommended for close contacts
Meningococcus	No	Yes	No	Recommended for those at increased risk including asplenia/polysplenia, high-risk travel, terminal complement deficit, including prior to eculizumab
Rabies	No	No	No	Consider for those with risk of significant post-HT exposure
Human papilloma virus	No	Yes	No	Approved age 9–26 years
Varicella Herpes zoster	Yes	Consider	Yes	Not needed if seropositive
Mumps, measles, rubella	Yes	Yes	Yes	Not needed if born before 1957

Adapted from Mehra et al. [9]
dT diphtheria and tetanus toxoids, *Tdap* tetanus, diphtheria, pertussis
Consideration should be given to avoid administration of live viral vaccination within 4 weeks of anticipated transplantation.

multi-organ function, (5) infections and vaccination, (6) preventive and malignancy and 6) general consultations (Table 19.10). While the patient is on the waiting list must be closely monitored and some of the tests will be reevaluated periodically.

Table 19.10 Recommended test for basal heart transplant evaluation

Complete History and Physical examination Weight/BMI
Assessment of HF severity
Cardiopulmonary exercise test with RER; echocardiogram, right heart catheterization; left heart catheterization (if indicated)
Immunocompatibility
ABO, HLA tissue typing (only at transplant), PRA and flow citometry
Evaluation of multi-organ function
Routine lab work (basic metabolic panel, complete blood test, liver function test) PT/INR Urinalysis 24-h urine collection for protein and creatinine GFR (MDRD) Pulmonary function test Chest X-ray Abdominal ultrasound Carotid Doppler (if indicated or >50 years) Dental examination Ophthalmologic examination (if diabetic) CT scan (in selected patients) Ankle-brachial indices (if >50 years or with ischemic heart disease)
Preventive and Malignancy
Stool for occult blood Colonoscopy (if indicated or >50 years) Mammography (if indicated or >40 years) Gyn/Pap (if indicated ≥18 years sexually active) PSA and digital rectal exam (men > 50 years) Serum protein electrophoresis (if multiple myeloma multiple is clinically suspected)
Infectious evaluation
Hep B surface Ag, surface Ab and core Ab Hep C Ab HIV RPR Immunoglobulin G for herpes simplex virus, CMV, toxoplasmosis, Epstein-Barr virus and varicella PPD
General consultations
Social work Psychiatry and Psychosocial evaluation If indicated: nephrologist, infectious disease, pulmonologist, oncologist, etc

Future Directions

- Improve risk stratification of advanced heart failure patients to select the best candidates for heart transplantation.
- Better understanding what are absolute and relative contraindications for decision making, particularly in a growing population of potential candidates for heart transplantation with older age, frailty and several comorbidities.
- Given the shortage of donors, advances in mechanical circulatory support devices allow having the end-stage heart failure patient on the waiting list for longer periods of time and in the best conditions until there is a suitable donor.

The predictions of outcomes after heart transplantation is still challenging and the correct selection of the recipient is a key factor for improving them.

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Chapter 20
Heart Transplantation

Liviu Klein

Introduction and Epidemiology

Despite advances in the treatment of heart failure, the prognosis of patients with advanced (stage D) heart failure remains poor, with a 5-year survival of only 20 % [1]. In this population, heart transplantation is the most effective therapy for prolonging survival. Other indications for heart transplantation include nonrevascularizable coronary artery disease with intractable angina, malignant ventricular arrhythmias and primary cardiac tumors [2]. In the current era, the median life expectancy after heart transplantation is around 11 years, and the conditional median survival among transplant recipients surviving the first year is 14 years (Fig. 20.1) [3]. While better patient selection, donor heart preservation techniques, immunosuppression, and cytomegalovirus prophylaxis have contributed to improvements in survival over the past three decades, the majority of the gains have been in the first post-transplant year. Cardiac allograft vasculopathy, non-skin malignancies, rejection, and infections, continue to limit long-term survival after heart transplantation.

The number of heart transplants performed worldwide is limited due to donor availability. This number has not increased in the past decade, with only about 2300 adult heart transplants being performed annually in the United States, and about 1200 in Europe [4]. An important demographic change of transplant recipients has been a shift toward transplanting older patients. While median age of transplant recipients has been stable over the past decade at 54 years, the proportion of recipients at extremes of age has increased. Between 1982–1985 and 2006–2013, the proportion of recipients aged 60–69 years increased from 14 to 24 % [3]. Some centers list these older recipients, particularly those with comorbidities, on an "alternate list," allowing them to receive

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M. Dorobanțu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_20

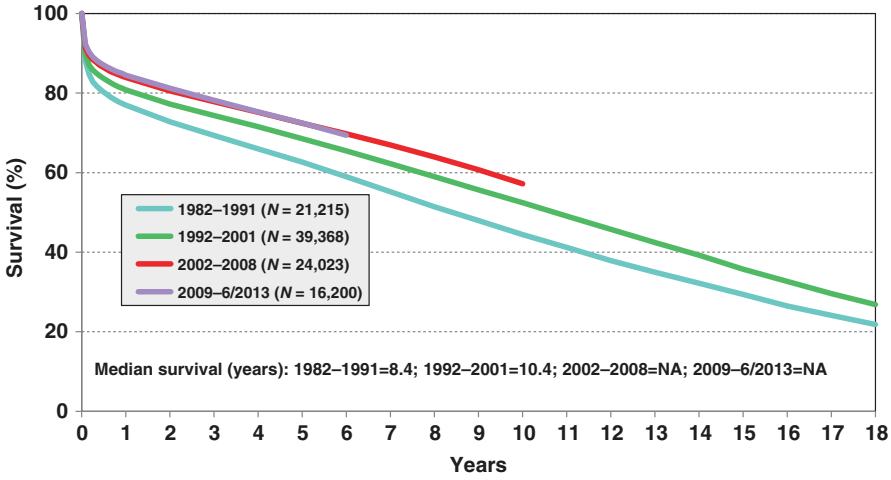

Fig. 20.1 Survival after heart transplantation (Reproduced from Ref. [3], with permission)

organs of lower quality that might not be accepted for younger candidates. This practice has the potential to expand the donor pool and increase the number of transplants performed, but its impact on long-term post-transplant outcomes is unknown. Active research into improved preservation methods, allowing transport of organs over longer distances, and heart donation after cardiac death may expand the number of transplants possible in the future. The use of ex vivo perfusion (Organ Care System) has been shown recently to be equivalent in terms of graft survival to the traditional cold storage [5] and allowed recovery of hearts from deceased cardiac donors, successfully yielding normal graft function at 3 months post-transplant [6]. The number of recipients bridged to transplant with ventricular assist devices has increased dramatically over the last decade; in 2013, 48 % of adult recipients in the United States were bridged with ventricular assist devices, compared to only 18 % in 2000 [3]. Other important changes in heart transplant recipients over the past two decades have included increasing recipient body mass index (over 20 % of recipients in the United States in 2006–2013 were obese), increasing proportion of women (up to 25 %), increasing proportions of recipients with diabetes (up to 25 %), or dialysis (for combined heart-kidney transplant), and prior malignancy (up to 7 %) [3]. Fewer patients have been hospitalized at the time of transplantation, and a greater proportion has been sensitized to human leukocyte antigens (HLAs) with panel reactive antibody greater than 10 % [3].

Donor-Recipient Matching and Organ Allocation Procedures

Donor-recipient matching is based on ABO blood group compatibility, body size, and the absence of recipient preformed antibodies to the donor's HLA. For kidney transplant recipients, superior outcomes were obtained among those matched at 6/6 loci compared to those matched at fewer loci [7], suggesting that HLA matching

Table 20.1a Listing criteria for heart transplantation in the United States

Status 1 A	Mechanical circulatory support
	Ventricular assist device (for 30 days after implantation, or indefinitely if device related – complications)
	Total artificial heart
	Intra aortic balloon pump
	Extracorporeal circulatory support (ECMO)
	Continuous mechanical ventilation
	Continuous infusion of IV single inotrope (high dose) or dual inotrope (any dose) with continuous invasive hemodynamic monitoring (Swan Ganz catheter)
Status 1B	Ventricular assist device
	Continuous infusion of IV inotropes
Status 2	Does not meet the criteria for status 1 A and 1B
Status 7	Temporarily unavailable to receive organ transplantation

Table 20.1b Listing criteria for heart transplantation in Eurotransplant

High Urgency Status (national; international)	Mechanical circulatory support with device related - complications
	Continuous infusion of IV single inotrope (high dose) with continuous invasive hemodynamic monitoring (Swan Ganz catheter) and signs of end organ failure (sodium < 136 mEq/L; increasing creatinine; increasing hepatic transaminases; symptomatic cerebral perfusion deficit)
Transplantable	Ventricular assist device
	Continuous infusion of IV inotropes
Non-transplantable	Temporarily unavailable to receive organ transplantation

would be desirable in heart transplantation as well. Unfortunately, this is not practical due to the small numbers of patients involved and the long distances required for the donor organs to travel. Hearts are more sensitive to prolonged preservation times than kidneys, and the benefits of HLA matching would likely be outweighed by the increased ischemic time due to longer transport distances. The Organ Procurement and Transplantation Network, administered by the United Network for Organ Sharing, coordinates organ allocation in the United States. In Europe, the organ allocation is coordinated by national agencies (e.g. United Kingdom, France, Spain, Italy), or transnational agencies (e.g. 8 countries in Eurotransplant). The goals for these non-profit agencies are to increase the effectiveness and efficiency of organ sharing and equity in the national systems of organ allocation and to increase the supply of donated organs available for transplantation.

Heart allocation is fairly similar in the United States and Europe and is currently based on recipient priority on the waiting list (Tables 20.1a and 20.1b) and geography. Hearts are first allocated to compatible higher status recipients (Status 1 in the United States; national and international High Urgency Status in Europe) at local centers, followed by compatible higher status recipients within a 500 miles radius, and then local Status 2 recipients followed by Status 2 recipients within 500 miles. Offers are then expanded to distances greater than 500 miles, based on a 500 miles radius, until the donor hearts are placed. In the US, a new proposal for

organ allocation designed to increase the survival on the heart transplant list and to more equitably distribute the organs to the highest risk patients is currently being debated [8].

Immunosuppression Therapy

Immunosuppression therapy can be divided in three separate phases, each with its individual particularities. First, induction therapy may be used in the early post-operative period to obtain rapid and intense immunosuppression, reducing the risk of acute rejection. Second, maintenance immunosuppression regimens aim to prevent allograft rejection and cardiac allograft vasculopathy while minimizing infections, malignancies, and toxicities. Finally, treatment of acute rejection targets the rapid resolution of the rejection episode and aims to prevent or reverse graft dysfunction.

Induction Therapy

Although high-dose corticosteroids are used routinely in the immediate post-transplant period, the antibody induction therapy is only used in about half of transplant programs, often selectively, based on patient rejection risk level. These agents include polyclonal anti-T cell antibodies [rabbit anti-thymocyte globulin (rATG)] and monoclonal anti interleukin 2 (IL-2) antibodies (basiliximab). Induction provides intensive immunosuppression in the early post-transplant period when the risk of acute rejection is highest and allows delayed introduction of calcineurin inhibitor agents in patients with renal dysfunction or in those at high risk for renal dysfunction. These agents may reduce the incidence of early rejection compared to no induction therapy; however there are no differences in the incidence of long-term rejection episodes. Induction therapy may be associated with an increased risk of infection, although this risk may be lower with basiliximab than with rATG. In contrast, the risk of rejection and graft loss may be lower in patients receiving rATG. Neither agent increases the risk of malignancy long term [9–12].

Maintenance Immunosuppression

The most commonly used maintenance immunosuppression regimen is a triple-therapy combination of corticosteroids, a cell cycle inhibitor and a calcineurin inhibitor. This approach targets multiple facets of the immune system simultaneously (Fig. 20.2) [9], and allows the use of lower doses of individual agents with different side effect profiles, thus minimizing toxicity.

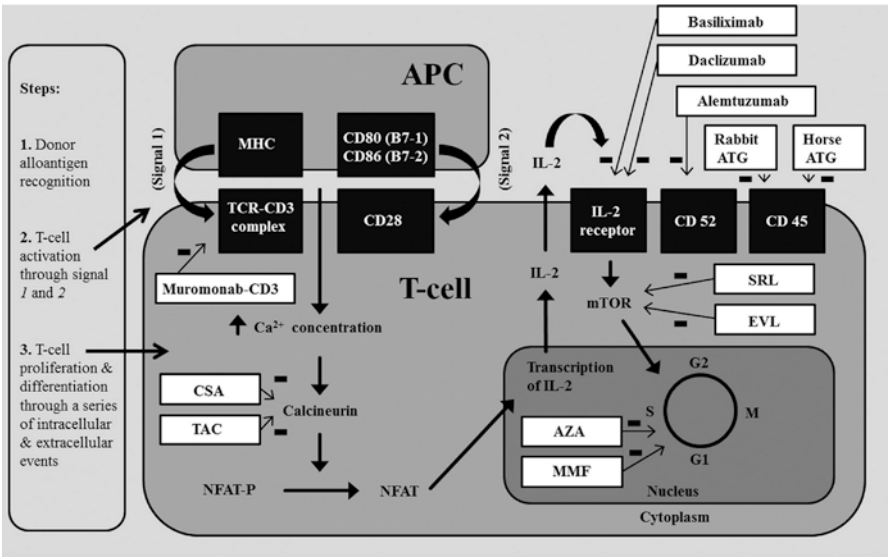

Fig. 20.2 Immunologic mechanisms leading to graft rejection and sites of action of immunosuppressive drugs (Reproduced from Ref. [9], with permission)
Figure showing the initiation of the adaptive immune response against the donor heart, beginning with the recognition of an alloantigen by a naive T-cell, followed by T-cell activation, proliferation and differentiation. The mechanisms of action of different immunosuppressive drugs on T-cells are also shown in the figure
Abbreviations: *APC* antigen-presenting cell, *ATG* antithymocyte globulin, *AZA* azathioprine, *CSA* cyclosporine, *EVL* everolimus, *G1* cell cycle gap phase 1, *G2* cell cycle gap phase 2, *IL-2* interleukin-2, *M* cell cycle mitosis phase, *MHC* major histocompatibility complex, *MMF* mycophenolate mofetil, *mTOR* mammalian target of rapamycin, *NFAT* dephosphorylated nuclear factor of activated T-cells, *NFAT-P* phosphorylated nuclear factor of activated T-cells, *S* cell cycle synthesis phase, *SRL* sirolimus, *TAC* tacrolimus, *TCR* T-cell receptor, − indicates inhibition
Corticosteroids, which are not described in the figure, have multiple mechanisms of action that affect both the innate and adaptive immune system. In lymphocytes, however, they primarily act through the inhibition of the two transcription factors activator protein-1 and nuclear factor kappa-light-chain-enhancer of activated B-cells (NF- B)

Corticosteroids are nonspecific immunosuppressive and anti-inflammatory agents, acting at multiple sites of the immune system to alter cytokine expression and leukocyte activity. They are an important component of all three phases of immunosuppression and are associated with numerous short and long-term adverse effects. The usual doses are in the range of 500–1000 mg of methylprednisolone daily for 2–3 days, for the induction and rejection phase. The long-term maintenance consists of tapering doses of prednisone over time, usually over the first 6–12 months post-transplant in the majority of patients [9, 13]. The steroid weaning schedule is individualized and may need to be altered in high-risk patients, such as those with acute rejection episodes in the first year or highly sensitized patients [13]. Most commonly, the side effects of corticosteroids are related to hyperglycemia, increased risk of infections, weight gain, psychosis and osteoporosis.

The two cell cycle inhibitors used in transplantation are azathioprine and mycophenolate mofetil. Mycophenolate mofetil is an antimetabolite that blocks purine synthesis, inhibiting B and T lymphocyte proliferation. It is usually started at 500–1000 mg twice daily, from the first day post transplantation. Common toxicities include nausea, vomiting, diarrhea, and leukopenia. The gastrointestinal side effects can be resolved by adjusting the dose or schedule, or by using the available enteric-coated formulation (e.g. mycophenolic acid) [9, 14]. Leukopenia is a frequent side effect and may be dose limiting or necessitate leukocyte growth factor stimulators (e.g. filgrastim) to support the white cell count [9]. Several studies have shown the superiority of mycophenolate mofetil over azathioprine in the prevention of treated rejection episodes, allograft vasculopathy, reduced risk of malignancy and over survival among heart transplant recipients [15–17].

Calcineurin inhibitors, cyclosporine and tacrolimus, bind to specific intracellular proteins, forming complexes that inhibit calcineurin-mediated transcription of IL-2 and suppressing T lymphocyte growth and differentiation [9]. They are started at low doses, 2–3 days after transplantation, when the renal function has stabilized, and gradually increased. The target plasma concentration is higher in the first 60 days (200–350 ng/mL for cyclosporine and 10–15 ng/mL for tacrolimus) then gradually decreases over time in order to avoid side effects (150–300 ng/mL for months 2–6, and 150–250 ng/mL after 6 months for cyclosporine; 8–10 ng/mL for months 2–6, and 5–8 ng/mL after 6 months for tacrolimus). Common side effects include hypertension (more with cyclosporine), dyslipidemia (more with cyclosporine), hyperglycemia (more with tacrolimus), renal insufficiency, neurotoxicity (i.e. tremors and headaches), and electrolyte abnormalities (i.e. hyperkalemia; more with tacrolimus). Cyclosporine may also cause gingival hyperplasia and hirsutism. Both agents are highly effective in preventing rejection, although tacrolimus may be associated with fewer acute rejection episodes [18–20].

The proliferation signal inhibitors, also known as mammalian target of rapamycin (mTOR) inhibitors, include sirolimus and everolimus, and inhibit mTOR, an intracellular kinase activated by PI3-K, thus inhibiting cellular division. Several studies showed that these agents reduce the risk of invasive cytomegalovirus disease, cardiac allograft vasculopathy, and malignancy [9]. When used, they generally replace mycophenolate mofetil in the immunosuppressive regimen. Levels should be measured at least 5 days after adjustment of the dose, when a steady state is achieved. When used in combination with tacrolimus, the optimal trough target level for everolimus is between 3 and 8 ng/mL. The corresponding optimal trough level for sirolimus is 4–10 ng/mL. Their use is limited by toxicity, which includes poor wound healing, capillary leak with peripheral edema and serositis (pleural and pericardial effusions), oral ulcerations, hypertriglyceridemia, pulmonary toxicity, bone marrow suppression, and potentiation of calcineurin inhibitors-induced renal dysfunction. In general, everolimus seems to be better tolerated than sirolimus. They are usually used as secondary agents in the treatment of cardiac allograft vasculopathy, or in patients with malignancies or renal dysfunction [21–24].

Mechanisms and Diagnosis of Cardiac Allograft Rejection

Allograft rejection is an intense immunologic response mediated by T lymphocytes and directed against donor antigens. Although HLA antigens have been traditionally recognized as the culprit for rejection, there is mounting evidence that non HLA antigens play a significant role; these non-HLA antigens are the Major Histocompatibility Complex class I related chain A (MICA) or B (MICB), endothelial antigens, and vimentin [9]. The donor antigens are presented to the recipient T cells by the antigen-presenting cells, triggering a series of stimulatory signals and leading to the activation of the Tcells (Fig. 20.2). This activation results in expression of IL-2 and other inflammatory cytokines, which will lead to the proliferation and differentiation of a large number of effector T cells that will react to myocardial or coronary endothelial cells displaying antigens on their surface. The effector T cells can mediate cellular rejection (through direct cytotoxicity of CD8 T cells and the activation of macrophages by CD4 T cells) or antibody-mediated (humoral) rejection (through activation of B cells to produce donor-specific antibodies) [9]. In cellular rejection, T cells, macrophages, and plasma cells infiltrate the myocardium and cause myocyte necrosis, resulting in the characteristic biopsy finding of mononuclear cell infiltration. In antibody-mediated rejection, donor-specific antibodies produced by plasma cells bind to the capillary endothelium, leading to complement binding and cell damage. Acute graft rejection accounts for approximately 10 % of all deaths in the first 3 years post transplant, although cellular and antibody-mediated rejection also contribute to chronic graft dysfunction and coronary allograft vasculopathy and are therefore likely to contribute to an even greater proportion of overall deaths [9].

Acute cellular rejection is characterized by T lymphocyte-mediated myocyte damage. Endomyocardial biopsy findings include perivascular or interstitial mononuclear inflammatory cell infiltrates with or without associated myocyte damage, edema, hemorrhage, or vasculitis (Fig. 20.3a, b). The grading system for acute cellular rejection ranges from grade 0 (no histologic evidence of rejection) to grade 3R (severe rejection) (Table 20.2a). The risk of acute cellular rejection is greatest in the first 3 months following transplantation and decreases over time. About a third of transplant recipients will have one or more episodes of rejection in the first 12 months, but only about 10–15 % will actually require specific treatment. The risk factors for acute cellular rejection include younger age at transplantation, female sex, multiparity, black race, and greater HLA mismatch [25].

Pre-existing or de novo donor specific antibodies may recognize donor antigens on the graft at any time post-transplant and antibody binding may initiate complement activation and lead to myocyte damage. Antibody mediated rejection includes a spectrum of patterns ranging from clinically silent evidence of antibody binding by immunofluorescence staining on myocardial biopsy to severe graft dysfunction. The International Society for Heart and Lung Transplantation recently developed a standardized grading based on histologic and immunohistochemical findings (Table 20.2b) [26]. It is now recognized that antibody mediated rejection is associated with increased risk of death, graft loss, and development of coronary allograft vasculopa-

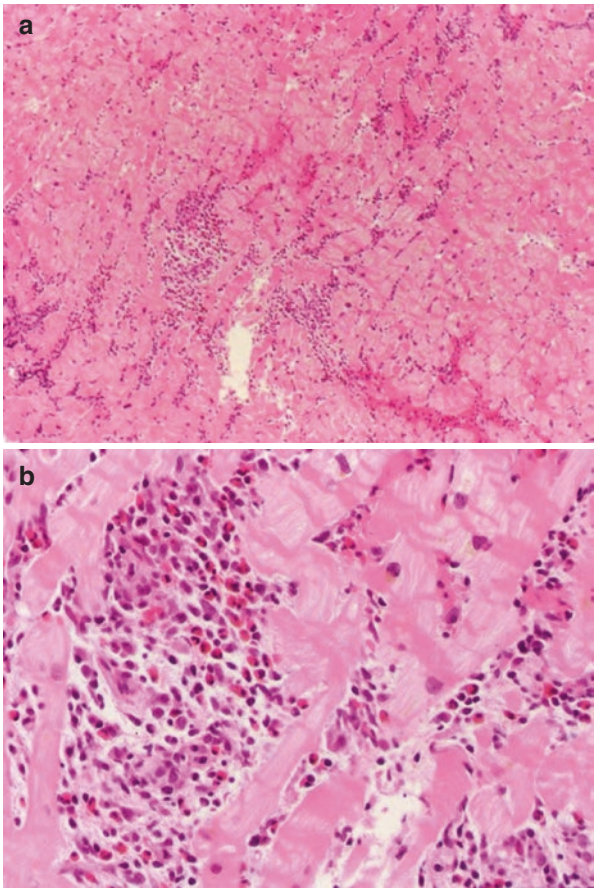

Fig. 20.3. (**a**) Perivascular and interstitial inflammation with focal destruction of myocytes. (**b**) Magnification of the above, showing presence of lymphocytes and eosinophils, and myocyte damage. Endomyocardial biopsy stained with H&E showing acute cellular rejection (grade 2) in a 29 year old man that was non compliant with his anti rejection medications and presented to the hospital 7 months post transplantation with heart failure symptoms and new onset atrial fibrillation

Table 20.2a Diagnosis of acute cellular rejection

Grade 0 (negative)	No evidence of rejection
Status 1 (mild)	Interstitialand/orperivascularinfiltratewithupto1focusofmyocytedamage
Status 2 (moderate)	Two or more foci of in filtrate with associated myocyte damage, eosinophilic infiltration
Status 3 (severe)	Diffuse infiltrate with multifocal myocyte damage, and/or edema, and/or hemorrhage. And/or vasculitis

thy. Risk factors include high pre-transplant panel reactive antibody, positive B-cell flow cytometry cross-match, retransplantation, multiparity, blood transfusions, and ventricular assist device use pre transplant [26].

The gold standard for diagnosing rejection is represented by the endomyocardial biopsy, usually performed from the right ventricle using the right internal jugular approach under fluoroscopic or echocardiographic guidance. This procedure is

Table 20.2b Diagnosis of acute antibody-mediated rejection

pAMR0 (negative)	Histologic and immunopathologic studies negative
pAMR1h (histopathologic alone)	Histologic findings present; immunopathologic findings negative
pAMR1i (immunopathologic alone)	Immunopathologic findings present; histologic findings negative
pAMR2 (pathologic)	Histologic and immunopathologic findings positive
pAMR3 (severe pathologic)	Interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis, and/or karyorrhexis, and marked edema and immunopathologic findings are present

generally safe and well tolerated, but may be associated with rare complications including tricuspid valve damage, right ventricular perforation, arrhythmias, and vascular access complications. The use of long biopsy sheaths with a preformed curve pointing towards the interventricular septum alleviates most of these concerns [27]. The invasive nature of the biopsies has led to many investigations trying to validate noninvasive ways to diagnose rejection (e.g. tissue Doppler echocardiography, cardiac magnetic resonance imaging), but only a few have succeeded in being meaningful clinically.

Gene expression profiling has emerged as the only clinically meaningful, widely used, noninvasive method of screening for acute cellular rejection, mainly in low-risk heart transplant recipients. The AlloMap® method evaluates peripheral mononuclear cell RNA expression of 11 genes that have been shown to discriminate between rejection and absence of rejection episodes. A score between 0 and 40 is assigned to each sample; scores of less than 34 are associated with low probability of grade 2 and 3 rejection, while those greater than 34 are unable to rule out rejection and indicate the need for endomyocardial biopsy. Although the initial studies [28, 29] showed that rejection monitoring with AlloMap® was not associated with an increased risk of serious adverse outcomes compared to a strategy of routine biopsies in patients at least 6 months post-transplant, this strategy has recently been demonstrated to be non-inferior to routine biopsies beginning as early as 55 days post-transplant [30]. Limitations to a widespread use of the AlloMap® test include the test's inability to detect antibody-mediated rejection, and lack of test validity in the context of high-dose corticosteroid therapy (more than 20 mg prednisone daily), recent blood transfusion, recent administration of leukocyte growth factor stimulators or multi organ transplant.

Treatment of Cardiac Allograft Rejection

Management of Acute Cellular Rejection

Clinical decisions regarding management of acute cellular rejection are influenced by both the histologic rejection grade and the patient's clinical status, including the presence of graft dysfunction (i.e. echocardiographic evidence of decreased ejection

fraction, ventricular hypertrophy as sign of myocardial edema, or grade II or greater diastolic dysfunction), arrhythmias or hemodynamic instability.

Mild (grade 1R) cellular rejection is typically not treated, and the presence of this finding on biopsy has not been associated with adverse outcomes [31]. Persistent grade 1R may lead to the intensification of the background immunosuppression and targeting higher plasma levels of calcineurin inhibitors. Moderate grade 2R rejection without hemodynamic compromise can be treated with oral pulse steroids, such as prednisone 50 mg twice daily for 3 days, with subsequent rapid tapering. Moderate rejection with evidence of graft dysfunction is typically treated with intravenous steroids, such as methylprednisolone 500 mg daily for 3 days, with subsequent slow tapering. Any evidence of hemodynamic compromise or persistent graft dysfunction in the setting of moderate or severe cellular rejection requires inpatient treatment with regimens that include intravenous pulse steroids, intensified maintenance immunosuppression, and cytolytic therapy (rATG). Patients presenting with severe hemodynamic compromise (i.e., cardiogenic shock) should be treated aggressively and empirically without awaiting biopsy results and should receive treatment for both cellular and antibody-mediated rejection in addition to hemodynamic support (e.g., inotropic support, intra-aortic balloon pump, or percutaneous mechanical circulatory support) [32].

Management of Antibody-Mediated Rejection

Management of antibody-mediated rejection is very empiric and varies by transplant center, severity of biopsy findings, graft function, and the presence of donor specific antibodies [33]. Typical treatment includes combination of high-dose intravenous corticosteroids (e.g. methylprednisolone 500 mg daily for 3 days), plasmapheresis or immunoadsorption, intravenous immunoglobulins, rATG, and rituximab, with subsequent increased doses of oral steroids [33–37].Recently, bortezomib, a proteasome inhibitor that depletes plasma cells, and eculizumab, a monoclonal antibody directed against the terminal complement component C5, have demonstrated clinical efficacy in the kidney transplant patients diagnosed with humoral rejection [38], and have been used off label in heart transplant patients. The treatment of patients with donor specific antibodies but no graft dysfunction or biopsy evidence of antibody-mediated rejection *or* that of patients with biopsy findings but no donor specific antibodies or graft dysfunction is controversial. Some centers use long-term photophoresis and rituximab or bortezomib in order to bring the levels of donor specific antibodies to undetectable levels. Although this strategy has been effective in several case series, the mortality and morbidity of this approach are quite substantial, mostly due to the associated infectious complications [39].

Long-Term Complications of Immunosuppression Therapy

Infections

A major consequence of long-term immunosuppression is the increased risk of infection. Infection is the leading cause of death in the first post-transplant year when immunosuppression is most intense, but remains a risk in the long term as well. In the first month post-transplant, most infections are bacterial and related to nosocomial organisms. After this initial period, patients are at risk for common infections with typical community-acquired pathogens as well as for more opportunistic infections with organisms such as Cytomegalovirus, Aspergillus fumigatus, Candida species, Pneumocystis jirovecii, Mycobacterium species, Nocardia species, and Toxoplasma gondii. Most patients receive antifungal prophylaxis with fluconazole (100 mg weekly) or nystatin (oral suspension 4 times daily),and anti Toxoplasma and Pneumocystis prophylaxis with sulfamethoxazole and trimethoprim (160/800 mg three times weekly) for the first post transplant year, or during acute rejection episodes requiring prolonged course of high dose steroids [40, 41]. Prophylaxis against Cytomegalovirus has significantly decreased the mortality and morbidity in transplant patients, and it is based on the mismatch status between recipient and donor. For highest risk patients (donor positive/ recipient negative), the prophylaxis with valganciclovir (900 mg daily, adjusted for renal function) lasts 6 months. These high-risk recipients may also receive Cytomegalovirus immunoglobulins (starting the first week post transplant and ending at week 16) that may further decrease the risk of infection. For lower risk patients (recipient positive) the prophylaxis with valganciclovir can last for only 3 months, unless induction therapy has been used, in which case the prophylaxis is extended to 6 months. For the lowest risk recipients (donor negative/ recipient negative), prophylaxis is designed to cover other herpes viruses, and consists of acyclovir or valacyclovir for 3 months [42]. Cytomegalovirus prophylaxis is reinstituted in the setting of acute rejection episodes requiring prolonged course of high dose steroids.

When transplant patients present with symptoms of infection, clinicians need to have a low threshold for starting therapy right away and evaluate for even more rare organisms as sources of infection.

Malignancy

Long-term immunosuppression places transplant recipients at an increased risk of malignancy. In fact, malignancies are the second leading cause of death in patients who survive 5 years from heart transplantation. Skin malignancies account for the greatest number of cancers, followed by lymphoproliferative disorders [43].

While transplant recipients are at increased risk for non-cutaneous solid organ cancers, including lung, kidney, and colon, they appear to be at lower risk for prostate and breast cancers [44, 45]. Due to the increased incidence of malignancies post transplant, it is imperative that all transplant candidates undergo a thorough pre transplant screening in order to exclude incipient stages of cancers. Current recommendations for cancer screening in transplant population do not differ from age-appropriate recommendations in the general population with the exception of skin examinations, which are recommended on an annual basis after transplant [32].

Post-transplant lymphoproliferative disease is a heterogeneous group of disorders occurring in 1–2 % of cardiac transplant recipients, ranging from an infectious mononucleosis-like syndrome to aggressive lymphomas [45]. The majority of cases are associated with reactivation of or primary infection with Epstein-Barr virus. Other risk factors include cytomegalovirus infections, intensity and duration of immunosuppression, extremes of age at time of transplantation, and genetic factors. The mainstay of therapy is reduction of immunosuppression, though this leads to a response in only half of patients and durable remission in even fewer. In addition, switching from mycophenolate mofetil to proliferation signal inhibitors has been shown to induce remission [46]. Rituximab has been a valuable addition to the treatment regimen, resulting in dramatically improved outcomes when used as part of the initial treatment strategy [47].

Cardiac Allograft Vasculopathy

Cardiac allograft vasculopathy is the leading cause of late-onset graft failure and mortality in heart transplant recipients. It occurs in up to 18 % of patients during first year post-transplant and in over 50 % of patients by 10 years post-transplant [3]. Unlike conventional atherosclerotic coronary disease, cardiac allograft vasculopathyis characterized by diffuse concentric and longitudinal narrowing of the main coronary arteries and their small branches. Histology of the affected vessels demonstrates concentric thickening of the intimal layer with increased numbers of smooth muscle cells and foam cells within a connective tissue matrix, although fibrofatty plaques can also be seen [48]. Surface endothelial erosion, fibrous cap thinning, and plaque erosion are uncommon. The pathogenesis of cardiac allograft vasculopathy involves vessel inflammation and endothelial injury. Risk factors include traditional atherosclerotic risk factors (diabetes, hypertension, obesity, cigarette smoking, and hyperlipidemia) and non-traditional transplant-related factors (HLA mismatch, number of rejection episodes, cytomegalovirus infection, donor age, and traumatic mechanism of donor brain death) [48, 49]. Prevention strategies include controlling the traditional atherosclerotic risk factors and addition of statins early after transplantation, irrespective of cholesterol values. Indeed, use of pravastatin has been shown to decrease the incidence of cardiac allograft vasculopathy in heart transplant recipients [50].

Table 20.3 Diagnosis of cardiac allograft vasculopathy

CAV0 (not significant)	No detectable angiographic lesion
CAV1 (mild)	Angiographic left main <50 %, or primary vessel with maximum lesion of <70 %, or any branch stenosis <70 % (including diffuse narrowing) without allograft dysfunction
CAV2 (moderate)	Angiographic LM ≥50 %; a single primary vessel ≥70 %, or isolated branch stenosis ≥70 % in branches of 2 systems, without allograft dysfunction
CAV3 (severe)	Angiographic LM ≥50 %, or two or more primary vessels ≥70 % stenosis, or isolated branch stenosis ≥70 % in all 3 systems; or CAV1 or CAV2 with allograft dysfunction (defined as LVEF <46 % usually in the presence of regional wall motion abnormalities) or evidence of significant restrictive physiology (which is common but not specific)

Because most transplanted allografts lack innervation, patients are unlikely to experience angina in the presence of hemodynamically significant cardiac allograft vasculopathy, and may present late with heart failure symptoms, ventricular arrhythmias or heart block, or sudden death. Screening is therefore necessary, and most centers perform coronary angiography after the first transplant year and annually or in alternate years thereafter. Coronary angiography may demonstrate diffuse narrowing of vessels, distal pruning of small branch vessels, or focal stenoses (Table 20.3) [51]. The addition of intravascular ultrasound (IVUS) has allowed greater sensitivity for early detection of allograft vasculopathy, and measurement of intimal thickness with IVUS provides important prognostic information [52]. Progression of intimal thickness over 0.5 mm in the first year after transplant predicts increased risk of death, graft loss, nonfatal cardiovascular events, and the development of angiographic vasculopathy within 5 years. Use of proliferation signal inhibitors has been advocated in these patients, in order to prevent the development or slow the progression of vasculopathy [22]. Optical coherence tomography performed as an adjunct to coronary angiography provides high-resolution imaging of the coronary arteries and allows measurement of intimal thickness and characterization of wall tissue, and allows early identification of cardiac allograft vasculopathy in patients with angiographically normal coronary arteries [53]. In order to minimize the frequency of coronary angiography and associated risks, dobutamine stress echocardiography has been used as an alternative to angiography in patients without coronary allograft vasculopathy or in those with longstanding stable disease. This modality has been shown to correlate well with findings at angiography and is also predictive of cardiovascular events in transplant recipients [54].

Novel methods of noninvasive screening, such as 64-slice coronary computed tomography angiography or cardiac magnetic resonance imaging, have been tested in recent years. A recent meta-analysis of trials of 64-slice coronary computed tomography angiography for the detection of coronary allograft vasculopathy found a sensitivity of 97 % and negative predictive value of 99 % for stenoses over 50 % detected on conventional angiography [55]. However, the sensitivity dropped to 81 % and specificity dropped to 75 % when compared to detection of intimal thickening greater than 0.5 mm by IVUS [55]. The main limitation of computed tomog-

raphy angiography is the high resting heart rates of transplant recipients with denervated grafts. In addition, although it offers the advantage of noninvasive diagnosis, it does not avoid the risks of iodinated contrast agents and radiation.

Coronary allograft vasculopathy remains a major limitation to survival in heart transplant recipients and effective treatment options are still lacking. Beside the use of statins, modification of traditional cardiovascular risk factors and immunosuppression with mTOR inhibitors, therapy with diltiazem (and possibly amlodipine) may be beneficial in the prevention of vasculopathy [56]. In patients with established allograft vasculopathy, focal coronary stenoses may be treated with drug-eluting stents [57]. Surgical revascularization may offer palliation in selected patients with multivessel disease, although poor distal targets preclude this option in most transplant recipients. Retransplantation remains the only definitive treatment in these cases [32].

Hypertension

Hypertension is common after heart transplantation, occurring in up to 95 % of transplant recipients. The excess risk of hypertension is attributable primarily to the use of calcineurin inhibitors because of both direct effects and the associated renal insufficiency [58]. The incidence of hypertension is lower in patients treated with tacrolimus than with cyclosporine A [59]. Among calcium channel blockers, diltiazem is often used because its inhibition of cytochrome P450 (CYP450) 3 A4 allows a reduction in calcineurin inhibitors dose and because of reported favorable effects on cardiac allograft vasculopathy [59]. Post transplantation hypertension frequently is difficult to control and often requires a combination of several antihypertensive agents [59].

Diabetes Mellitus

De novo diabetes occurs in a third of heart transplant recipients [60]. A number of factors, including pre-transplantation diabetes, glucocorticoids, and calcineurin inhibitors (especially tacrolimus), contribute to the high prevalence of diabetes [60]. Diabetes is associated with a worse long-term survival in heart transplant recipients. Aggressive management of diabetes is needed in order to improve long-term outcomes.

Dyslipidemia

Lipid abnormalities are present in 60–80 % of heart transplant recipients [32]. Calcineurin inhibitors, prednisone, and mTOR inhibitors sirolimus and everolimus all exacerbate hyperlipidemia. The benefits of statins in heart transplant recipients

are even greater than in the general population and may be due to both cholesterol lowering and immune modulating effects, with decreasing incidence of transplant vasculopathy. Due to lower chance of interaction with immunosuppression drugs and lack of or low metabolism by cytochrome enzymes, pravastatin and rosuvastatin are the preferred agents [32, 59].

Chronic Renal Insufficiency

Renal insufficiency is a common adverse effect of calcineurin inhibitors, and no effective therapy has been developed to prevent this problem. Creatinine levels greater than 2 mg/dL occur in a third of heart transplant recipients by5 years after transplantation, and up to 5 % ultimately develop end-stage renal disease requiring dialysis [32]. There is no data whether ACE inhibitors or angiotensin receptor blockerscan slow the progression of calcineurin inhibitors-induced renal disease.

Conclusions

For carefully selected patients, heart transplantation offers markedly improved survival and quality of life. Heart transplantation continues to evolve with new advancements in the preoperative, perioperative, and postoperative management of heart transplantation patients, leading to improved survival. With ongoing research, further advances in immunosuppression and prevention of rejection, infection, malignancy, and cardiac allograft vasculopathy will lead to continued improvement in post-transplant outcomes. Noninvasive methods of monitoring for rejection and cardiac allograft vasculopathy will further improve the quality of life of transplant recipients while minimizing complications associated with invasive procedures. The holy grail of immune tolerance remains beyond our reach at the present time, but has the potential to completely alter the solid organ transplantation landscape and will continue to be a target of active research.

Future Directions

- Increased utilization of ex-vivo perfusion systems as well of novel cold perfusion solutions will increase the use of donors currently deemed as marginal or at too far of a distance for procurement.
- New organ allocation policies will impact the waiting list status and patients on mechanical circulatory support will likely be gradually transformed in destination therapy, rather than true bridge to transplantation.

- Use of novel agents (e.g. bortezomib, eculizumab) will allow a greater number of patients to undergo successful desentization at acceptable risks in order to allow successful transplantation.
- Combination of calcineurin inhibitors and mammalian target of rapamycin inhibitors will allow for greater preservation of the graft function and minimization of end organ damage.
- Novel techniques such as circulating cell-free DNA will enable noninvasive diagnosis of heart transplant rejection and of several infections, leading to more personalized approach in immunosuppression and the ability to prescribe "anti-rejection treatment on demand" when the molecular signature becomes abnormal.

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Part IV
Particular Forms of Heart Failure

Chapter 21
Heart Failure and Hypertension

Tatiana Kuznetsova and Nicholas Cauwenberghs

Epidemiology

A major burden of modern society is the progressive increase in age-associated disorders such as heart failure (HF) [59]. Symptomatic HF is affecting nearly 15 million Europeans and 10,000 people are newly diagnosed every day [59]. In the US, HF contributes to an economic burden close to $40 billion per year and affects 1–2 % of the US population [39]. With the high prevalence of systemic hypertension, obesity and diabetes mellitus in our society, it is expected that the incidence of HF will continue to increase [39]. Figure 21.1 highlights that the actual burden of HF exceeds the projected burden according to the American Heart Association [39, 53]. With the increasing prevalence of symptomatic HF there is a need for early and accurate diagnosis and a better treatment regimen in helping people deal with this progressive chronic condition.

While traditionally associated with the concept of pump failure or reduced left ventricular (LV) ejection fraction (EF), it has become widely recognized that HF can occur even when EF is preserved, constituting the syndrome of HF with preserved EF (HFpEF) or so called diastolic HF [53] which is characterized by impaired LV relaxation, increased LV stiffness, and modified extracellular matrix proteins. The majority of the patients with HFpEF have a history of hypertension [53]. HFpEF now accounts for more than 50 % of the HF hospitalizations. Symptomatic HF with or without reduced EF has a poor prognosis [10, 46, 52]. In the recent meta-analysis which included 10,347 patients with HFpEF and 31,625 patients with HF and reduced EF (HFrEF), the authors compared survival in these groups using individual patient data [46]. Overall, there were 121 [95 % confi-

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M. Dorobanțu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_21

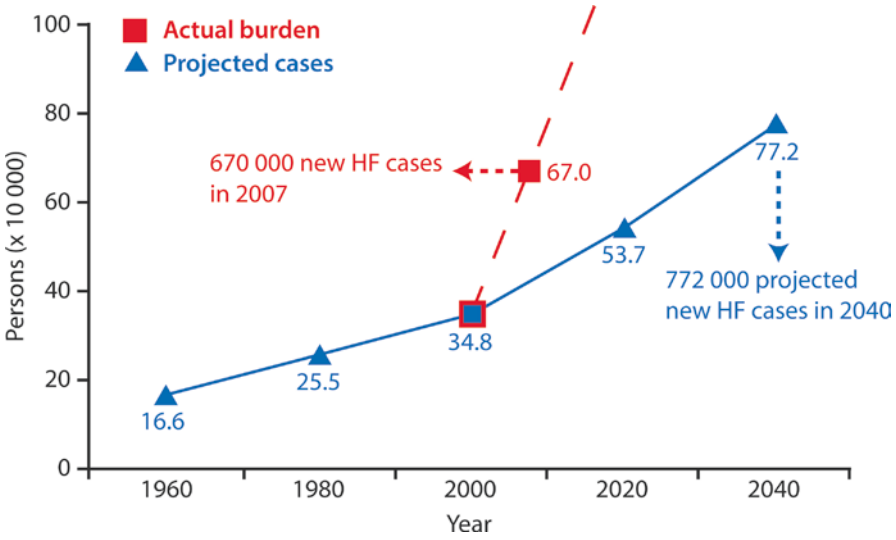

Fig. 21.1 Burden of HF. The actual burden of HF exceeds the projected burden based on a stable incidence of 10 per 1000 person-years in subjects aged > 65 year old (reproduced from Lam et al. [2] and Owan et al. [53] with permission)

dence interval (CI): 117, 126] and 141 (95 % CI: 138, 144) deaths per 1000 patient-years in patients with HFpEF and HFrEF, respectively [46]. Although the majority of resources are currently allocated to managing patients with symptomatic disease, in order to change the epidemic of HF, more resources need to be allocated to earlier recognition of HF as well as management of risk factors. Identifying patients at the early stages of HF would allow the institution of more aggressive risk management strategies and will likely decrease the progression to symptomatic disease.

HF is a progressive disorder that culminates with time and retards the standard of life of a person. HF begins with risk factors for LV dysfunction (e.g., hypertension and diabetes), proceeds to asymptomatic maladaptive LV remodeling (e.g., LV hypertrophy) and dysfunction (e.g., impaired ventricular relaxation or/and elevated LV filling pressure), and then evolves into clinically overt HF, disability and death [25]. Thus, the process of myocardial remodeling starts before the onset of symptoms (Fig. 21.2). Current guidelines distinguish four stages of HF, with stage A representing subjects who are at high risk for HF, because of hypertension, obesity and/or diabetes, but with still normal LV structure and function and no symptoms of HF [25]. Stage B includes patients with structural and/or functional LV abnormalities without clinical symptoms of HF (asymptomatic HF). Stage C represents patients with structural and/or functional LV abnormalities and symptoms of HF (symptomatic HF). Finally, stage D refers to patients with refractory symptoms of HF, requiring specialized intervention. Community-based studies [4, 40] identified the most important risk factors and underscored the magnitude of the population at

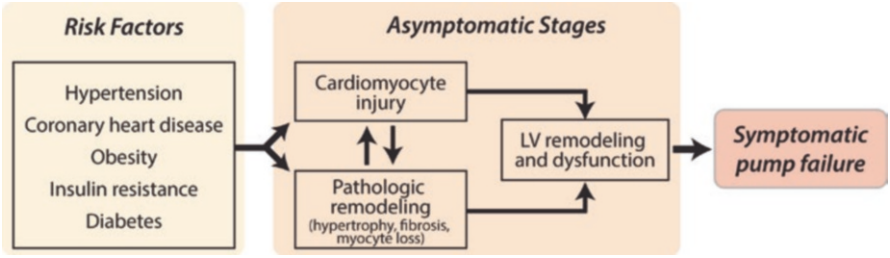

Fig. 21.2 Schema of progression from risk factors to clinically overt HF.

risk for progression to clinically overt HF. For instance, the Framingham study demonstrated that the hazard for developing HF in hypertensive patients, compared to normotensive subjects was approximately twofold in men and threefold in women after adjustment for age and other HF risk factors [40]. The 5-year survival rate for hypertensive symptomatic HF was 24 % for men and 31 % for women [40]. In Olmsted population 56 % of adults 45 years of age were classified as being in stage A (risk factors) or B (asymptomatic LV dysfunction) [4]. Transition from stage B to stages C is associated with a 5-fold increase in mortality risk [4], which underscored the importance of correct identifying persons at stage B for early diagnosis and intervention.

Role of Echocardiography in HF Staging in Patients with Hypertension

A routine physical examination does not allow diagnosing systolic or diastolic LV dysfunction in the preclinical phase (stage B). Similarly, a physical examination cannot accurately characterize the LV volumes and cardiac output. As a rapid and accurate modality, echocardiography can improve the non-invasive detection and definition of the hemodynamic and morphologic changes in HF [28].

The echocardiographic techniques to assess early subclinical changes in LV systolic and diastolic function evolved rapidly over the past 10 years. Nowadays, Tissue Doppler Imaging (TDI) and speckle tracking provide additional information about global and regional cardiac function over and beyond conventional echocardiography. TDI measures the velocity of mitral annular motion or myocardial wall, which reflects the shortening and lengthening of the myocardial fibers along the LV long-axis during the cardiac cycle [17, 45].

On the basis of color Doppler myocardial imaging, 1-dimensional regional systolic deformation (strain) and strain rate (SR) can be derived from tissue velocity measurements. Strain and SR quantifies the actual deformation of the myocardium (expressed as a percentage) in systole and diastole [17]. The major limitation of color Doppler myocardial imaging in the assessment of LV systolic strain is the

dependency on the angle of the ultrasound beam and the difficulties in assessing regional LV torsional movement. Newer techniques, such as "speckle tracking" algorithms, involve identification of multiple unique patterns of echocardiographic pixel intensity that are automatically tracked throughout the cardiac cycle. Each pixel's angular displacement is averaged to provide a measurement of both degree and direction of rotational motion for each segment of the myocardium. This method is not limited by angle dependency and compares favorably with magnetic resonance imaging [70].

LV Remodeling in Hypertensive Heart Disease

The normal heart is an efficient muscle that is designed to serve both as pump and integrator of two independent vascular systems, the pulmonary and systemic circulations. Conditions such as hypertension can cause LV remodeling or hypertrophy in order to accommodate an increased load. Indeed, hypertension induces a compensatory thickening of the ventricular wall in an attempt to normalize wall stress. Therefore, patients with hypertensive heart disease usually present with concentric remodeling or concentric LV hypertrophy, but have a normal-sized LV chamber and normal EF [16].

Worsening of LV geometry is associated with increased risk of cardiovascular outcome. A number of studies documented the relationship between LV hypertrophy (increased LV mass index) detected by electrocardiography and echocardiography and an adverse prognosis. A meta-analysis combined 48,545 subjects from 20 prospective studies and showed that the adjusted risk of future cardiovascular morbidity associated with baseline LV hypertrophy ranged from 1.5 to 3.5, with a weighted mean risk ratio of 2.3 for all studies combined [67]. The adjusted risk of all-cause mortality associated with baseline LV hypertrophy ranged from 1.5 to 8.0, with a weighted mean risk ratio of 2.5 for all studies combined (Fig. 21.3).

Another meta-analysis evaluating cardiovascular outcome in subjects with LV concentric remodeling (normal LV mass index and increased relative wall thickness) compared with those with normal geometry [54]. During the follow-up, 7465 subjects with concentric remodeling experienced 852 cardiovascular events. When compared with normal geometry, the overall adjusted hazard ratio was 1.36 (95 % CI 1.03–1.78; $P<0.03$) for concentric remodeling. Moreover, subgroup meta-analysis showed that increased cardiovascular risk in subjects with concentric remodeling was more relevant in studies evaluating hypertensive patients and reporting both fatal and non-fatal cardiovascular events [54]. Recently, Framingham investigators also reported in longitudinal echocardiographic study that exposure to multiple cardiovascular risk factors, such as elevated blood pressure and greater body mass index, were associated with the development of abnormal LV geometry [41].

Several mechanisms may explain why adverse LV remodeling/hypertrophy is a harbinger of adverse cardiovascular outcomes. Firstly, LV hypertrophy or remodeling may lead to diastolic filling abnormalities that predispose to congestive

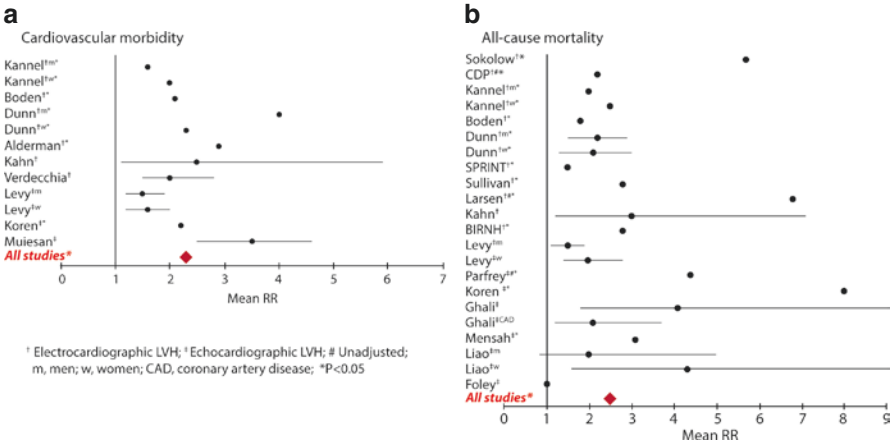

Fig. 21.3 Mean risk ratios (RR) (*solid circle*) and, when available, 95 % confidence interval (*horizontal lines*) of baseline LV hypertrophy for subsequent cardiovascular morbidity (panel **a**) and all-cause mortality (panel **b**) in available studies (reproduced from Vakili BA et al. [67] with permission)

HF. Secondly, maladaptive LV remodeling may lead to dysfunction of the autonomic nervous system, reduce coronary reserve and increase LV oxygen requirements. Thirdly, it may predispose to ventricular arrhythmias and a greater risk of sudden death.

LV Diastolic Dysfunction

In parallel to changes in cardiac geometry, LV diastolic function tends to worsen over the adult life course in particular in patients with hypertension and hyperinsulinemia [37]. Diastolic dysfunction refers to a condition in which abnormalities in LV function are present during diastole. The gold standard for assessing diastolic function remains the LV pressure-volume relationship, but this requires an invasive approach. Conventional echocardiography together with Doppler measurements of transmitral and pulmonary veins flows, and the TDI mitral annular velocities created the possibility of detection of subclinical deterioration of LV diastolic function [49]. However, these techniques are complex and no single measurement on its own reflects diastolic function. Thus, a comprehensive assessment of a number of variables is required to evaluate diastolic function as correctly as possible [22].

Impaired myocardial relaxation, an early stage of LV diastolic dysfunction, is characterized by decreased transmitral early (E peak), and enhanced atrial (A peak) LV filling as well as less vigorous mitral annulus motion (e') during early diastole. On the other hand, one of the major unmet clinical needs is to improve non-invasive assessment of LV filling pressure, another feature of LV diastolic dysfunction. Some

experts suggested that the Doppler blood flow and the TDI mitral annulus velocities can reflect in some degree elevated LV filling pressure. For instance, combining early transmitral blood flow velocity with early mitral annular velocity (E/e' ratio) might be a tool for estimating LV filling pressure [27, 51]. The majority of patients with elevated LV end-diastolic filling pressure in the presence of normal EF (>50 %), as invasively determined in several previous studies from pressure-volume loops, had an E/e' ratio between 8 and 15 [51]. Ommen et al. [51] suggested that an accurate prediction of LV filling pressures for an individual patient requires further characterization of the intermediate E/e' group, for instance by measurement of left atrial volume and blood flow in the pulmonary vein. Thus, non-invasive echocardiographic imaging criteria for evaluation of LV filling pressure still require further validation and refinement.

Prevalence and Determinants of Diastolic Dysfunction in the Community

Presently, few population studies [1, 29, 35, 58] described the prevalence of preclinical LV diastolic dysfunction, using the new TDI indexes along with classical pulsed wave Doppler velocities. These studies applied a comprehensive Doppler analysis to grade LV diastolic dysfunction in older adults (aged 60–86 years) [1], in subjects aged 45 years or older [58], or in the general population (aged 17–89) [29, 35]. The reported prevalence of diastolic dysfunction in these studies varied from 27.3 to 34.7 %, and was influenced by a number of factors, including the characteristics of the population studied, and the criteria applied to diagnose LV diastolic dysfunction.

Studies in the general population [35, 62] demonstrated that LV relaxation as reflected by the Doppler indexes substantially decreased with age not only in the whole study sample, but also in a selected healthy reference population. Current recommendations propose criteria to diagnose diastolic dysfunction, which are not standardized for age [49]. It is likely that by ignoring age and by applying the same threshold values for the Doppler indexes throughout the age range, one may underestimate the prevalence of subclinical diastolic dysfunction (impaired relaxation), especially in young subjects with risk factors, such as hypertension, obesity and diabetes.

Moreover, the risk of diastolic dysfunction increased significantly and independently with higher body mass index, heart rate, systolic blood pressure, serum fasting insulin and creatinine (Fig. 21.4) [35]. Women were more at risk than men (Fig. 21.4). In a cross-sectional study of participants of the Flemish Study on Environment Genes and Health Outcomes (FLEMENGHO), about 50 % of hypertensive subjects had impairment of LV diastolic function, whereas only

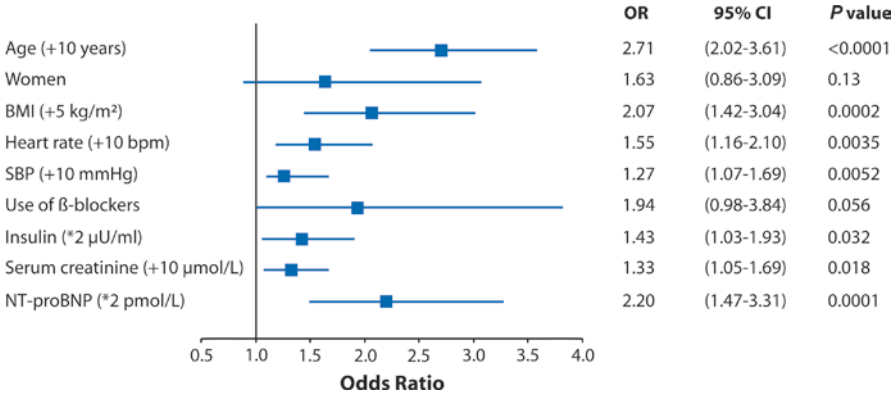

Fig. 21.4 Association between diastolic dysfunction and clinical and biochemical characteristics. *Black squares* and *horizontal lines* represent the odds ratio (OR) and 95 % confidence intervals for the mutually adjusted covariates, identified by stepwise regression (reproduced from Kuznetsova et al. [35] with permission)

12 % of normotensive subjects could be classified as having abnormalities of LV diastolic function [35].

Prognostic Significance of LV Diastolic Dysfunction

Recent clinical and community-based studies explored the prognostic role of classical Doppler and the new TDI-derived indexes. Transmitral E/A ratio and mitral annular early diastolic velocity (e') as well as E/e' ratio had an independent prognostic value in patients with overt HF [2, 19, 50], hypertension [64, 71] or myocardial infarction [24]. For instance, three studies [2, 19, 50] in patients with symptomatic HF demonstrated that high E/e' independently predicted cardiac mortality and HF re-hospitalization. These studies provided thresholds for the E/e' ratio in a range from 12.5 to 15. Moreover, in the ASCOT trial [64] E/e' was the strongest independent predictor of fatal and nonfatal cardiac events in a cohort of 980 high-risk hypertensive patients. The authors demonstrated that in an adjusted model, a 1-unit rise in the E/e' ratio was associated with a 17 % increment in risk of cardiac events ($P = 0.003$). Wang et al. [71] reported that low TDI e' velocity independently predicted cardiac mortality in 174 patients with hypertension.

On the other hand, community-based studies are essential to investigate the natural history of subclinical diastolic LV dysfunction and to determine its prognostic significance. So far, few studies explored the prognostic role of echocardiographic indexes reflecting LV diastolic function. In the Cardiovascular Health Study (mean age, 73 years) [5], the adjusted risk of symptomatic HF was highest at the extremes

of the distribution of the transmitral E/A ratio. The relative risk was 1.88 (95 % CI, 1.33–2.68) for an E/A ratio of less than 0.7 and 3.50 (CI, 1.80–6.80) for an E/A ratio higher than 1.5, compared with intermediate values. Similarly, among 3008 American Indians (mean age, 60 years) enrolled in the Strong Heart Study [9], all-cause and cardiac mortality also had a U-shaped relation with the E/A ratio. In the Copenhagen City Heart Study (n=2064; mean age, 60 years) [47], low systolic (s') and diastolic (e' and a') myocardial velocities derived from color Doppler imaging and averaged from 6 mitral annular sites were associated with increased risk of the combined end point (cardiovascular death or hospitalization due to either HF or myocardial infarction). In 793 FLEMENGHO participants we demonstrated that after adjustment for conventional cardiovascular risk factors, only TDI e' velocity analyzed as continuous variable was a significant predictor of fatal and nonfatal cardiovascular events [38]. We also found that TDI e' velocity improved the discrimination between subjects with and without events as compared to a model including only conventional cardiovascular risk factors [38].

In the FLEMENGHO cohort, we explored the predictive value of LV diastolic dysfunction grades based on conventional Doppler and new TDI velocities (categorical analysis) [38]. In this fully-adjusted analysis, hazard ratio of fatal and non-fatal cardiac events (4.50; $P = 0.002$) were significantly elevated in participants with increased LV filling pressure compared with subjects with normal diastolic function [38]. These findings are in line with report from the Olmsted study [58] which described the predictive significance of preclinical LV diastolic dysfunction, using also the comprehensive approach of assessing LV diastolic function. In multivariable-adjusted analyses while controlling for age, sex, and EF, mild diastolic dysfunction (HR, 8.31; $P < 0.001$) and moderate or severe diastolic dysfunction (HR, 10.17; $P < 0.001$) predicted of all-cause mortality. However, in this study, the authors did not adjust the models for other important cardiovascular risk factors, such as systolic blood pressure, body mass index, serum creatinine and total cholesterol.

LV Systolic Dysfunction

LV systolic function was initially quantified by contrast cineventriculography, using EF (the ratio of stroke volume divided by end-diastolic volume) before the introduction of echocardiography. Traditionally, EF measurement is used to diagnose of HF. The view that systolic function is entirely normal in patients with symptomatic HF and preserved EF has been challenged [13, 61]. The majority of the patients with HFpEF have a history of hypertension. As we already mentioned in the previous section, geometric remodeling of the LV is one of the key futures of hypertensive heart disease. Patients with maladaptive LV remodeling have increased wall thickness and myocardial fibrosis, particularly in the subendocardium [26]. The contraction of the myocardial layer, which is located in the subendocardium, is mainly responsible for systolic longitudinal shortening [23]. Thus, early subclinical changes of systolic function can be more readily detected by analyzing longitudinal

deformation (strain) and in the LV basal segments, because the gradient of average wall stress increases from the apex to the base [14].

LV longitudinal strain might be a sensitive tool in the detection of subclinical systolic dysfunction associated with adverse LV remodeling in hypertensive heart disease and might be important for risk stratification of patients with hypertensive heart disease [65]. Clinical studies in hypertensive patients [6] and in general population [36] showed that the LV longitudinal strain measured at baseline segments using the color Doppler imaging technique correlated inversely with mean arterial pressure and basal wall thickness. Another study in hypertensive patients with symptomatic heart failure [31] showed that the speckle tracking technique, by providing the combined assessment of LV longitudinal, radial and circumferential function, is a promising tool in the diagnosis of systolic LV dysfunction. As recommended in the recently published Task Force [70], LV global longitudinal strain appears to be the most robust and reproducible echocardiographic metric as compared to circumferential and radial strain, and, therefore, it might be easy implemented in clinical practice.

Recent clinical and community-based studies explored the *prognostic role* of the different LV systolic deformation indexes. In the TOPCAT trial [63], global longitudinal strain was a powerful predictor of HF hospitalization, cardiovascular death, or resuscitated cardiac arrest in a cohort of 447 HF patients with preserved EF. The authors demonstrated that in an adjusted model a 1-unit decrease in global longitudinal strain was associated with a 14 % increment in risk of primary outcomes ($P = 0.003$) [63]. In 1768 asymptomatic participants (mean age, 65 years) enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA) [11], LV circumferential strain assessed by MRI provided incremental predictive value for incident HF. In the Framingham Heart Study (n = 2831; mean age, 66 years) [12], LV global longitudinal strain was borderline associated with incident coronary heart events (hazards ratio per standard deviation decrement 1.29; $P = 0.05$), whereas circumferential strain was a significant predictor of incident HF (1.79; $P<0.0001$). Decrements in longitudinal and circumferential strain were significantly related to all-cause mortality in the Framingham study [12]. In the FLEMENGHO study [32], participants belonging to the low sex-specific quartile of the distribution of the LV global longitudinal strain measured at the mid-wall level of myocardial wall (<18.8 % in women and <17.4 % in men) were older, more likely to have risk factor such as hypertension, previous history of cardiac disease, higher body mass index and total cholesterol. While adjusting for these risk factors in multivariable Cox models, only in the lower global longitudinal strain quartile group the risk for cardiovascular and cardiac events was significantly higher than the average population risk (Fig. 21.5). These findings suggest that the LV strain deformation might contribute to risk stratification of patients with hypertension.

Because LV hypertrophy [34] and diastolic function [38] are significant prognostic markers of cardiovascular events in addition to global longitudinal strain, we explored the risk for cardiovascular and cardiac events with increasing number of having any of three LV abnormalities [32]. Figure 21.6 illustrated that incidence rate of the composite cardiovascular events increased with increasing number of the LV

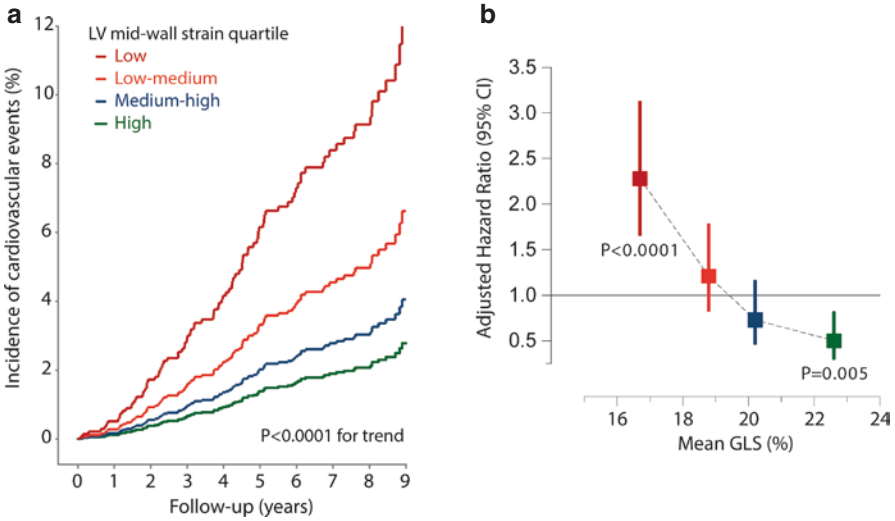

Fig. 21.5 (Panel **a**)*:* Multivariable-adjusted cumulative incidence estimates for fatal and nonfatal cardiovascular events. *P* values are for trend across the four quartiles of LV global longitudinal strain (GLS). Incidence was standardized to the mean values of the covariables (sex, age, body mass index, systolic blood pressure, serum cholesterol, current smoking, antihypertensive drug treatment, diabetes mellitus, and a history of cardiac disease) in the total study population. (Panel **b**): Multivariable-adjusted hazard ratios (95 % CI) for cardiovascular events by sex-specific quartiles of LV mid-wall strain in 791 subjects. The hazard ratios express the risks in quartiles compared with the average risk in the whole cohort and were adjusted as described above (reproduced from Kuznetsova et al. [32] with permission)

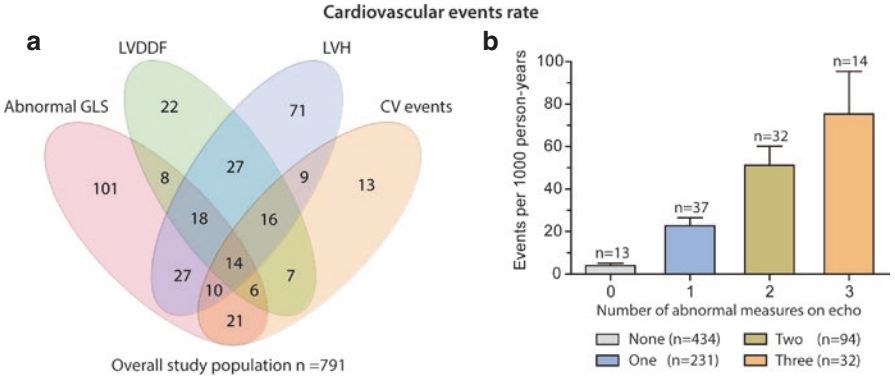

Fig. 21.6 (Panel **a**)*:* Venn diagrams demonstrating the overlap between abnormal global longitudinal strain (GLS), LV diastolic dysfunction (LVDDF), and left ventricular hypertrophy (LVH) in the whole cohort (n = 791). The Venn diagrams also show the incidence of cardiovascular events. (Panel **b**): Crude incidence rates of fatal and nonfatal cardiovascular events by the number of abnormal echocardiographic findings (reproduced from Kuznetsova et al. [32] with permission)

abnormalities, suggesting that all these features (abnormal global longitudinal strain, LV hypertrophy and diastolic function) are useful for risk stratification in the community. Therefore, the comprehensive assessment of cardiac function and structure in which global longitudinal strain plays a major role would be important for risk stratification.

Biomarkers

Contrary to popular belief, HF is difficult to diagnose. There is no system of diagnostic criteria that is considered a golden standard. Biomarkers might be used as a vital tool in differentiating high-risk patients among the rest of the population. According to the recent guidelines testing for BNP or NT-ProBNP is recommended for symptomatic HF diagnostics followed by an ultrasound of the heart if the test is positive [55]. Cardiac specific biomarkers such as BNP/NT-proBNP and high sensitive troponin are the gold standard for the diagnosis of cardiac diseases such including symptomatic HF [30, 60]. BNP is released from cardiomyocytes in response to an increase of atrial or ventricular diastolic stretch to stimulate natriures and vasodilatation and to facilitate LV relaxation and, therefore, might vary with the degree of LV diastolic dysfunction [48]. On the other hand, cardiac troponins release from cardiomyocytes due to normal cardiomyocyte turnover, or due to pathological myocyte necrosis, apoptosis, and increased cardiomyocyte wall permeability [72]. Along these lines, recent studies demonstrated that both high-sensitivity troponin T and NT-proBNP are very useful in identifying subjects with *early stages of cardiac maladaptation* in the community (left atrial enlargement, LV hypertrophy or diastolic dysfunction) [15, 20, 57].

In the future biomarker testing for detection of early stages of HF should go beyond the use of natriuretic peptide or troponin. There is going to be increased adoption of emerging biomarkers pathophysiological relevant to HF mechanisms such as those related to inflammation, metabolic dysregulation, and myocardial fibrosis. Indeed, inflammatory mediators may play a key role in the progression to HF in patients with hypertension [18]. Experimental and clinical studies demonstrated that the overexpression of cytokine cascades contributes to the process of LV remodeling by inducing myocytes hypertrophy, activation of the fetal gene expression program, degradation of the extracellular matrix, as well as progressive myocytes loss through apoptosis [44, 68]. Nowadays, a multiplex panel of 63 cytokines could be used to identify a set of inflammatory biomarkers that are associated with early LV remodeling and dysfunction as captured by echocardiography. Using this panel, we have recently demonstrated that cytokines related to inflammasome activation, mainly interleukin-18 (IL-18), CXCL9 (MIG) and hepatocyte growth factor, were significantly elevated in hypertensive patients with early asymptomatic stages of HF [33]. Previous studies also demonstrated that growth differentiating factor-15, a stress responsive cytokine, is associated with LV hypertrophy and HF [3]. Moreover, in the FLEMENGHO cohort, elevated baseline fasting insulin levels, a

marker of insulin resistance, were strongly associated with worsening of LV diastolic function during follow-up [37].

Cardiomyocyte micro-injury may be also associated with dysregulation of the collagen deposition process. A diffuse deposition of collagen fibers (mainly type I) in the interstitial and perivascular space characterizes the myocardial fibrosis that develops in HF whatever its cause. Indeed, the severity of myocardial collagen deposition is associated with serum levels of the C-terminal propeptide of procollagen type 1 (PICP) in HF patients [42, 56]. Collagen cross-linking determines the stiffness of the collagen type I fiber and its resistance to degradation by matrix metalloproteinase-1 (MMP-1), resulting in diminished cleavage of a small C-terminal telopeptide of the fiber (CITP) [43]. With regard to this, López et al. have recently shown that a low serum CITP/MMP-1 ratio is independently associated with a high myocardial collagen cross-linking and is an independent predictor of hospitalization in symptomatic HF patients of hypertensive etiology [43]. Building on these results, it is likely that patients with hypertension and with evidence of inflammasome activation and disturbances in the quality and quantity of the myocardial collagen matrix will be at increased risk of HF and, therefore, these biomarkers could be useful as an additional tool for earlier recognition and prognosis of HF.

Randomized trials are the gold standard for establishing the effectiveness of biomarker guided strategies. However, currently there are very few of such trials in HF patients. On the other hand, having such trials will increase the degree of evidence for biomarker-guided therapy in the management of hypertensive patients with cardiac maladaptation.

Prevention of HF in Patients with Hypertension

Recent HF recommendations place important emphases to preventive strategies in high-risk group patients (e.g. hypertension and diabetes). This would be important as currently there are no novel therapies in high-risk groups addressing specific mechanisms of adverse cardiac adaptation leading to symptomatic HF.

There is overwhelming evidence that primary prevention of symptomatic (congestive) HF is strongly dependent on blood pressure reduction. Verdecchia et al. undertook a meta-regression analysis to investigate the blood pressure-related and unrelated effects of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), or calcium-channel blockers (CCBs) in the prevention of CHF in patients with hypertension or high cardiovascular risks [69]. For this meta-analysis the authors selected 31 eligible trials, which included 225,764 patients and 6469 incident cases of congestive HF. This analysis provides clear evidence that blood pressure reduction is important for the prevention of congestive HF in patients with hypertension. Overall, the risk of congestive HF decreased by 24 % ($P < 0.001$) for each 5 mmHg reduction in systolic BP. On the other hand, the risk of congestive HF was 19 % less with ACEIs/ARBs than CCBs ($P < 0.001$). Another meta-analysis

which compared effect of beta-blockers with other antihypertensive agents in hypertensive patients, demonstrated that there was similar but no incremental benefit of beta-blockers for the prevention of congestive HF [7]. It has been also shown that the antihypertensive treatment of elderly patients who are 80 years of age or older was beneficial especially in regard to incident cases of congestive HF [8]. Indeed, in this clinical trial, active treatment with the diuretic indapamide, with or without ACEI perindopril, was associated with a 64 % reduction in the rate of congestive HF (95 % CI, 42–78; $P < 0.001$).

Adverse LV remodeling and LV diastolic dysfunction may precede development of HF in hypertensive patients. Blood pressure-lowering therapy also reduces LV mass and improves LV diastolic function which is important for prevention of symptomatic HF [21, 66]. Recent meta-analysis combined the 75 relevant publications involved and 6001 patients suggested that beta-blockers show less regression of LV mass as compared with other antihypertensive drug classes, including ARBs [21]. A clinical trial including 228 patients with uncontrolled hypertension, demonstrated that the degree of improvement in TDI early mitral annular velocity (e') was associated with the degree of systolic blood pressure reduction [66]. Patients who achieved the lowest systolic blood pressure demonstrated the highest TDI e' (better myocardial relaxation), independent of starting blood pressure. These data provide further support that achieving optimal blood pressures may be an effective means to reverse LV hypertrophy and improve LV diastolic function, which are features of cardiac target-organ damage in hypertension.

Conclusion

As shown by epidemiological studies, hypertension is one of the most important modifiable risk factors for the development of symptomatic HF. HF is one of the life-threatening conditions. Despite the high prevalence, HF is underdiagnosed as most patients incorrectly attribute the signs and symptoms to growing older. Currently there is an unmet need to identify easily applicable and cost-effective strategies for the early detection of asymptomatic HF stages in patients at risk. Identifying patients at the early stages of HF would allow the institution of more aggressive risk management strategies and will likely decrease the progression to symptomatic disease.

In this regard, conventional echocardiography combined with TDI and speckle tracking techniques is a sensitive tool to assess early subclinical changes in systolic and diastolic LV function in patients at risk. Impairment of LV diastolic as well as systolic function appears very early in the course of hypertensive heart disease. Because systole and diastole are active and complementary components of the cardiac cycle, they are both contributing to overall myocardial performance. LV systolic and diastolic dysfunction coexists to varying degrees. Community-based studies revealed a higher than hitherto expected prevalence of LV systolic and diastolic dysfunction. The new echocardiographic indexes used to assess LV function

contain additive prognostic information over and beyond traditional cardiovascular risk factors and, therefore, might be used for assessing cardiovascular risk in a population-based cohort. These initial observations should be further validated in regard to the prognosis associated with early symptom-free LV dysfunction in hypertensive heart disease.

Stiffening of the large arteries is a common feature of ageing, leads to isolated systolic hypertension, and is exacerbated by many common disorders, such as hypertension and diabetes mellitus. The heart typically adapts to confront higher and later systolic loads by both hypertrophy and LV stiffening. Increased vascular loading on the heart likely contributes to LV dysfunction. Ventricular-arterial coupling disease has to be further explored in subjects with subclinical LV dysfunction.

A panel of biomarkers pathophysiologically relevant to maladaptive ventricular remodeling and dysfunction is needed for the diagnosis, risk stratification, and follow-up of patients at risk for HF. In the future, HF therapy is going to utilize a combination of multiple markers for risk assessment and diagnosis. Many of these biomarker tests are going to combine into a panel test rather than compete individually. Genetic risk markers and peripheral serum biomarkers need to be incorporated in algorithms for risk stratification of patients with hypertensive heart disease and to identify the optimal timing and type of therapy.

Future Direction Box

- Identifying patients at high risk of developing symptomatic HF and other cardiovascular outcome is an important step to an effective preventive strategy.
- Current "state of the art" management of subclinical LV remodeling and dysfunction relies only on the control of risk factors, such as hypertension, diabetes and kidney dysfunction.
- Existing imaging techniques should be further validated in terms of HF progression or the prediction of cardiovascular morbidity and mortality.
- A validated set of biomarkers pathophysiologically relevant to maladaptive ventricular remodeling and dysfunction is needed for the diagnosis, risk stratification, and follow-up of patients at risk for HF.
- Randomized controlled trials are needed for establishing the effectiveness of biomarker guided strategies.
- HF therapy is going to utilize a combination of imaging markers and biomarkers for risk assessment and diagnosis.

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Chapter 22
Right Heart Failure

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Abbreviations

ARVC	Arrhythmogenic right ventricular cardiomyopathy
BNP	B-type natriuretic peptides
CMR	Cardiac magnetic resonance
CT	Computed tomography
ECG	Electrocardiography
EF	Ejection fraction
HF	Heart failure
HIF1a	Hypoxia-inducible factor 1a
IVS	Interventricular septum
LV	Left ventricle/ventricular
LVAD	Left ventricular assist device
mROS	Mitochondria-derived reactive oxygen species
RA	Right atrium/atrial
RV	Right ventricle/ventricular
RVAD	Right ventricular assist device
2DE	Two-dimensional echocardiography
3DE	Three-dimensional echocardiography

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M. Dorobanțu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_22

Introduction

The International Right Heart Foundation Working Group defines right heart failure (HF) as a clinical progressive syndrome due to an alteration of structure and/or function of the right heart circulatory system that leads to suboptimal delivery of blood flow (high or low) to the pulmonary circulation and/or elevated venous pressures—at rest or with exercise [1]. Right HF represents a disturbance in any component of the right heart circulatory system including systemic veins, right atrium (RA), coronary sinus and cardiac venous drainage, tricuspid valve, right ventricle (RV), pulmonary valve, and pulmonary artery system up to the pulmonary capillaries.

The RV failure is a major component of a pathophysiological entity that can result in right heart circulatory failure [1]. It is typically associated with increased RV afterload and/or preload, consequent dilatation of right heart chambers and tricuspid regurgitation. The prevalence of chronic right HF is difficult to estimate, but its predominant underlying conditions (i.e. left-sided heart failure and pulmonary hypertension) are common [2, 3]. Acute RV failure is observed in 3–9 % of all acute HF admissions, and the in-hospital mortality of these patients ranges from 5 to 17 % [4].

Heterogeneity in RV failure manifestation, underlying factors and etiology necessitates individualized clinical management. Although research in this area is traditionally focused on the failing left ventricle (LV), in recent years RV anatomy, physiology, dysfunction, and management gained more attention. In this chapter we have summarized the state-of-the-art principles pertaining to chronic RV failure, its etiology, clinical presentation, comprehensive assessment, treatment, and prognosis.

Anatomy and Mechanics of the Right Ventricle

The unique RV features allow its efficient functioning as a volume-loaded pump moving the entire systemic venous return into the pulmonary circulation for gas exchange, so that its stroke volume is identical to that of the LV despite the less stroke work. Having thin walls and generating lower ejection fraction (EF) than the LV even under normal conditions, the RV is more compliant and more sensitive to both acute and chronic pressure loading than the LV [5].

The major mechanisms contributing to the pump function in RV are different from those in LV and include (i) inward movement of the RV free wall, (ii) contraction of the longitudinal myocytes drawing the tricuspid annulus toward the apex, (iii) interventricular septum motion and (iv) circumferential shortening of the RV outflow tract. The extent of the contribution of these components varies in different conditions (Fig. 22.1) [6, 7]. The contraction of the RV is sequential, starting with the trabeculated myocardium and ending with the contraction of the RV outflow tract with 25–50 ms delay [8]. In addition to myocardial contractility itself, RV systolic

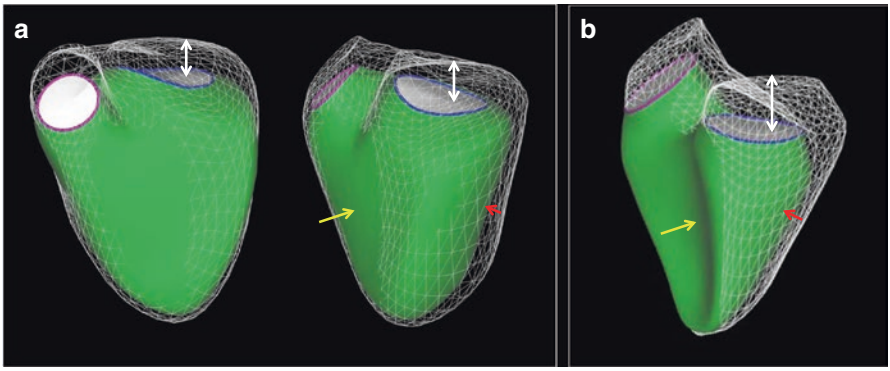


Fig. 22.1 Surface rendered three-dimensional models of the RV obtained by 3D echocardiography (*green models*) combined with the wire-frame (*white cage*) display of the end-diastolic volume in a patient with RV failure due to severe pulmonary hypertension (**a**) and in a normal individual (**b**). Surface rendered dynamic model changes its size and shape throughout the cardiac cycle enabling the visual assessment of the RV dynamics. Figure illustrates the unequal impairment of three main mechanisms of the RV systolic function in pulmonary hypertension patient with significantly decreased longitudinal contraction and amplitude of tricuspid annulus motion towards the apex (*white arrows*), loss of concave shape of the IVS and its motion pattern (*yellow arrows*) and less impaired inward movement of the RV free wall (*red arrows*)

function integrates preload, afterload, pericardial constraint, interaction with the LV, and cardiac rhythm [4]. The preload is related to venous return, which depends on the pressure gradient between the peripheral vasculature (where the mean systemic filling pressure is approximately 7–10 mmHg), and the RA (where the pressure is usually 0 mmHg at rest) [9]. RV afterload is very low under normal conditions, and blood flows from the RV into the pulmonary circulation both during systole and during the early part of diastole almost without isovolumetric relaxation period [9].

Such functional characteristics of the RV allow it to accommodate successfully large variations of blood flow thorough the right chambers, but they make the RV quite sensitive to even small increase in afterload. Under changing loading conditions the RV performance varies in accordance to two basic hemodynamic principles: heterometric adaptation in increasing preload (Starling's law) and homeometric adaptation in increasing afterload (Anrep's law) [10]. Subsequently, RV failure develops when increase in contractility of the RV is insufficient to compensate for the increase in pulmonary vascular resistance, and RV-pulmonary artery uncoupling occurs [11].

Etiology and Pathogenesis of Right Ventricular Failure

In the setting of chronically increased afterload, the RV responds by developing progressive hypertrophy (homeometric adaptation) and increased size (heterometric adaptation), which initially allow it to maintain RV flow output adapted to metabolic demand at rest [12]. As RV dysfunction progresses to overt RV failure, the

significant dilatation and shape alterations of the RV occur and tricuspid regurgitation aggravates, leading to progressive venous congestion and advanced clinical symptoms [4].

The causes of RV failure are numerous, but RV pressure overload, especially due to increased LV filling pressures remains the leading one (Table 22.1). Elevated left-sided filling pressures not only increase pulmonary pressure passively but also lower vascular compliance, thereby augmenting pulsatile RV afterload [13]. Over time, LV failure may also precipitate pulmonary arterial vasoconstriction and/or remodeling, further elevating afterload.

RV contractility itself may be affected in LV heart failure patients. The RV performance significantly depends on the LV functionality through the main anatomical determinants of ventricular interdependence, such as interventricular septum (IVS), pericardium, and the continuity between myocardial fibres of both ventricles. Up to 40 % of the RV contractile force was estimated to originate from the LV contraction [8]. Leftward shift of the IVS at the RV overload may cause compression of the LV, impair its filling, and ultimately lead to reduced contractility [6, 8].

Other factors potentially contributing to the development of RV failure include primary reduction of RV myocardial contractility (due to the same pathological process that affects LV myocardium or different ones), inflammation, oxidative damage, epigenetical determinants, and abnormal cardiac energetics [16].

Severe impairment of RV function after heart transplant or implantation of LV assist devices (LVAD) is relatively new but important etiology of RV failure. RV failure occurs in 2–3 % patients after a heart transplant and up to 44 % patients who received LVAD constituting a major cause of postoperative morbidity and mortality [4, 17, 18]. In heart transplant, the following main mechanisms are responsible for the development of RV failure: (i) in donors, brain death itself can cause a significant decrease in RV function, which was shown to be more prominent than in the LV [19]; (ii) pre-existing pulmonary hypertension in the recipient; and (iii) cardiopulmonary bypass, which may increase pulmonary vascular resistance particularly in patients with abnormal pre-operative values [20, 21].

In patients with LVAD, despite the fact that unloading of the heart with LVAD is supposed to improve the RV function in a long-term, early postimplantation period poses specific risks for the RV. Leftward shift and change in motion of the IVS caused by reduction in LV end-diastolic volume after successful LVAD implantation leads to an increase in RV end-diastolic volume and impairs its contractility while venous return increases and RV has to generate larger output to match the LVAD work. RV function may also be compromised due to progressing tricuspid regurgitation caused by the position of the septum, increased preload or tricuspid annulus distortion in high LVAD flow [18]. In most cases, the RV functionality is restored soon after intervention, but occasionally RV function continues to deteriorate and the clinical syndrome of RV failure develops [21].

Despite recent advances in early diagnosis and prediction of the RV failure development secondary to increased left-sided filling pressures [14], its pathways are yet to be fully understood. Our knowledge is incomplete predominantly due to a lack of experimental studies on modeling the development of right HF, and from

Table 22.1 Etiology of the right ventricular heart failure [14, 15]

Secondary right ventricular failure	
Increased afterload	Pulmonary hypertension, group 1–5: Primary pulmonary arterial hypertension Pulmonary hypertension due to left heart disease Atrial or ventricular disorders Valvular disease Pulmonary hypertension due to lung diseases Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions Pulmonary embolus (septic, amniotic, fat, air, injectate and other) Pulmonary valve stenosis Right ventricular outflow tract obstruction Hypoxic pulmonary vasoconstriction Vaso-occlusive sickle cell crisis Systemic RV Double-chambered RV Tetralogy of Fallot[a] Mechanical ventilation
Increased preload	Tricuspid regurgitation Pulmonary regurgitation Carcinoid syndrome Atrial/Ventricular septal defect Anomalous pulmonary venous return Sinus of Valsalva rupture into the RA Coronary artery fistula to RA or RV
Decreased preload	Tricuspid stenosis Superior vena cava syndrome Hypovolemia Systemic vasodilatory shock (anaphylaxis, extensive burn injury, sepsis and other) Tamponade Constrictive pericarditis
Primary right ventricular failure	
	Arrhythmogenic right ventricular cardiomyopathy Uhl's abnormality Right ventricular infarction Acute right ventricular ischemia in setting of right ventricular pressure overload Isolated RV myocarditis RV non-compaction cardiomyopathy Sarcoidosis Endomyocardial fibrosis Isolated RV Takotsubo cardiomyopathy Sepsis RV dysfunction after exercise Human immunodeficiency virus infection Microvascular diseases and capillary rarefaction

Abbreviations: *RA* right atrium, *RV* right ventricle
[a]Combined load conditions, also in TOF patients post repair

attempts to extrapolate mechanisms of chronic RV failure using results of research originally designed to study acute RV failure [16]. Results of the recent studies on molecular signaling and metabolic changes in the failing RV may contribute to our understanding of the mechanisms of RV failure development.

A metabolic shift from mitochondrial oxidative phosphorylation to cytoplasmic glycolysis has been identified by increased uptake of fluorodeoxyglucose-PET scan seen in patients with RV failure due to pressure overload [22] and by direct measurement of metabolism in an RV working heart model [23]. This metabolic alteration is accompanied by a reduction in fatty acid oxidation, predominantly through the changes in mitochondrial membrane potential. Compensatory mechanisms under ischemic conditions in hypertrophying myocardium, developed through an increase in RV afterload due to an impaired right coronary artery flow in pulmonary arterial hypertension [24], include alterations in production of some metabolites. Specifically, reduced levels of mitochondria-derived reactive oxygen species (mROS) [25], and increase in production of hypoxia-inducible factor 1a (HIF1a) promotoing angiogenesis are considered important factors helping the cells to cope with the stress and counteract the increased oxygen demands of a hypertrophied RV.

In decompensated RV settings, however, situation is quite opposite. Reduced production of HIF1a and a decrease in glucose oxidation accompanied by an increase in mROS levels have a negative impact on angiogenesis, facilitates myocardial apoptosis, and ultimately lead to the exacerbation of ischemia in the RV and development of a syndrome of pronounced RV failure in patients with pulmonary hypertension [14, 25]. It is therefore apparent that the glycolytic shift occuring in the RV is a maladaptive response and can ultimately lead to the RV decompensation.

Hemodynamic Consequences of the Right Heart Failure

The main hemodynamic consequences of the RV failure are venous congestion and low cardiac output. Factors, contributing to hemodynamic impairment in patients with RV failure, include RV systolic and diastolic dysfunction, tricuspid regurgitation, ventricular interdependence, brady- or tachyarrhythmias. Hypotension may further aggravate RV dysfunction by leading to RV ischemia.

RV failure develops in phases. Initially RV dysfunction leads to impaired RV filling and increased RV diastolic pressure and RA pressure. As RV dysfunction progresses to overt failure, the RV becomes more spherical and tricuspid regurgitation aggravates. This is accompanied by an increasing RV volume overload and together with RV systolic failure leads to a progressive venous congestion and decrease cardiac output [15] potentially resulting in congestive hepatopathy, as well as cardiac cirrhosis in more advanced cases.

Ventricular interdependence contributes significantly to the low cardiac output state causing a leftward shift of the IVS and changing LV geometry. The adverse effect may be even more prominent is acute settings, exacerbated by

increased constraining effect of the pericardium, which in turn reduces the LV distensibility and its preload ultimately leading to drop in stroke volume [4]. Additionally, both RV diastolic dysfunction and tricuspid regurgitation may accentuate right-to-left shunting through a patent foramen ovale and lead to hypoxemia.

Importantly, in some patients with advanced stages of the RV failure, pulmonary arterial pressure may go down as a consequence of significant tricuspid regurgitation, fluid retention, low cardiac output, and/or functioning intracardiac shunt. Therefore, pulmonary pressure values in such patients should be always interpreted with caution taking into account the degree of RV failure and all possible confounders [15].

Stages of RV Failure

Haddad et al. described the development of RV failure as a chain of consecutive stages including progression from asymptomatic RV dysfunction to symptomatic RV failure and finally to refractory RV failure (Table 22.2) [15]. It's worth noting that patients with refractory RV failure associated with pulmonary arterial hypertension may show a significant improvement in RV function after lung transplantation [15]. This finding highlights the potential of RV recovery and the marked load dependence of commonly used indexes of RV contractility.

Clinical Presentation and Assessment of the Right Heart Failure

Clinical Symptoms and Signs

The clinical presentation of RV dysfunction includes signs of progressive venous congestion and symptoms related to the main cause of the right HF, such as chest pain in myocardial infarction, dyspnea in pulmonary hypertension, ventricular arrhythmias or sudden cardiac death in arrhythmogenic right ventricular cardiomyopathy (ARVC). Early symptoms are typically induced by exertion and include fatigue, shortness of breath, palpitations, weakness, and dizziness. Symptoms at rest appear in more advanced stages. Peripheral oedema and cool extremities, progressive abdominal distension, as well as clinical signs of decrease cardiac output will develop with progressing RV failure [4] (Table 22.2). The clinical presentation of RV failure may also vary according to the particular cause of RV dysfunction, as well as other concomitant diseases.

The typical physical signs of right HF include an accentuated pulmonary component of the second heart sound, an RV third heart sound, a pansystolic murmur of tricuspid regurgitation, a diastolic murmur of pulmonary regurgita-

Table 22.2 Stages and clinical symptoms of chronic right ventricular heart failure [15]

Stage	Definition	Patients' categories	Clinical symptoms
A	At risk of RV failure, but without structural right heart disorders and symptoms of heart failure	LV or valvular heart disease (at compensated stage) Pulmonary hypertension (at early well compensated stage) Family history of ARVC Atherosclerosis Use of cardiotoxins or stimulants Chest radiation therapy	Asymptomatic or symptoms related to underlying pathology
B	RV dysfunction, but without symptoms of RV failure	LV failure or valvular heart disease Pulmonary hypertension ARVC Congenital heart disease (selected forms) History of RV myocardial infarction Tricuspid or pulmonary valve disease (at compensated stage)	No symptoms of right heart failure at rest Symptoms related to underlying pathology
C	RV failure with current or prior symptoms of heart failure at rest	All causes of RV failure (Table 22.1)	Fluid retention Fatigue Reduced exercise tolerance Palpitations Symptoms related to underlying pathology
D	Refractory RV failure	All causes of RV failure (Table 22.1)	Marked symptoms at rest despite maximal medical, interventional or surgical treatment Low cardiac output Refractory life threatening arrhythmias

Abbreviations: *ARVC* arrhythmogenic right ventricular cardiomyopathy, *LV* left ventricle, *RV* right ventricle

tion, signs of concomitant LV dysfunction, and paradoxical pulse. Elevated jugular venous pressure, peripheral oedema, congestive hepato/splenomegaly, pericardial effusion and ascites are commonly seen in patients with advanced disease; anasarca is usually associated with an acute decompensation of chronic RV failure [4]. Telangiectasia, and palmar erythema suggest significant liver involvement and development of congestive hepatopathy or cardiac cirrhosis. Protein-losing enteropathy may lead to profound hypoproteinemia, malnutrition, and immunological deficiencies [15]. Careful clinical examination may help to identify an underlying cause of RV failure.

Electrocardiography

An electrocardiogram (ECG) may provide an additional evidence of RV remodeling and help to detect an underlying cardiac pathology. However, it is important to note that a normal ECG does not exclude the diagnosis of right HF and pathological ECG is more likely to be seen at developed stages of RV dysfunction. ECG abnormalities reflecting the right heart remodeling may include right axis deviation, RV and RA hypertrophy, (in)complete right bundle branch block, and QTc prolongation (Table 22.3) [2]. Supraventricular arrhythmias (atrial flutter, atrial fibrillation, paroxysmal atrial tachycardia) may occur in advanced disease, especially in pulmonary hypertension patients; ventricular arrhythmias are common in some specific forms of RV failure (i.e. ARVC or sarcoidosis).

Underlying causes of the RV failure potentially detectable using ECG include RV myocardial infarction, ARVC, left heart disease, and some other conditions. Specific electrocardiographic characteristics of these pathologies are summarised in Table 22.3.

Laboratory Markers

Currently there are no validated RV failure-specific biomarkers [3]. Consequently, the clinical utility of B-type natriuretic peptides (BNP) and cardiac troponin testing depends on the clinical context in which RV failure presents. In patients with chronic thromboembolic pulmonary hypertension, BNP levels tend to correlate with adverse RV remodeling and can be useful in identification of RV dysfunction [30]. Additionally, significantly elevated levels of BNP in patients with LV systolic dysfunction could be indicative of high risk of RV failure [31], and associated with increased mortality rates in patients with pulmonary arterial hypertension [32]. Novel biomarkers for detecting RV failure are under evaluation [33, 34].

Echocardiography

While the LV morphology and contractility are commonly characterized in the echocardiographic reports in the most comprehensive manner, RV function is often missing or reported as “normal” or “depressed” at best. We agree with the Authors argue that its evaluation should become routine [21]. Standardized echocardiographic views, which should be obtained for a comprehensive assessment of the RV, are described in Chap. 4 (Fig. 4.1). An echocardiographic evaluation of the RV in heart failure patients should include assessment of its shape, position and motion of the IVS, estimation of the RV size, functions and mechanics, and assessment of wall motion abnormalities.

Table 22.3 Typical ECG findings in patients with right heart failure

Findings	ECG Criteria
RV hypertrophy	Predominantly tall R waves (as part of Rs, R, or Qr complexes) in Right precordial leads (suggesting pressure overload) Or Incomplete RBBB pattern (suggesting volume overload); Right axis deviation; ST depression and T-wave inversion in right precordial leads; Deep S waves in the precordial leads (in patients with chronic nonobstructive lung disease) [26]
RA hypertrophy	Tall upright P wave in lead II (>2.5 mm [0.25 mV]) often with a peaked or pointed appearance (p pulmonale); Prominent initial positivity of the P wave in V1 or V2 (1.5 mm [0.15 mV] or more) [26]
Complete RBBB	QRS duration ≥ 120 ms; rsr', rsR', or rSR' in leads V1 or V2; S wave of greater duration than R wave or > 40 ms in leads I and V6; Normal R peak time in leads V5 and V6 but >50 ms in lead V1 [27]
Incomplete RBBB	QRS duration between 110 and 120 ms; Other criteria are the same as for complete RBBB [27]
RV myocardial infarction	Q waves in right-sided chest leads V3R, V4R, And/or ST elevation (in case of acute myocardial infarction) [28]
ARVC	Repolarization abnormalities: Major Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 years of age (in the absence of complete RBBB); Minor Inverted T waves in leads V1 and V2 in individuals >14 years of age (in the absence of complete RBBB) or in V4, V5, or V6; Inverted T waves in leads V1, V2, V3, nad V4 in individuals >14 years of age in the presence of complete RBBB Depolarization/conduction abnormalities: Major Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3). Arrhythmias: Major Nonsustained or sustained VT of LBBB morphology with superior axis; Minor Nonsustained or sustained VT of RV outflow tract configuration, LBBB morphology with inferior axis or with unknown axis >500 premature ventricular contractions per 24 h on Holter monitoring [29]

Abbreviations: *ARVC* arrhythmogenic right ventricular cardiomyopathy, *ECG* electrocardiography, *LBBB* left bundle branch block, *RA* right atrium, *RBBB* right bundle branch block, *RV* right ventricle, *VT* ventricular tachycardia

RV Shape

The complex shape of the RV cannot be simplified to a spherical or bullet-like morphology. Its assessment is challenging even in normal individuals and for a long time was limited to calculation of the eccentricity index and evaluation of septal

flattening by two-dimensional echocardiography (2DE) using the parasternal short-axis and the right ventricle focused apical 4-chamber views. Under altered loading conditions, the normal crescent shape of RV changes due to flattening of the IVS (Fig. 22.2). LV takes the shape of the letter 'D', which may be a sign of the RV volume overload if the flattening of the septum is present mainly during diastole, or RV pressure overload if the septum flattening persists during systole. At the

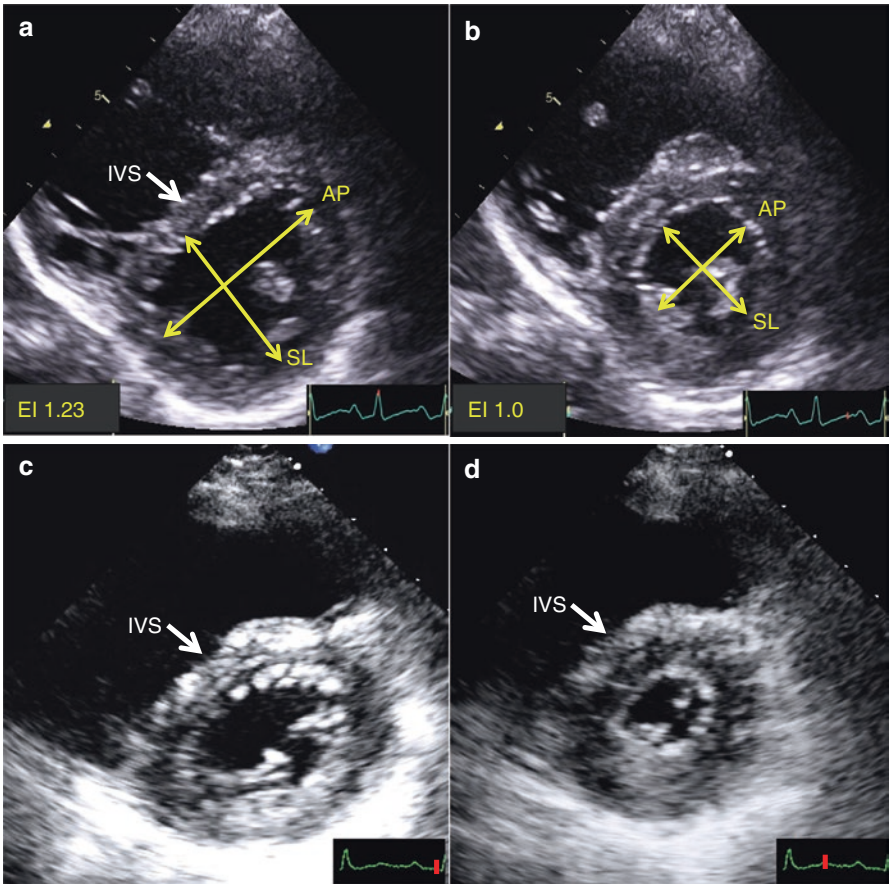


Fig. 22.2 Assessment of the right ventricular shape and interventricular septum motion in parasternal short-axis view at the level of papillary muscles. Stop-frame 2DE images from a patient with an isolated RV volume overload due to severe tricuspid regurgitation (**a**, **b**) and from a patient with pressure overload due to severe pulmonary arterial hypertension (**c**, **d**). In patients with RV volume overload the leftward septal shift and flattening are observed during diastole with LV taking the shape of the letter 'D' (**a**), whereas a circular profile of LV cavity is maintained during systole (**b**). In patients with RV pressure overload the septal flattening and deformation of the LV are maintained also during systole (**c**, **d**). Eccentricity index allows to quantitate the LV shape changes by dividing LV antero-posterior diameter by septo-lateral diameter both during systole and diastole. An eccentricity index value greater than 1 at end-diastole is a strong indicator of RV volume overload (**a**). At end-systole or during the whole cardiac cycle it suggests the RV pressure overload. Abbreviations: *AP* antero-posterior diameter, *EI* eccentricity index, *IVS* interventricular septum, *SL* septo-lateral diameter

advanced stage of the disease, an altered shape of the RV may be maintained during the entire cardiac cycle. Eccentricity index had been suggested for quantitative assessment of changes in LV shape (Fig. 22.2). Normal individuals have a value of 1 both during systole and diastole indicative of the circular shape of the LV in transverse sections. Eccentricity index higher than 1 at end diastole is highly suggestive for RV volume overload and at end systole or during the whole cardiac cycle – for RV pressure overload [35].

Despite the fact, that the RV wall stress was shown to be a major factor in the RV failure development [36], for a long time there was no evidence supporting poor outcomes or increased mortality in patients with adverse RV shape changes independent on those predicted by size and functional parameters. The methodology which allows to assess three-dimensional echocardiography (3DE) -derived global and regional RV shape indices based on analysis of the RV curvature was recently developed and tested in normal subjects and in patients with pulmonary arterial hypertension (Fig. 22.3) [37]. It was demonstrated that in patients with pressure overload the RV exhibits differences in regional curvature with the curvature of the RV inflow tract being a more robust predictor of death than RV EF, RV volumes, or other regional curvature indices [37]. This promising methodology could potentially be used for a more effective assessment of the RV remodeling in heart failure patients, and might be useful as a biomarker of a treatment response.

RV Size

RV dilatation is a typical finding in HF patients and develops both in volume and pressure overload. Visual assessment of the RV size may be performed from the apical 4-chamber view using an approximation that the area of normal RV should not exceed two-thirds of the LV (Fig. 22.4). It is worth noting that this assumption may be misleading in patients with the LV dilatation.

Quantitative assessment of RV size by 2DE relies on several dimensions obtained at end diastole from different echocardiographic views (Table 22.4). Current guidelines show how to perform the recommended RV linear and area measurements with RV outflow tract distal diameter being the most reproducible [38, 39]. Despite being easily obtainable and fast, due to the crescentic shape of the RV, diameters may vary significantly with minor rotation or tilting the transducer and should be performed only in standard recommended views [38, 40]. Additionally, the lack of precise anatomic landmarks to define the RV standard views may lead to an under- or overestimation of RV size. Care should be taken to obtain the true RV focused 4-chamber image with the LV apex at the centre of the scanning sector, while displaying the largest basal RV diameter and thus avoiding foreshortening. The accuracy of RV measurements may be compromised also when the RV free wall is not well defined. Adjusting the gain settings and compression is essential to achieve a good image quality. 2DE assessment of the RV appears to be even less accurate in patients with dilated RV, which is common in RV heart failure [41]. Abnormality thresholds for RV 2D linear and area dimensions are listed in Table 22.4.

Some RV dimensions are of special importance in particular conditions, i.e. the proximal RV outflow tract diameter is useful in the diagnosis of arrhythmogenic right ventricular cardiomyopathy, and the distal RV outflow tract is required for the calculation of Qp/Qs in the presence of intracardiac shunts [39].

In addition to linear and area measurements, RV wall thickness is another parameter routinely measured by 2DE when assessing the RV geometry, especially in patients with RV pressure overload. It is recommended to use the zoomed image of

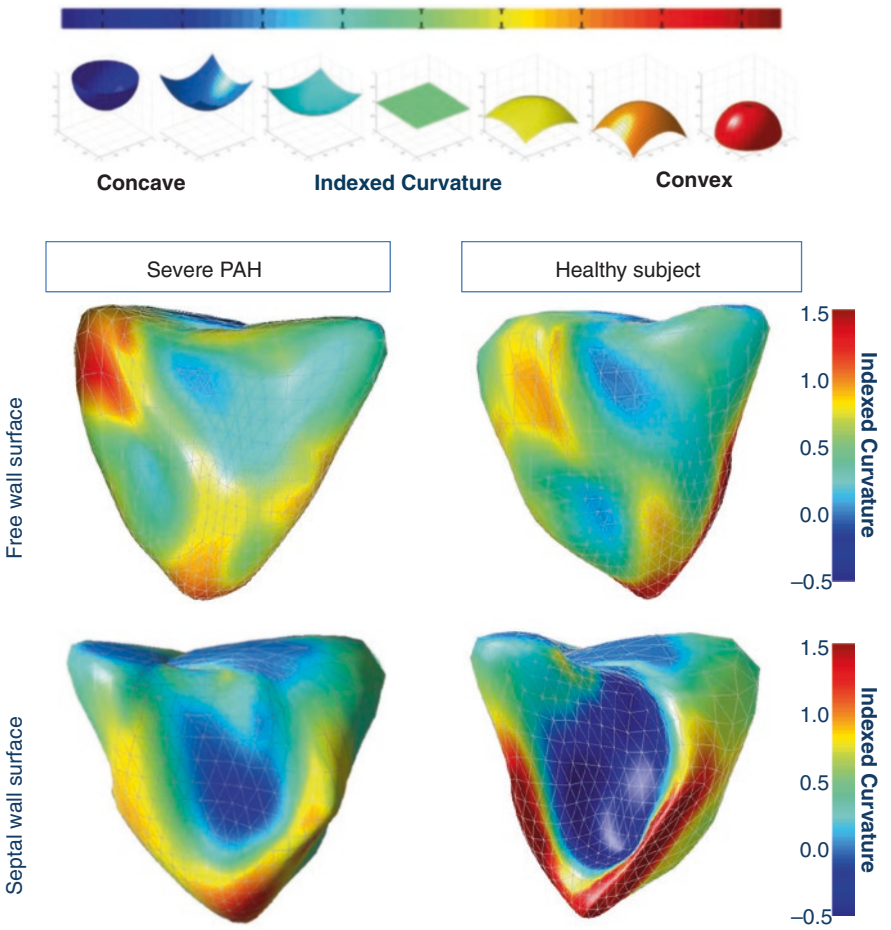


Fig. 22.3 Colour-coded map of mean 3D curvature values obtained in a patient with pulmonary arterial hypertension (*left panel*) and a normal subject (*right panel*). The 3D endocardial surface was color-coded to depict local 3D curvature values: *blue* denotes more concave surface and *red* denotes more convex. In pulmonary hypertension patient, the apex is more round and the septum is less concave (Courtesy of Prof. R. Lang and Dr. K. Addettia, Cardiac imaging laboratory University of Chicago, IL, USA). Abbreviations: *PAH* pulmonary arterial hypertension

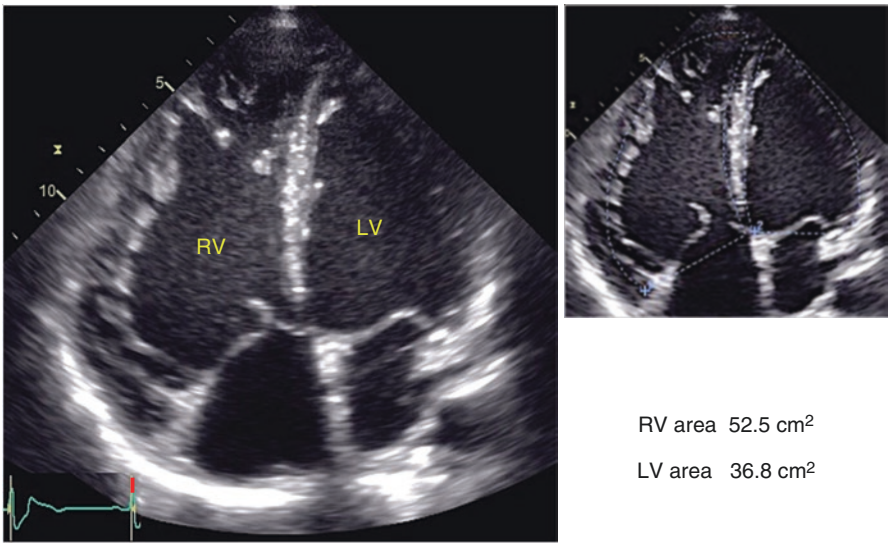


Fig. 22.4 Apical 4-chamber view of the patient with surgically corrected tetralogy of Fallot demonstrating significant dilatation of the RV which end-diastolic area exceeds the area of non-dilated LV

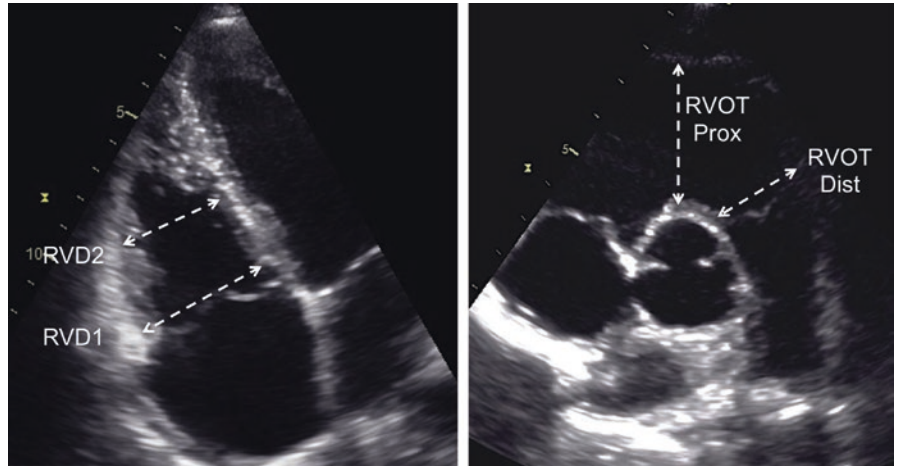
the RV free wall from subcostal 4-chamber view for measurements of its thickness at end diastole in the subtricuspidal region, because of its higher reproducibility (Table 22.4) [39].

Unlike 2DE, 3DE allows to obtain full volume datasets derived from either a single beat capture or consecutive multibeat volumes stitched together with higher temporal and spatial resolution (Fig. 4.9). 3DE measurements are closely correlated (but slightly underestimate) with RV volumes measured by cardiac magnetic resonance (CMR) both in children and adults [42–45], and by volumetric thermodilution during cardiac catheterization [46]. Normative data for 3DE RV volumes including age-, body size-, and sex-specific reference values based on large cohort studies of healthy volunteers has recently become available [47, 48]. Recent chamber quantification guidelines for the first time included recommendations for 3D analysis of the RV specifying RV end-diastolic volume of 87 ml/m^2 in men and 74 ml/m^2 in women, and RV end-systolic volume of 44 ml/m^2 in men and 36 ml/m^2 in women as the upper limits of normal (Table 22.4) [38].

RV Function and Mechanics

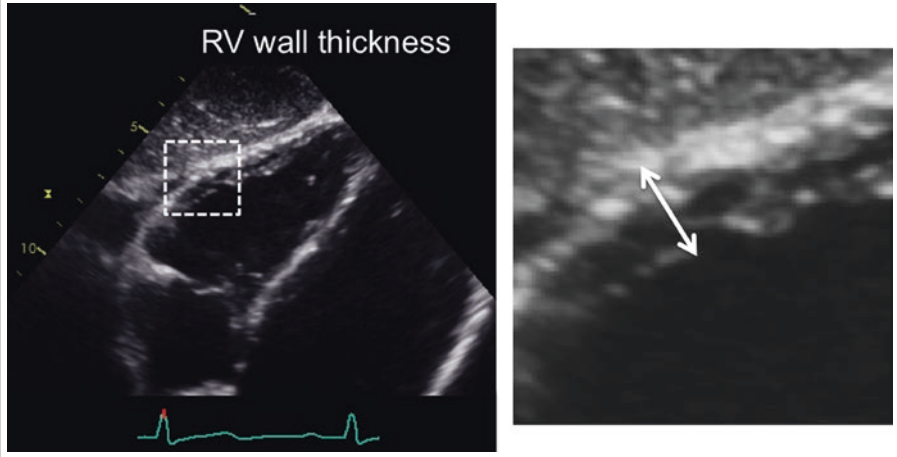
Nowadays, with an implementation of modern echocardiographic modalities including 3DE techniques and 2D speckle tracking echocardiography, assessment of RV function is shifting from predominantly qualitative evaluation to a quantitative one using more accurate parameters not relying on geometrical assumptions

Table 22.4 Normal echocardiographic values for the right ventricular size [38]

Dimension	Normal values (mean ± SD)	Abnormality threshold	Echocardiographic imaging
RV basal diameter (mm)	33 ± 4	>41	
RV mid diameter (mm)	27 ± 4	>35	
RVOT proximal diameter (mm)	28 ± 3.5	>35	
RVOT distal diameter (mm)	22 ± 2.5	>27	

(continued)

Table 22.4 (continued)

Dimension	Normal values (mean ± SD)	Abnormality threshold	Echocardiographic imaging
RV wall thickness (mm)	3 ± 1	>5	
RV EDA (cm^2)			

Men Women	17 ± 3.5 14 ± 3	>24 >20
RV EDA indexed to BSA (cm^2/m^2)		
Men Women	8.8 ± 1.9 8.0 ± 1.75	>12.6 >11.5
RV ESA (cm^2)		
Men Women	9 ± 3 7 ± 2	>15 >11
RV ESA indexed to BSA (cm^2/m^2)		
Men Women	4.7 ± 1.35 4.0 ± 1.2	>7.4 >6.4

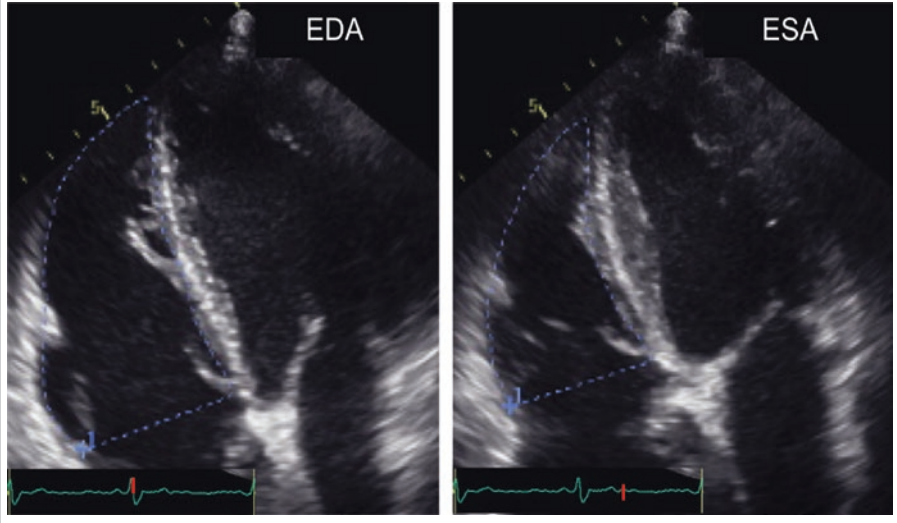


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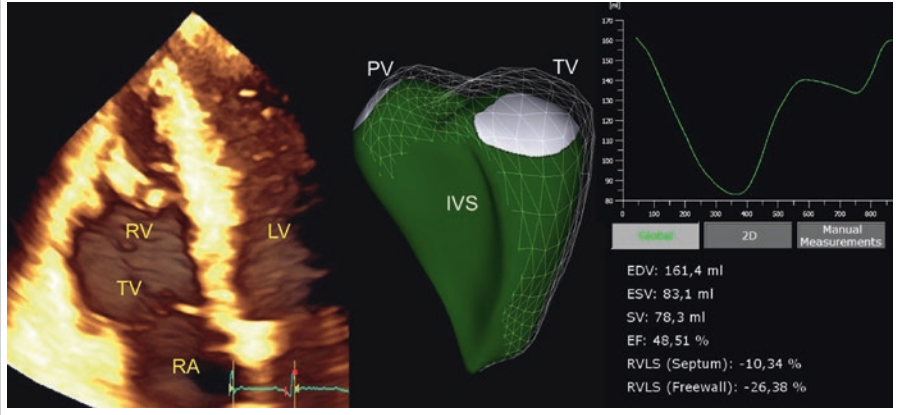
Table 22.4 (continued)

Dimension	Normal values (mean ± SD)	Abnormality threshold	Echocardiographic imaging
EDVi (ml/m^2)			
Men Women	61 ± 13 53 ± 10.5	>87 >74	
ESVi (ml/m^2)			
Men Women	27 ± 8.5 22 ± 7	>44 >36	

Abbreviations: *BSA* body surface area, *EDA* end-diastolic area, *EDVi* index of end-diastolic volume, *ESA* end-systolic area, *ESVi* index of end-systolic volume, *IVS* interventricular septum, *LV* left ventricle, *PLAX* parasternal long-axis view, *PV* pulmonary valve, *RA* right atrium, *RV* right ventricle, *RVD1* RV basal diameter, *RVD2* RV mid diameter, *RVOT* RV outflow tract, *SD* standard deviation, *TV* tricuspid valve

about RV shape. Contemporary approach to the evaluation of RV global and regional function as well as myocardial mechanics is discussed in the Chap. 4.

Pulmonary Artery Pressure

The evaluation of the pulmonary artery pressure is an essential step in echocardiographic assessment of patients with RV failure. Prognostic value of pulmonary hypertension in HF was established in high quality studies [49, 50]; the survival and disease progression in these patients strongly correlate with the ability of the RV to adapt to the chronically elevated pulmonary pressure [51]. There are several methods of echocardiographic assessment of pulmonary pressure (Table 22.5, Fig. 22.5) with the estimation of pulmonary arterial systolic pressure by peak velocity of tricuspid regurgitant jet being the most common and feasible (Fig. 22.5a). However, advanced stages of RV failure including severe tricuspid regurgitation often preclude an accurate assessment of systolic pulmonary pressure due to an early equalization of RV and RA pressures resulting in significant underestimation the RV-RA gradient using simplified Bernoulli equation [39, 52]. Therefore, echocardiographic assessment of pulmonary pressure should be always performed using several techniques and taking into account all possible confounders.

Other Imaging Modalities

Prior to introduction of 3DE, CMR and computed tomography (CT) have been the only imaging modalities capable of providing accurate diagnostic information on the RV size and function and especially morphological evaluation of the RV outflow tract. Despite several important limitations, CMR is still considered a gold-standard for the assessment of RV volumes and EF. Providing standardized methodologies are strictly adhered to, CMR measurements show high reproducibility with interobserver variability <7 % for the end-diastolic volume, <14 % for the end-systolic volume, and <20 % for RV mass [53]. CMR provides unique opportunity for measuring RV mass. It has been validated against explanted hearts both in normal animals and in experimental animals with myocardial infarction and pulmonary hypertension, demonstrating a strong correlation between RV mass obtained from CMR and from autopsy [54]. Prognostic importance of CMR-derived information was demonstrated in patients with RV failure and pulmonary hypertension both at baseline and at follow-up and can be used for monitoring of the treatment success [55–57]. CMR is also the first choice imaging modality for tissue characterization of the RV providing accurate information about myocardial fibrosis, inflammation, or intramyocardial fat accumulation (Fig. 22.6). In patients with congenital heart disease, the presence of RV myocardial scar was shown to be a risk factor for adverse events during follow-up [58]. The extent of fibrosis correlated with regional and global RV dysfunction in patients with

Table 22.5 Main echocardiographic parameters of pulmonary hemodynamic [2, 39]

Parameter	Normal range	Main principles	Pitfalls and limitations
Systolic PAP	≤35 mm Hg (or V_{TR} ≤2.8 m/s)	sPAP = $4(V_{maxTR})^2$ + RA pressure	Not applicable in patients with RVOT obstruction, pulmonary valve stenosis or prosthetic valve, severe TR Requires high quality spectral Doppler signal of TR
Mean PAP	<25 mm Hg	1. mPAP = $4(V_{earlyPR})^2$ + RA pressure; 2. mPAP = 79 − (0.45 × AT); 3. mPAP = 90 − (0.62 × AT), for patients with AT<120 ms; 4. mPAP = 0.61 × sPAP + 2; 5. mPAP = = 1/3(sPAP) + 2/3(dPAP)	Measurements of PR velocity requires high quality spectral Doppler signal of PR AT is dependent on heart rate and cardiac output AT is dependent on position of Doppler sample volume
Diastolic PAP	–	dPAP = $4(V_{edPR})^2$ + RA pressure	Less correlates with invasively measured pressure Less established diagnostic and prognostic value Requires high quality spectral Doppler signal of TR
Mean RA pressure	<5 mm Hg	1. RA pressure 3 mm Hg (range, 0–5 mm Hg) if IVC diameter <2.1 cm and respiratory collapse >50 %; 2. RA pressure 15 mm Hg (range, 10–20 mm Hg) if IVC diameter >2.1 cm and respiratory collapse <50 %; 3. RA pressure 8 mm Hg (range, 5–10 mm Hg): other combinations of IVC diameter and collapsibility index.	IVC may be dilated independently of pulmonary artery pressure in specific groups of individuals (i.e. young individuals, athletes, mechanically ventilated patients; patients with narrowing of IVC-RA junction) Requires patients' collaboration The estimation of RA pressure by IVC size and dynamics is encouraged for the estimation of sPAP on the basis of the tricuspid regurgitant jet velocity, rather than assuming a constant RA pressure for all patients
Pulmonary vascular resistance	<1.5 WU	PVR = (V_{TR}/VTI $_{RVOT}$) × 10 + 0.16	Requires high quality PW Doppler signal of RVOT flow and CW Doppler signal of TR Not reliable in patients with very high PVR (>8 WU, as determined by invasive hemodynamic measurements)

Abbreviations: *AT* pulmonary artery flow acceleration time, *dPAP* diastolic pulmonary artery pressure, *IVC* inferior vena cava, *mPAP* mean pulmonary artery pressure, *PAP* pulmonary artery pressure, *PR* pulmonary regurgitation, *PVR* pulmonary vascular resistance, *RA* right atrium, *RV* right ventricle, *RVOT* RV outflow tract, *sPAP* systolic pulmonary artery pressure, *TR* tricuspid regurgitation, $V_{earlyPR}$ the early velocity of the PR jet, V_{edPR} end-diastolic PR velocity, V_{maxTR} peak velocity of the tricuspid regurgitant jet, VTI_{RVOT} time velocity integral of RVOT flow

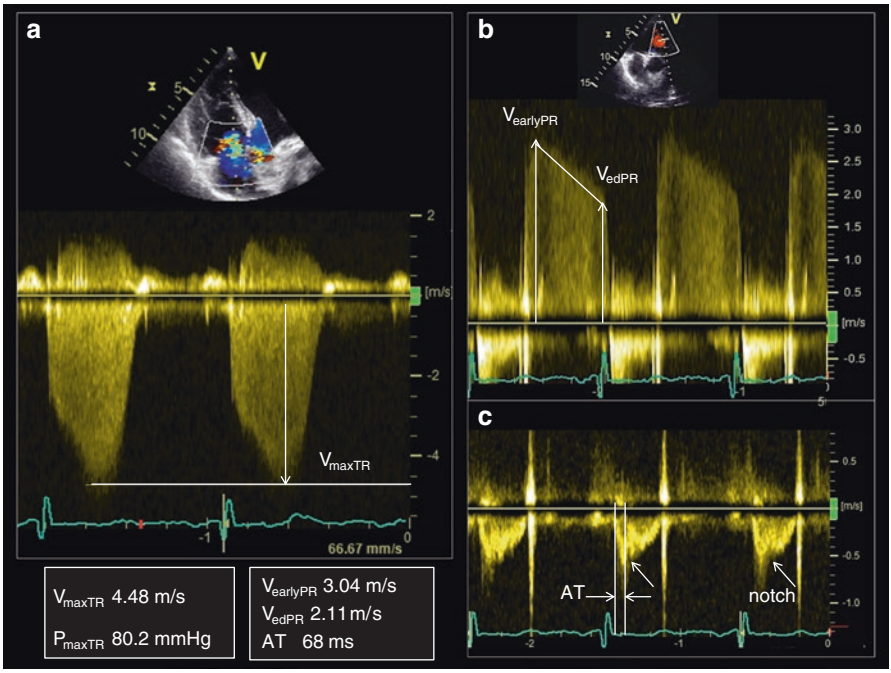


Fig. 22.5 The principal methods of echocardiographic assessment of pulmonary artery pressure in a patient with severe pulmonary hypertension. Panel (**a**) shows the estimation of pulmonary arterial systolic pressure by peak systolic velocity of tricuspid regurgitant jet (sPAP calculated using a formula $4(V_{maxTR})^2$ + RA pressure was 83.3 mmHg by). Panel (**b**) demonstrates the measurements of early proto-diastolic and end-diastolic velocity of pulmonary valve regurgitation necessary for calculation of mean and diastolic pulmonary artery pressure (mPAP calculated using a formula $4(V_{earlyPR})^2$ + RA pressure was 40.0 mmHg; dPAP calculated using a formula $4(V_{edPR})^2$ + RA pressure was 20.8 mmHg). Panel (**c**) shows typical shape of RVOT flow in pulmonary hypertension by pulse wave Doppler with short acceleration time and a notching (*arrow*) of the curve caused by deceleration of flow in late or in mid-systole due to early wave reflexion on proximal obstruction and/or pulmonary arterial stiffening. Acceleration time is used for estimation of mean pulmonary artery pressure (mPAP calculated using a formula $90 - (0.62 \times AT)$ was 47.7 mmHg). Abbreviations: *AT* pulmonary artery flow acceleration time; *dPAP* diastolic pulmonary artery pressure, *mPAP* mean pulmonary artery pressure, *RA* right atrium, *RV* right ventricle, *RVOT* RV outflow tract, *sPAP* systolic pulmonary artery pressure, $V_{earlyPR}$ the early velocity of the PR jet, V_{edPR} end-diastolic PR velocity, V_{maxTR} peak velocity of the tricuspid regurgitant jet

repaired tetralogy of Fallot and was associated with an increased risk of ventricular arrhythmias [59].

Due to the significant radiation exposure, lower temporal resolution and use of nephrotoxic contrast agents, multidetector cardiac CT cannot be recommended for routine evaluation of RV morphology and function. However, it provides an accurate and reproducible assessment of the RV volumes and EF (described in Chap. 4) and can be a reliable alternative in patients not suitable for echocardiography or CMR. Additionally, due to its high spatial resolution, CT gives precise diagnostic information on the systemic veins and pulmonary arteries, and it is

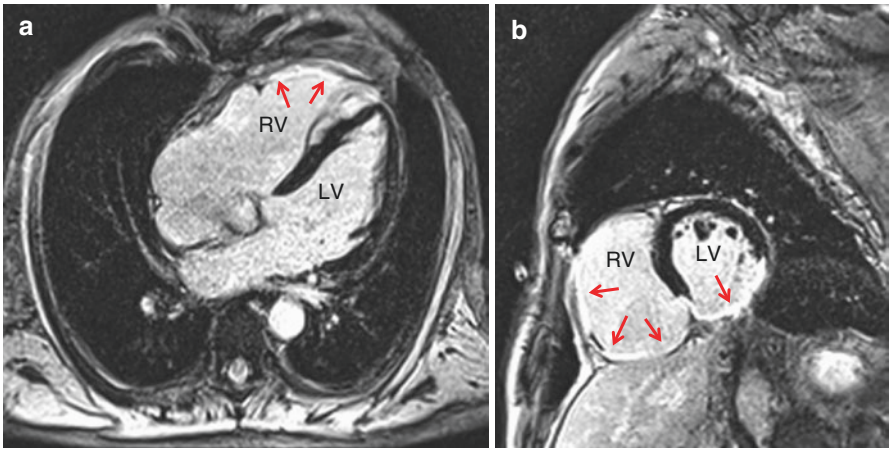


Fig. 22.6 Cardiac magnetic resonance showing the extensive regions of late gadolinium enhancement in the RV free wall and inferior wall of the LV (*red arrows*) in apical four-chamber view (**a**) and short axis view (**b**). Late enhancement indicates the fibrosis of the RV and LV myocardium in a patient with LV inferior and RV myocardial infarction and severe RV failure. Abbreviations: *LV* left ventricular, *RV* right ventricle

usually indicated in patients with RV failure linked to pulmonary (vascular) disorders [2, 60, 61].

Invasive Hemodynamic Assessment

Invasive haemodynamic assessment is used in unexplained diagnostic or therapy-resistant cases and allows to obtain continuous information about right and left atrial pressure, cardiac output, and pulmonary vascular resistance. Right heart catheterisation is recommended to confirm the diagnosis of pulmonary hypertension, it can be also used to assess the severity of hemodynamic impairment and to undertake vasoreactivity testing of the pulmonary circulation in selected patients [2]. However, the procedure only allows for an indirect description of RV function with RA pressure used to estimate RV end-diastolic volume (as a marker of preload), pulmonary arterial pressure or pulmonary vascular resistance (as a marker of afterload) and stroke volume (as a marker of RV contractility) [12].

Evaluation of the adequacy of RV-arterial coupling is another implication of the right heart catheterization. The end-systolic to arterial elastances ratio derived from synchronized volume and pressure measurements is a promising parameter of RV function and its (dys-)ability to adapt to increased afterload. Pressure measurements can be obtained during a right heart catheterization and volume measurements by integration of Doppler pulmonary flow velocity, CMR or 3DE [12, 14]. Measures of coupling are particularly attractive because they may help to identify subclinical

right HF. Thus, impaired RV–pulmonary artery coupling in systemic sclerosis-associated pulmonary hypertension compared with idiopathic pulmonary arterial hypertension was recently demonstrated using this technique when other imaging and hemodynamic variables failed to discriminate between these two groups [62]. However an invasive approach and practical difficulties of this method prevent it from being widely integrated into routine assessment.

Despite the fact, that reported procedure-related morbidity (1.1 %) and mortality (0.055 %) rates appeared to be low when performed at specialized centres [63], cardiac catheterization should only be administered upon completion of other investigations. It can help to address specific queries resulting from other investigations if necessary and avoid an invasive procedure where an alternative diagnosis has been established using non-invasive techniques [2].

Prognostic Impact of the Right Heart failure

The prognosis of right HF is strongly associated with its underlying cause. Patients with RV volume overload, pulmonary stenosis, and Eisenmenger syndrome usually have the best long- term prognosis [15]. Reduced exercise tolerance is an important risk factor for death or hospitalization in patients with RV failure associated with pulmonary hypertension and congenital heart disease [63]. Other prognostic factors include the severity of RV systolic and diastolic dysfunction, the extent of neurohormonal activation, chronotropic incompetence, cardiac arrhythmias, LV systolic dysfunction, and the degree of renal and hepatic function impairment [15, 64, 65].

Management of RV Failure

The evidence behind the current treatment strategies in right HF is not as well established as the evidence that guides the management of chronic HF resulting from LV dysfunction [14, 15].

The management of RV failure should be specific to the settings in which RV failure occurs and include therapy tailored to its particular cause. The treatment goals should be focused on improving the RV contractility, supporting its overall functionality by optimization of its preload and afterload, managing the consequences of RV failure, and alleviating distressing physical and emotional symptoms (pain, breathlessness, anxiety, etc.) (Fig. 22.5) [4, 15].

As RV failure is usually associated with RV volume overload, diuretics are often the first option in most patients with signs of venous congestion and well maintained arterial blood pressure, as they help to reduce both preload and afterload [21]. In addition to diuretics therapy, moderate sodium restriction and daily measurements of weight are recommended to minimize the fluid retention. However, diuretics should be administered with caution with the central venous pressure monitoring

where needed, as patients with RV failure are preload-dependent. Ventricular interdependence is another important factor to be considered in individualized treatment regimens. Thus, volume loading may increase pericardial constraint and decrease cardiac output through the mechanism of impaired LV preload; alternatively, hypovolemia may decrease RV preload and cardiac output [15].

Drug regimens aimed on reduction of the afterload of the RV are similar to those used for treatment of pulmonary hypertension [2]. More recent therapeutic developments for normalization of RV afterload and contractility improvement include sildenafil, nitric oxide, inotropes, and mechanical support.

Maintenance of sinus rhythm and atrioventricular synchrony is especially important in RV failure because atrial fibrillation and high-grade atrioventricular block may have profound hemodynamic consequences.

Dosed physical activity may be beneficial in patients with pulmonary hypertension and RV dysfunction. Recent randomized studies in chronic pulmonary hypertension patients have shown that aerobic exercise training significantly improves tolerance to physical exercise, cardiorespiratory function and quality of life compared to untrained control group [66, 67].

Timely detection and correction of factors associated with unfavourbale outcomes and disease progression are essential in clinical management of RV failure. These factors include noncompliance with medication or diet; use of medications such as nonsteroidal antiinflammatory drugs, nondihydropyridine calcium channel blockers, and antiarrhythmic drugs; systemic factors such as sepsis, anemia, high-output state, hypoxemia, and hypercapnia; cardiovascular factors including arrhythmias, myocardial ischemia, and pulmonary emboli; obstructive sleep apnea; and high altitude [15].

Mechanical circulatory support of the RV may be required in acute decompensation of severe chronic RV failure and in certain clinical situations such as RV myocardial infarction, following LVAD implantation, or primary graft failure after heart transplantation [4]. Correct timing of the LVAD implantation is the most important factor contributing to the treatment success and also helping to avoid significant, potentially irreversible end-organ injury. RV assist devices (RVADs) can be implanted either surgically or percutaneously. Although in some studies successful prolonged use of paracorporeal RVADs for weeks or even months was reported [68], they are currently approved for up to 4 weeks [4]. Currently, options for long-term RV mechanical circulatory support and RVADs' use as the destination therapy are very limited with the cardiac transplant being the ultimate treatment for refractory RV failure (Fig. 22.7) [4].

Conclusions

RV failure is a complex clinical condition associated with a poor prognosis in most patients with cardiac disease and its accurate diagnosis and treatment requires comprehensive knowledge of RV anatomy and mechanics. Further improvements in

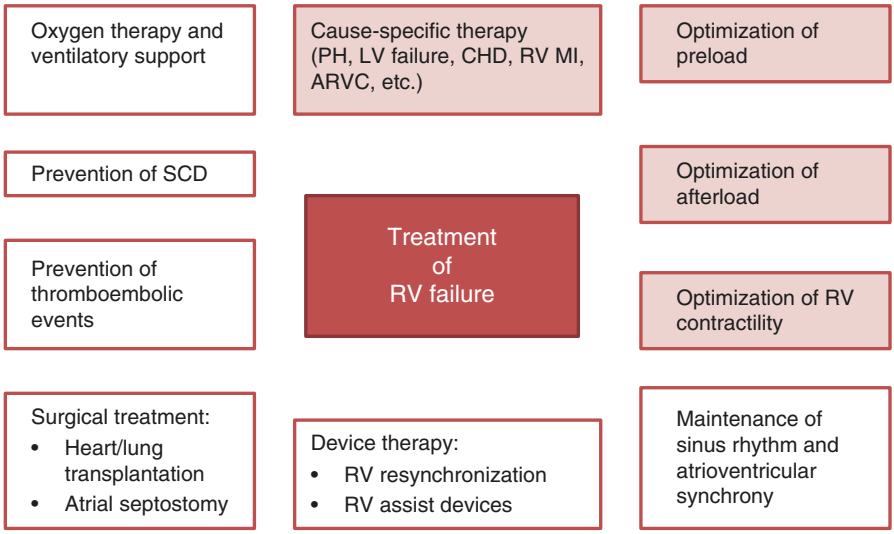


Fig. 22.7 Main components of the RV failure management. It should always be tailored therapy to its specific etiology and include optimization of the RV preload, afterload and contractility. Abbreviations: *ARVC* arrhythmogenic right ventricular cardiomyopathy, *CHD* congenital heart disease, *LV* left ventricular, *MI* myocardial infarction, *PH* pulmonary hypertension, *RV* right ventricle/ventricular, *SCD* sudden cardiac death

routine use of modern non-invasive imaging modalities for better evaluation of RV function, rapid identification and appropriate management of underlying causes, as well as advanced knowledge of supportive treatment measures are needed for an effective management of this condition.

Future Directions

Future research should aim at identifying novel genetic and epigenetic factor as well as molecular pathways involved in the development of right HF and the pathophysiology of this disorder. The outcome studies are needed to determine the most robust imaging parameters to stratify patient prognosis and monitoring treatment in RV failure by different etiologies. Knowledge gaps and lack of conclusive evidence regarding RV-specific treatment approaches should be addressed through development of more effective management strategies specifically tailored to the right heart pathology. Validation of biomarkers for early identification patients with RV dysfunction or at risk of its development will help in development of a comprehensive RV failure managements strategy.

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Chapter 23
Acute Heart Failure

Veli-Pekka Harjola, Héctor Bueno, and John T. Parissis

Definition

Acute heart failure (AHF) is one the most common causes of hospitalization in the elderly patients. We refer to AHF as the rapid (within minutes or days) development or progression of symptoms and/or signs of heart failure requiring urgent medical evaluation and treatment (pharmacological and/or non-pharmacological). AHF may present as a first occurrence (*de novo*) or, more frequently, as a consequence of acute decompensation of chronic HF, and may be caused by primary cardiac dysfunction or more frequently precipitated by extrinsic factors in patients with chronic heart failure. AHF may eventually be triggered by these factors in patients with previously normal or near normal cardiac function. Primary cardiac causes of AHF may result from disorders of the myocardium, endocardium, heart valves or pericardium. Acute myocardial dysfunction (ischemic, inflammatory or toxic), acute valve insufficiency or pericardial tamponade are among the most frequent acute primary cardiac causes of AHF. Decompensation of chronic stable cardiac diseases can occur without known precipitant factors but more often one or more factors, such as infections, severe hypertension, rhythm disturbances, noncompliance with diet or cardiovascular medications are present (Table 23.1).

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M. Dorobanțu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_23

Table 23.1 Factors associated with the development of acute heart failure

Primary cardiac dysfunction	Triggers/precipitants
Mechanism	**Precipitants often leading to rapid deterioration**
New-onset, de-novo heart failure	C – Acute coronary syndrome
Decompensation of chronic heart failure	H – Hypertensive crisis
Cause	A – Rapid arrhythmia or severe bradycardia/conduction disturbance
Myocardial dysfunction	M – Mechanical complication (e.g. rupture of free wall, interventricular septum or papillary muscle after ACS; mitral valve chordal rupture, post-traumatic)
LV systolic dysfunction	P – pulmonary embolism
LV diastolic dysfunction	Other:
RV dysfunction	Cardiac tamponade
Valvular heart disease	Surgery and perioperative problems
Pericardial disease	Peripartum cardiomyopathy
	Precipitants usually leading to less rapid deterioration
	Concurrent diseases
	Infections (pneumonia, sepsis, endocarditis)
	Exacerbation of COPD/asthma
	Anaemia
	Kidney dysfunction/deterioration
	Endocrine (thyroid decompensations, excess catecholamine production)
	Uncontrolled hypertension
	Fluid overload
	Arrhythmias, bradycardia, and conduction disturbances not leading to sudden, severe change in heart rate
	Aortic syndromes
	Non-adherence to diet/drug therapy
	Iatrogenic causes
	Drugs causing salt retention (NSAIDs, coxibs, steroids)
	Negative inotropics (verapamil, diltiazem)
	Cardiotoxic drugs (alcohol, chemotherapies)
	Drug interactions

ACS acute coronary syndrome, *AHF* acute heart failure, *COPD* chronic obstructive pulmonary disease, *LV* left ventricular, *RV* right ventricular, *NSAID* non-steroidal anti-inflammatory drug

The pathophysiologic mechanisms causing symptoms and signs of AHF are venous congestion and reduced cardiac output impairing peripheral perfusion. Pulmonary congestion causes dyspnea, the cardinal clinical manifestation of AHF. In AHF it is usually more prominent than systemic congestion, and may be mild or lead to severe pulmonary edema. Right heart congestion may also be present, more frequently in acutely decompensated chronic HF, and will manifest as jugular venous distension, peripheral edema, hepatomegaly or splanchnic congestion. When cardiac output is compromised, symptoms or signs of peripheral perfusion impairment may be present. This may be transient (i.e. fatigue, reduced tolerance to exercise or digestion) or persistent such as low blood pressure, oliguria, confusion, and mottling of the skin or *livedo reticularis*. When systemic perfusion

is significantly compromised patients present with cardiogenic shock (CS), a clinical condition with very high short-term mortality.

Therefore, AHF is a complex syndrome that can occur in patients with severe cardiac disease or with near normal hearts, be triggered by none, one single critical precipitant or various, be isolated or accompanied by several comorbidities (Fig. 23.1). This produces a wide variability in the presentation, severity, response to treatment and prognosis of AHF, ranging from relatively benign to a short-time life-threatening condition.

Classification

Given the complexity of AHF, the variety of factors involved, clinical presentations, etiologies and potential mechanisms involved (Fig. 23.1), no single classification can fit in all clinical and prognostic relevant aspects. Therefore, several overlapping classifications based on different criteria have been proposed. Approximately 2/3 of patients with AHF present as acute decompensations of chronic HF while the others do not have a prior history of HF (*de novo* AHF). Probably, the simplest and most useful classifications are those based on clinical presentation at admission. The

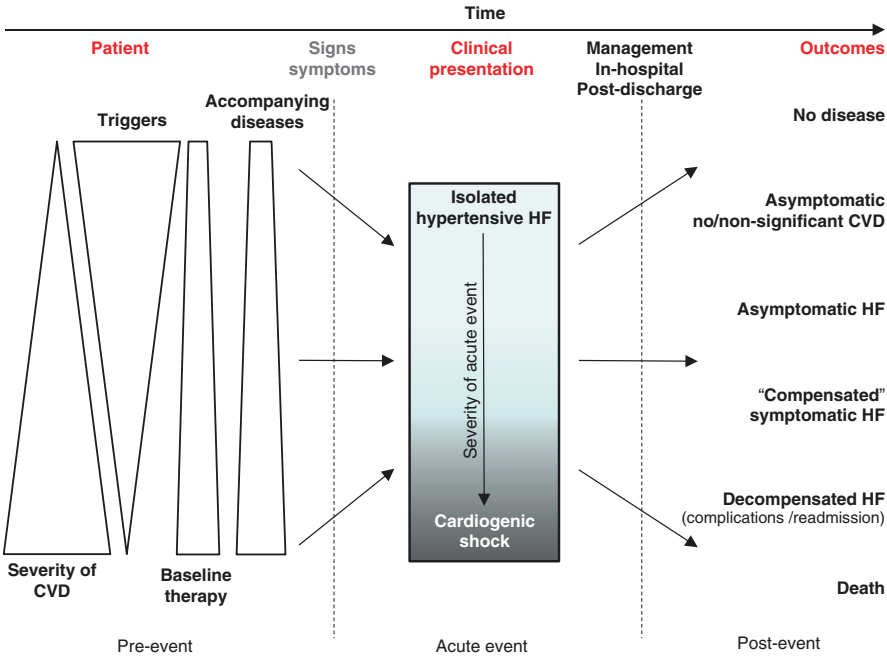

Fig. 23.1 Factors influencing the heterogeneity in etiology, clinical presentation and outcomes in patients with acute heart failure (CVD: cardiovascular disease; HF: heart failure) [3].

classification according to the level of SBP at presentation is easy to use and has a strong prognostic value. Thus, patients presenting with SBP >140 mmHg (hypertensive AHF) account for roughly half of AHF cases and have a good short- and long-term prognosis. Patients with low SBP (i.e. <90 mmHg (hypotensive AHF), are a minority (<8 %) but show the worst prognosis, with in-hospital mortality rates >15 %, particularly when signs of hypoperfusion are present (CS). In these patients, short-term mortality exceeds 30 %. The approximately other 40 % of patients with AHF present have SBP between 90 and 140 mmHg and show and intermediate risk compared with the previous two groups, with in-hospital mortality rates between 8 and 10 % [23].

One other popular classification based on physical examination, and therefore available immediately on admission, reflects the presence, or not, of clinical symptoms/signs of congestion and/or peripheral hypoperfusion [4]. The presence of congestion, either pulmonary (orthopnea, paroxysmal nocturnal dyspnoea) or systemic (peripheral oedema, jugular venous engorgement, congestive hepatomegaly, ascites, hepatojugular reflex) is defined as 'wet' vs. 'dry' for patients without congestion. Symptoms or signs of peripheral hypoperfusion (cold and clammy extremities, oliguria, mental confusion, dizziness, narrow pulse pressure) is defined as 'cold' vs. 'warm' patients for those in whom hypoperfusion is absent. It is important to emphasise that hypotension most frequently accompanies but does not equal hypopefusion. In some cases hypotension is associated with adequate perfusion. The combination of these options gives four groups: warm and dry (well perfused without congestion), warm and wet (well perfused but congested), cold and dry (hypoperfused without congestion), cold and wet (hypoperfused and congested). This classification has been proposed as a guide for initiating early medical treatment in patients with AHF [2].

Two popular classifications for AHF were developed in patients with acute myocardial infarction. Killip and Kimball [5] based on clinical status at admission, developed a classification with strong prognostic value for short-term mortality still used: Class I, no clinical signs of HF. Class II, HF with rales, S_3 gallop. Class III, with frank acute pulmonary oedema. Class IV, CS: hypotension (SBP <90 mmHg), and evidence of peripheral vasoconstriction such as oliguria, cyanosis and diaphoresis. Forrester et al. developed a classification based on cardiac index and pulmonary capillary wedge pressure (PCWP) to guide medical treatment in patients with AMI. Thus, patients in subset I would not require specific treatment, patients in subset II (high PCWP only) would mostly need diuretic therapy, patients in stage III (low CI, low PCWP) volume loading and patients in subset IV, inotropics or mechanical support [6].

Diagnostic Evaluation

The first step in diagnosis is ruling out alternative causes for dyspnea or patient´s other symptoms and signs (i.e. pulmonary infection, severe anaemia, acute renal failure). Despite advances in biomarkers and imaging, the diagnosis of AHF is based

on a careful history and physical examination. The initial diagnosis of AHF is based on the presence of clinical symptoms and signs and further confirmed by appropriate additional investigations such as ECG, chest X-ray, laboratory assessment (with specific biomarkers) and echocardiography. Typically, the clinical picture reflects fluid retention (pulmonary congestion and/or peripheral oedema) and less often is related to reduced cardiac output with peripheral hypoperfusion. Symptoms of AHF are manifestation of congestion, reflecting elevated ventricular filling pressures – left-sided may be characterized by orthopnea, paroxysmal nocturnal dyspnea, breathlessness at rest or with minimal exertion, whereas right-sided by peripheral oedema, ascites, symptoms of gut congestion. Systematic physical examination is essential in the diagnostic process of AHF and should always contain an evaluation of:

(a) Peripheral perfusion for which low systolic blood pressure and cold skin temperature are most accessible measures of hypoperfusion; additionally patient may present confusion, dizziness, anuria/oliguria.
(b) The presence of signs associated with elevated filling-pressures (left-sided: bibasal rales, an audible third heart sound, an abnormal blood pressure response to the Valsalva maneuver or right-sided: elevated jugular venous distention, hepatojugular reflux, hepatomegaly, ascites, and peripheral oedema; pleural effusions are often seen in patients with a previous history of chronic HF).

The sensitivity and specificity of symptoms and signs to predict both clinical scenarios, i.e. elevated filling pressures or low cardiac output, is often not satisfactory, which leaves relatively big margin of uncertainty to confirm final diagnosis of AHF and initiate appropriate treatment. Thus, in the diagnostic algorithm, careful clinical evaluation should be followed by additional investigations.

A second step in diagnosis is checking if there is a precipitant that may be leading or participating in the development of AHF or if there are concomitant diseases that may be contributing to the symptoms (Fig. 23.1, Table 23.1). Some precipitants, such as very high blood pressure or rapid atrial fibrillation may trigger alone AHF, and these require immediate therapy. Identifying the presence of acute myocardial ischemia is also essential as it has its own specific treatment. Other precipitants or concomitant conditions may participate in the development or worsening of the disease (Table 23.1) and will need to be identified and corrected in addition to the general treatment of AHF.

Chest X-ray is one of the most useful test for the diagnosis of AHF. A standing chest radiograph showing pulmonary venous congestion, interstitial edema or cardiomegaly are the most specific test findings for AHF although the absence of congestion may be absent in up to 20 % of patients, particularly among those with late-stage HF in whom high pulmonary capillary wedge pressures and symptoms can coexist with few radiographic signs of HF [7]. Supine chest radiographs are of limited value in AHF. Chest X-ray is also useful to identify alternative noncardiac diseases that may cause or contribute to the patient's symptoms (i.e. pneumonia, nonconsolidative pulmonary infections etc.).

Although **ECG** is not useful *per se* for the diagnosis of AHF it may be very helpful in identifying signs of potential underlying cardiac diseases (i.e. Q waves for

chronic myocardial infarction, left bundle branch block for cardiomyopathy, low voltage for pericardial tamponade etc.) and precipitants, such as rapid atrial fibrillation or signs of acute myocardial ischemia, two of the most frequent triggers of AHF. On the other hand, the finding of an ECG without any abnormality may also be helpful as it has a high negative predictive value of 98 % for AHF [7].

Initial **laboratory test** in patients with suspected AHF should evaluate factors that may contribute to the disease, including glucose, renal function, sodium, potassium, liver function tests, and complete blood count. Also thyroid stimulating hormone and transferrin iron binding capacity may reveal correctable causes [2]. Noninvasive oxygen saturation should be measured in all patients. Depending on initial findings and clinical situation, venous or arterial blood gases may also be needed. In patients with dyspnea of unknown origin, natriuretic peptides are indicated due to their high sensitivity for HF. If the test is normal, AHF is highly unlikely (negative predictive value higher than 95 %). The most established biomarkers used for the diagnosis and management of AHF and the main causes of elevations of natriuretic peptides are listed below.

Biomarkers for the Diagnosis and Management of AHF

- BNP/NT-proBNP for diagnosis of AHF (especially for ruling-out AHF as the cause of dyspnea)
- High-sensitivity cardiac troponin for diagnosis of ACS complicating AHF
- Procalcitonin, CRP and leukocytes for diagnosis of infection complicating AHF
- MR-proANP may be used for diagnosis of AHF in grey zones of traditional natriuretic peptides
- Serum creatinine or Cystatin-C for evaluation of renal function and diagnosis of acute kidney injury
- D-dimer for the diagnosis (ruling-out) of pulmonary embolism complicating AHF

Main Causes of Elevated Natriuretic Peptide Concentrations

Cardiac

Systolic dysfunction of left and/or right ventricle.
Acute coronary syndromes
Left ventricular hypertrophy
Hypertrophic or restrictive cardiomyopathy
Valvular heart disease
Congenital heart disease
Atrial tachyarrhytmias
Myocarditis

Cardiac operations
Resuscitation
Cardioversion

Noncardiac

Elderly
Anemia
Renal dysfunction
Pulmonary diseases related with RV hemodynamic stress: obstructive sleep apnea, severe pneumonia, pulmonary hypertension, pulmonary embolism
Critical illness
Sepsis
Severe burns,
Other high cardiac output conditions (e.g. thyroid disorders)
Toxic-metabolic insults, including cancer chemotherapy and radiotherapy.

Echocardiography is the most readily available non-invasive test to evaluate structural or functional heart abnormalities. Identification of left or right ventricular systolic dysfunction, valvular abnormalities, pericardial diseases or other cardiovascular alterations is essential in therapeutic planning [1]. Therefore, an echocardiographic study should be done in every patient with AHF in whom previous cardiac function is not known and in those previously studied in whom changes may have occurred. In patients in whom there is suspicion of an acute life threatening structural or functional cardiac abnormality (i.e. acute myocardial ischemia without diagnostic ECG, mechanical complications, severe mitral regurgitation, aortic dissection) the investigation should be performed immediately as it will prompt immediate specific treatment. Echocardiography should preferably be performed within 48 h of admission to allow appropriate pharmacological treatment and long term care planning [2]. Repeat echocardiography is usually not needed for patients with known underlying cardiac condition in whom there is little clinical suspicion of a change in pathology.

Bedside **lung ultrasound** is useful in detecting AHF. The presence of sonographic B lines ("lung comets") correlate with elevated PCWP and extravascular pulmonary water [8], with sensitivity >86 % and specificity >95 % [10, 11], enhancing diagnostic accuracy of examination and measurement of natriuretic peptides [9]. Thus, chest ultrasound has been proposed as a point of care technique to diagnose AHF, particularly in the ED setting. It is also more accurate than auscultation or chest radiography for the detection of pleural effusion, consolidation, and alveolar interstitial syndrome in the critical care setting [12].

In patients with AHF and implantable pacemakers or cardioverter-defibrillators, these should be routinely interrogated to assess the occurrence of atrial and/or ventricular arrhythmias as precipitants to the episode. Some of these devices can monitor thoracic impedance, which may be helpful in confirming AHF when the diagnosis is not clear.

Invasive haemodynamic monitoring with pulmonary artery (Swan-Ganz) catheterization is, in general, not needed for patients with AHF and routine use of this technique is not indicated. However, it may be helpful in some cases, particularly in unstable patients (i.e. hypotension, shock) in whom the cause or mechanism is unclear.

Other investigations must be focused only to specific clinical suspicion of causes and precipitating factors. Consequently, coronary angiogram should be performed in patients with suspected ACS and lung CT to those with suspected pulmonary embolism. However, due to unspecificity of natriuretic peptides, troponins as well as D-dimer, imaging can not be done only based on abnormal laboratory values in any AHF patient.

Risk Stratification

The mortality in AHF varies according to different features, including the clinical presentation, cause, comorbidities, and other aspects associated with the syndrome. Clinical factors associated with worse prognosis include older age, higher heart rate, lower systolic blood pressure, or lower oxygen saturation on admission, need for inotropic support, the presence of ischaemic changes in ECG, recurrent hospitalisations, renal dysfunction, COPD, anaemia, cerebrovascular events, and peripheral vascular disease. The presence of depressed left ventricular ejection fraction or a restrictive physiology in echocardiography is more frequently present in patients with worse prognosis. Laboratory tests may also be helpful for risk stratification. Worse prognosis is associated with higher levels of natriuretic peptides, cardiac troponins, serum creatinine, urea or BUN or liver function tests. Lower serum sodium or haemoglobin levels are also associated with higher mortality. Other biomarkers of myocardial injury, fibrosis or renal dysfunction, such as ST2, MR-proadrenomedullin, or cystatin C can be used for risk stratification although their additive value to standard biomarkers in clinical practice is still unclear.

Management

General Management

The need for immediate monitoring, bedrest and start of medication depends on patient's clinical stability and severity of symptoms. The management of dyspneic patient should start early after arrival to emergency department [39]. Though the management most often includes initial bed rest in semirecumbent position, continuous ECG monitoring and intravenous line, the patient with mild symptoms do not need to be monitored in bed.

Most often pharmacological and non-pharmacological treatment must be administered in parallel with the diagnostic work-up. The management of AHF is mainly

aimed to alleviate congestion, and improve perfusion and symptoms immediately. Thus, the primary goal is not to improve long-term outcomes same way as treatments for chronic HF. However, a management should not increase mortality or hospitalization indeed. The key drugs for AHF treatment are oxygen, diuretics, and vasodilators. Opiates and inotropes are used more selectively, and mechanical circulatory support is required only rarely. Non-invasive ventilation is used commonly in pulmonary oedema, but invasive ventilation is required only in minority of patients. Blood pressure, heart rhythm and rate, peripheral oxygen saturation (SpO_2) with pulse oximeter, and urine output should be monitored on a regular and frequent basis until the patient is stabilized [2]. However, in order to avoid infectious complications, one should use urinary catheter only in those, mainly oliguric and critical, patients who need measurement of hourly diuresis.

Recently, aggressive fluid and sodium restriction (at maximum 800 ml fluid and 0.8 g salt per day) compared to control group without such restrictions was shown to have no effect on weight loss or clinical stability after three days but was associated with a significant increase in perceived thirst [13]. However, moderate salt restriction is recommended (maximum 6 g per day) [2]. The degree of fluid restriction should vary depending on the estimated fluid overload. In light of the recent data, 1500 ml per day is recommended as the minimum amount of fluid per day.

Recent data show that more than one-third of patients have persistent congestion at discharge despite therapy targeting decongestion in the clinical trial setting [14].

Prompt initiation of the diagnostic work-up and appropriate treatment is mandatory for all patients admitted with a diagnosis of AHF. Patients in cardiac arrest or who require immediate resuscitation are a distinct sub-group of AHF. For the vast majority of patients, initial assessment and continued monitoring of patient's vital cardio-respiratory functions is essential to evaluate whether ventilation, peripheral perfusion and oxygenation are adequate. Typically, diagnosis and early management occurs in the emergency department, where initial assessment to identify potential life-threatening conditions requiring immediate treatment is mandatory (Fig. 23.2).

Immediate Ventilatory and Hemodynamic Stabilization

Respiratory Distress with Hypoxaemia and Peripheral Desaturation; acute Respiratory Failure

In AHF, oxygen should not be used routinely in non-hypoxaemic patients. "Wet" patients with pulmonary congestion and hypoxemia (PaO_2 <60 mmHg) or low peripheral oxygen saturation (SpO_2 <90 %) should be treated with oxygen administration to maintain oxygen saturation within the normal range (i.e. 95 %). In ACS, improper use of supplementary oxygen in normoxemic patients may be harmful [40]. In COPD, over-oxygenation may suppress ventilation and lead to hypercarbia.

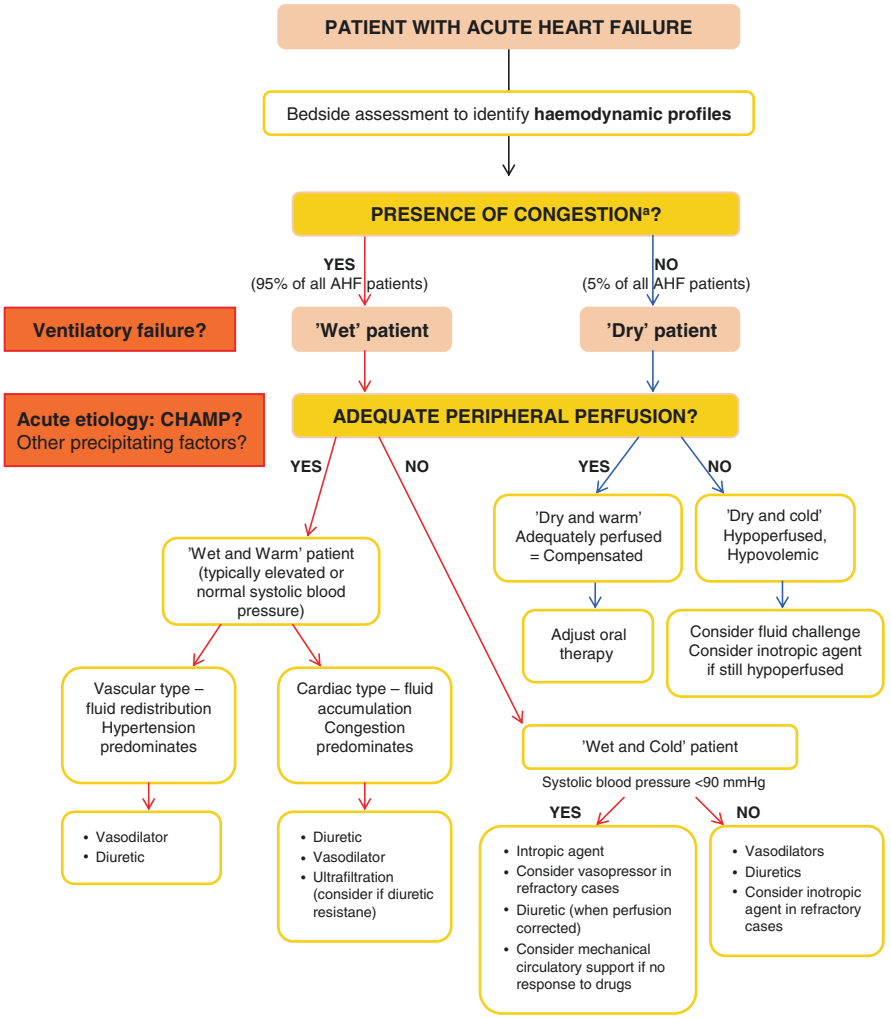

Fig. 23.2 Management of patients with acute heart failure based on clinical profile during early phase [3]. CHAMP, see Table 23.1

Ventilatory support with non-invasive ventilation (CPAP or NIPPV) should be considered in patients with significant respiratory distress, particularly for patients with acute pulmonary oedema [31]. Bilevel PPV allows also inspiratory pressure support that improves minute ventilation and is especially useful in patients with hypercarbia, most typically COPD patients. NIPPV in addition to standard medical care is an effective and safe intervention for the treatment of adult patients with acute cardiogenic pulmonary oedema.

Endotracheal intubation is rarely required and indicated only in patients with overt respiratory failure, failure to adequately respond to oxygen therapy and non-invasive ventilation, or who are inappropriate candidates for NIV because of

somnolence, anxiety or agitation. Caution has to be taken with regard side-effects of anesthetic drugs. Anesthetic drugs like propofol can induce hypotension, and have cardiodepressive side-effects. In contrast, midazolam may have less cardiac side effects and may thus be preferable in CS.

Cardiogenic Shock

Cardiogenic shock is the most severe form of AHF and the leading cause of death in acute myocardial infarction. CS is characterized by low cardiac output, hypotension and systemic hypoperfusion, resulting in end-organ dysfunction. In addition to acute cardiac cause, the contemporary diagnostic criteria for CS are 1) systolic blood pressure <90 mmHg for over 30 min despite adequate fluid resuscitation or need for vasopressor therapy to maintain systolic blood pressure ≥90 mmHg and 2) clinical signs of hypoperfusion (altered mental status, cold extremities or oliguria) or increased blood lactate level (>2–4 mmol/l). The diagnosis of CS can thus be made by clinical evaluation, instead of invasive assessment of pulmonary artery wedge pressure and cardiac index with pulmonary artery catheter routinely [1]. Electrocardiography (ECG) and echocardiography should be performed immediately after detection of the shock to assess the etiology of CS and to rule out mechanical complications. Low output syndrome caused by advanced chronic heart failure may clinically resemble CS, but the onset is more gradual and, due to adaptive mechanisms, patients may sustain the syndrome relatively long.

CS ranges from low-output advanced, end-stage chronic HF to new onset, de-novo CS. It is most often caused by STEMI or other acute coronary syndromes (80 %) [34]. The specific treatment is immediate revascularization. However, although in about 80 % of cases it is caused by ventricular dysfunction, mechanical complications such as acute mitral valve incompetence or ventricular septal defect may be the precipitant requiring immediate intervention with either circulatory support or urgent surgery in selected cases [16]. Other etiologies include chronic heart failure, valvular disease, myocarditis, Tako-Tsubo, high-risk pulmonary embolism among others. Pharmacologic therapy aims to improve organ perfusion by increasing cardiac output and blood pressure. After fluid challenge, pharmacologic management consists of inotropic agent and vasopressor as needed. Treatment is guided by the continuous monitoring of organ function and hemodynamics. Pulmonary artery catheter may be used. As vasopressor, norepinephrine is recommended (over dopamine) when mean arterial pressure needs pharmacologic support [35]. Dobutamine is the most commonly used adrenergic inotrope. Levosimendan may also be used [36] Phosphodiesterase III inhibitors may be another option, especially in non-ischemic patients. However, rather than combining several inotropes, mechanical circulatory support has to be considered when there is inadequate response. Extra-corporeal life support is a promising tool for both oxygenation and assistance for heart. Recently, the IABP-SHOCK II trial showed that use of intraaortic balloon pump (IABP) did not improve outcomes in patients suffering from AMI and CS [37, 38]. Therefore, routine use of IABP cannot be recommended [2].

Further Management – Initial In-hospital Phase

After stabilization of oxygenation, ventilation and circulatory status, the next step in clinical profiling is the identification of precipitants/causes leading to decompensation to avoid further deterioration and/or development of life-threatening conditions if not treated/corrected urgently (Fig. 23.2).

Acute Co-morbidities

Acute Coronary Syndrome

Coronary artery disease (CAD) is the most common cause of HF. Most patients admitted with AHF have a history of CAD often with prior myocardial infarction [45]. Acute myocardial ischaemia may cause AHF or trigger decompensation of chronic HF while AHF can lead to worsening of chronic myocardial ischaemia. In AHF registries, up to 40 % of patients may have acute coronary syndrome (ACS) as a precipitating factor [46]. More than one quarter of patients with myocardial infarction develop signs and symptoms of HF [44]. Early identification of ACS in patients with AHF is essential as this implies the need for urgent management per ACS guidelines [43]. Cardiogenic shock is the most severe form of AHF complicating ACS.

It is important to emphasise that the use of high sensitive cardiac troponin assays has led to a very high proportion of AHF patients showing elevated troponin levels in the early phase in the absence of clinically apparent ischaemia and ACS. Although this finding has prognostic implications, there is currently no evidence showing that a strategy to protect or prevent further myocardial injury would lead to improved outcomes.

Arrhythmias

Arrhythmias are a common precipitating cause in AHF, ranging between *15 and 30 %* [45, 46]. These range from tachyarrhythmias to severe bradycardia or conduction disturbance. This clinical profile at presentation warrants consideration of either electrical cardioversion or temporary pacing [2]. AHF patients with incessant ventricular arrhythmias constitute most challenging scenario, as arrhythmias and haemodynamic instability operate here in a vicious circle, perpetuating each other. Urgent angiography (with resultant revascularization, if needed) and electrophysiological testing with radiofrequency ablation are indicated in selected cases [47].

Patients with AHF and atrial fibrillation should be fully anticoagulated (e.g. with s.c. low-molecular weight heparin), if not already anticoagulated and with no contraindication to anticoagulation, as soon as AF is detected to reduce the risk of systemic arterial embolism and stroke. Electrical cardioversion is recommended in patients haemodynamically compromised by AF and in whom urgent restoration of sinus rhythm is required to improve the patient's clinical condition rapidly. Electrical

cardioversion or pharmacological cardioversion with amiodarone should be considered in patients when a decision is made to restore sinus rhythm non-urgently ('rhythm control' strategy). This strategy should only be employed in patients with a first episode of AF of <48 h duration (or in patients with no evidence of left atrial appendage thrombus on transesophageal echocardiography) [2]. Intravenous administration of digoxin, amiodarone and in patients with stable haemodynamics small doses of beta blocker should be considered for control of rapid ventricular rate in HFrEF and also cautious use of verapamil or diltiazem in HFpEF.

Pacing is recommended in patients haemodynamically compromised by severe bradycardia or atrioventricular block to improve the patient's clinical condition. Ventricular pacing may worsen stroke volume significantly.

Hypertensive Heart Failure

AHF precipitated by rapid and excessive increase in arterial blood pressure typically manifests as acute pulmonary oedema, though less extreme presentations are also common. Prompt reduction in blood pressure should be considered as a primary therapeutic target in this wet-warm, vascular type presentation. Aggressive blood pressure reduction with vasodilators initiated as soon as possible aiming to lowering by 25 % during the first hours, and cautiously thereafter [2, 48]. In a recent small clinical trial, intravenous calcium-channel blocker clevidipine safely and rapidly reduced blood pressure and improved dyspnoea [42].

Acute Mechanical Cause Underlying AHF

An acute mechanical cause may rapidly precipitate haemodynamic deterioration leading to AHF and often CS. It is relatively rare and usually occurs as a complication of ACS (ventricular septal defect, free wall rupture, acute mitral regurgitation). It is less frequently caused by aortic dissection, acute valvular incompetence (due to trauma or endocarditis), prosthetic valve failure or thrombosis. After diagnosis, generally by immediate echocardiography, either surgical or percutaneous intervention may improve the outcome in selected cases, if performed urgently [2].

Acute Pulmonary Embolism

Patients with acute pulmonary embolism who present with signs and symptoms of AHF, typically in the form of arterial hypotension and/or shock are in the highest risk group. The detailed diagnostic and therapeutic algorithms are presented in the recent ESC guidelines [41]. In brief, if acute pulmonary embolism is confirmed as underlying cause of haemodynamic compromise, immediate specific treatment is recommend with primary reperfusion either with thrombolysis, catheter-based approach or surgical embolectomy.

Cardiovascular Medication

Systematic approach with clear therapeutic goals and safety limits and regular, close monitoring of treatment response, e.g. symptom relief, urine volume or blood pressure control are essential for management. The medications should be chosen according to the patient's clinical profile, most importantly congestion and hypoperfusion.

Diuretics

In the treatment of patients with signs of fluid overload and congestion, especially wet and warm patients (cardiac type) diuretics are the mainstay of therapy. Diuretics increase renal salt and water excretion and may cause some vasodilation. However, in patients with signs of hypoperfusion one should correct perfusion before starting diuretics.

In AHF, intravenous furosemide is the most commonly used first-line diuretic. The dose should be modified according to previous renal function and previous dose of diuretics. Typically, the dose should be at least equal to the pre-existing oral dose used at home. Consequently, patients without a history of renal failure and without previous use of diuretics or de-novo AHF may respond to iv boluses of 20–40 mg whereas those with chronic renal failure and previous use of diuretics usually require higher doses like 40–80 mg iv. Torasemide is another alternative and dose is usually 10–20 mg iv [2]. There is no data to recommend one way of delivering diuretics over another, i.e. bolus dosing or continuous infusion [15].

In patients with insufficient response to furosemide, thiazide-type diuretics or mineralocorticoid receptor antagonists (most often spironolactone) can be combined. The decision depends on plasma potassium level and renal function. A combination of a loop and a thiazide (e.g. bendroflumethiazide) or thiazide-like diuretic (metolazone) is usually only needed temporarily and requires careful monitoring to avoid hypokalemia, renal dysfunction, and hypovolaemia [14].

Vasodilators

Vasodilators decrease both venous and arterial tone and thus preload and afterload. Consequently, they may also increase stroke volume [18].

Vasodilators are especially useful in hypertensive – wet and warm, vascular type-patients in which they should be uptitrated rapidly [49]. Vasodilators should be avoided in patients with systolic blood pressure <90 mmHg and in patients with symptomatic hypotension. Vasodilator should be used with caution in patients with significant mitral or aortic stenosis.

Nitrates include nitroglycerin and isosorbide dinitrate (ISDN). They can be given as sublingual tablets, oral spray, infusions, orally or by dermal patches. Tolerance to nitrates may occur and may necessitate change from nitrate e.g. to nitroprusside.

Intravenous nitrates when used in the treatment of AHF in emergency department, improve short-term symptoms and appear safe. However, they have not been shown to impact mortality [16]. Use of high dose transdermal and sublingual ISDN, in addition to standard AHF care, seems an interesting option that has to be explored [17].

Nitroprusside is a more pronounced arterial vasodilator. In hypertensive crisis, nitroprusside is preferred over nitrates. Prolonged use of sodium nitroprusside is limited by its potential toxic accumulation of isothiocyanate [18].

Nesiritide—a human BNP that acts mainly as a vasodilator— alleviates dyspnea but increases hypotension. It is current role among vasodilators is unsettled. Thus, nesiritide cannot be recommended for routine use in AHF [19].

Digoxin

Digoxin has cholinergic properties, and is a mild inotrope. It is mostly indicated in patients with atrial fibrillation and rapid ventricular rate and given in boluses of 0.25–0.5 mg iv, if not used previously.

Inotropes and Inodilators

Inotropes increase stroke volume and cardiac output, and decrease left ventricular filling pressure. They should be used in patients with reduced with organ hypoperfusion. Most commonly they are indicated in CS [2, 24]. Inotropes may also be effective in advanced heart failure patients with severely depressed left ventricular function and congestive heart failure. Dobutamine is the most commonly used inotrope. However, especially adrenergic inotropes (dobutamine, dopamine, epinephrine) may cause tachyarrhythmias, increase oxygen consumption and induce myocardial ischaemia. Inappropriate use of inotropes may increase mortality and inotropes have to be used with caution, as short as possible, starting low and with adequate monitoring [2, 21].

Levosimendan is a calcium sensitizing drug that enhances troponin C sensitivity to intracellular calcium, thereby enhancing cardiac inotropy and lusitropy. Levosimendan also causes peripheral vasodilation by opening smooth muscle ATP dependent potassium channels. Levosimendan may be better than dobutamine for treating AHF patients with a history of CHF or those on beta-blocker therapy [22].

Intravenous milrinone is a phosphodiesterase III inhibitor with inodilating action. It is not recommended in the treatment of patients hospitalized for an exacerbation of chronic heart failure. Milrinone may be especially deleterious in acutely worsened ischemic HF [23].

In theory, large doses (>5 μg/kg/min) of dopamine have inotropic activity via beta receptor activation and higher doses (10–20 μg/kg/min) vasoconstrictor activity via alpha adrenergic stimulation. However, the individual effects may vary a lot which makes these theories less well adapted to clinical practice. Dopamine was recently shown to be ineffective in improving diuresis in AHF [20].

The use of epinephrine (adrenaline) should be restricted for resuscitation protocols since it increases mortality when used in CS [25].

Vasopressors

Drugs with prominent peripheral arterial vasoconstrictor action such as norepinephrine (noradrenaline) may be given to patients in CS with marked hypotension. These agents are given to raise blood pressure and redistribute cardiac output from the extremities and splanchnic vascular beds to the vital organs. However, this is at the expense of an increase in LV afterload. Dopamine was compared with noradrenaline in treatment of various shock patients. A subgroup analysis suggested that noradrenaline would have less side-effects and lower mortality [26].

Other Pharmacological Therapy

Opiates relieve pain, dyspnea and anxiety. Common, dose-dependent side-effects include nausea, hypotension, bradycardia, and respiratory depression In AHF, opiates should be given cautiously and confined to patients with severe dyspnea, mostly with pulmonary oedema [2].

Anxiolytics or sedatives may be needed in a patient with anxiety or delirium. Cautious use of diazepam or lorazepam seems the safest approach [2].

Venous thromboprophylaxis with low-molecular weight heparin or another anticoagulant should be used [2].

Tolvaptan is a vasopressin antagonist that promote aquaresis. It may be temporarily used in resistant hyponatraemia. Thirst and dehydration are its typical side-effects [2].

Drugs Under Research

There are few drugs being investigated for the use in AHF. Among them are serelaxin, istaroxime, omecamtiv mecarbil and ularitide. Serelaxin is recombinant human relaxin-2 peptide, which regulates maternal adaptations in pregnancy. Serelaxin has potential benefits for decongestion given its effects on arterial compliance, cardiac output, and renal blood flow [27]. Istaroxime is a novel intravenous drug that both inhibits the activity of sodium-potassium ATPase and stimulates sarcoplasmic reticulum calcium ATPase isoform 2a (SERCA2a). It consequently improves both relaxation (lucitropy) and inotropy [28]. Omecamtiv mecarbil is a cardiac myosin activator. It increases the efficiency of heart muscle contraction via selectivity for a subset of cardiac myosins [29]. Ularitide is a synthetic analogue of urodilatin, a member of the family of A-type natriuretic peptides (ANP) [30]. We need to wait until results from ongoing trials to give recommendations for their use.

Devices

Ultrafiltration

Ultrafiltration involves removal of plasma water across a semipermeable membrane in response to a transmembrane pressure gradient. It can not be recommended as first line therapy [32, 33]. The use of ultrafiltration should be confined to patients that fail to respond to diuretic-based strategies.

Mechanical Circulatory Support

Mechanical circulatory support (MCS) is reserved to patients with cardiogenic shock that is unresponsive to pharmacological and other first-line management. MCS systems improve circulation by unloading the heart and maintaining appropriate end-organ perfusion. Short-term MCS from days to a few weeks is most commonly accomplished with percutaneous cardiac support devices. Intra-aortic balloon pulsation should not be used routinely in cardiogenic shock. The veno-arterial extracorporeal life support (ECLS), in other words, extracorporeal membrane oxygenation (ECMO) systems are relative easy and fast to implant and are being increasingly used. However, the evidence behind these strategies is still limited. A more comprehensive view about the short- and long-term MCS is given in another chapter of this book.

Criteria for Discharge from the Hospital and Follow up in High Risk Period

Patients should only be discharged when they have been hemodynamically stable, euvolaemic, have stable renal function, and have been established on oral medication for at least 24 h.

Chronic disease modifying, life prolonging medications (ACEi or ARBs, beta blockers and MRAs) should be continued at the highest tolerated dose and uptitrated or initiated again after clinical stabilization according to the patients' vital signs, hemodynamic status, underlying renal function and electrolyte values.

Follow-up plan must be in place prior to discharge and clearly communicated to the primary care team. Patients, ideally, should be seen by their general practitioner or primary care cardiologist within 1 week of discharge and by the hospital based cardiology team within 2 weeks [2]. All patients should be enrolled in disease management programme and followed up by a multi-professional heart failure service. They also ensure continuation and uptitration of disease modifying therapy for heart failure with reduced ejection fraction, if appropriate.

Compliance is listed among the most important precipitating factors for AHF. Recognition of compliance problems along with other potential precipitating factors is critical step for optimal management of AHF. On the other hand, every patient following an attack of AHF should have an acceptably detailed plan of care that ensures the achievement of optimal medical therapy and compliance with all the necessary measures. Table 4 describes the relevant actions for optimization of discharge and early follow up management in hospitalized HF patients.

Table 4. Instructions for the Optimization of Management of AHF Patients at Hospital Discharge

- Exacerbating factors addressed
- Transition from intravenous to oral therapies successfully completed
- Optimal decongestion and hemodynamics achieved
- Initiation or up-titration of pharmacologic therapy achieved and stable for 24 h, including chronic disease-modifying therapies for patients with reduced LVEF or cause of limitation of up-titration or intolerance to a drug documented
- Evaluation of co-morbidities
- Ambulation prior to discharge to assess functional capacity after therapy
- Patient and family education completed, including clear discharge instructions (daily weight measurements, diet instructions, vaccination, sodium intake etc.)
- Management plan documented and sent to those in charge of post-discharge care
- Follow-up programme scheduled, nurse visit or telephone follow-up 3 days after discharge in selected high-risk patients and doctor's office visit preferentially after 7–14 days
- Referral for disease management programme (e.g. evaluation for device therapy, heart transplantation or palliative care)

Future Directions

- The incidence of acute heart failure is increasing
- The role of early treatment in emergency department is underscored
- Results from randomized clinical trials will give us new data on intravenous drug therapies
- Patients must be clinically characterized in a systematic manner in order to provide individualized goal-directed treatment
- Treatment response has to be assessed systematically and decongestion has to be evaluated appropriately
- Cardiogenic shock remains a clinical challenge conferring high mortality
- More knowledge is needed about modern treatments of cardiogenic shock including pharmacotherapy and mechanical circulatory support
- More emphasis must be paid to prevent early rehospitalization after discharge from a hospital admission for AHF
- Ways to prevent early rehospitalization need to be explored

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Part V
Heart Failure in Special Populations

Chapter 24
Heart Failure in Oncologic Patients

Gina Biasillo and Daniela Cardinale

Abbreviations

AC	Anthracyclines
ACEI	Angiotensin-converting enzyme inhibitors
AMP	Adenosine Mono-Phosphate
ARB	Angiotensin receptor blocker
BB	Bbeta-blockers
BNP	Brain Natriuretic Peptide
CTX	Cardiotoxicity
DNA	Deoxy-ribonucleic acid
ECG	Electrocardiographic
ESMO	European Society of Medical Oncology
GLS	Global longitudinal strain
HER-2	Human epidermal growth factor receptor 2
HF	Heartfailure
ICOS	International Cardioncology Society
LVEF	Left ventricular ejection fraction
LVD	Left ventricular dysfunction
MUGA	Radionuclide multi-gated acquisition
NO	NitricOxide
RAS	Renin-angiotensin system
ROS	Reactive oxygen species
STE	Speckle-tracking echocardiography
TKIs	Tyrosine kinase inhibitors
Tn	Troponin
Top2	Toposomerase2
VEGF	Vascular Endothelial Growth Factor.

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M. Dorobanțu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_24

Introduction

Over the last few decades, improvements in early cancer detection and treatment breakthroughs – enhanced surgical approaches, as well as advances in therapeutics – have significantly improved survival of oncologic patients. However, a considerable price has been paid in terms of untoward side effects associated with treatment. In particular, both conventional and novel antineoplastic treatments may cause damage to the cardiovascular system. Cardiovascular disease is, at present, the second leading cause of long-term morbidity and mortality among cancer survivors. In this complex scenario, prevention, early diagnosis, and treatment of cardiovascular toxicity induced by anticancer treatment is an important medical issue. This problem is expected to intensify because of the increasing number of patients undergoing anti-cancer therapy, the improved efficacy of anti-cancer therapies, and the prolonged expectancy of life. Furthermore, cardiovascular toxicity represents an adverse event difficult to manage by the oncologist alone. A situation where the cardiovascular system is affected may require the review of the anticancer therapy, reducing cumulative dose, changing the administration schedule, or, in many cases, withdrawing the treatment altogether. These actions could negatively impact patients' outcomes. Therefore, collaboration with the cardiologist has become crucial to avoid the possibility that the development of the second disease does not lead to a reduction of therapeutic opportunities for the patient.

Clinical Presentation

The development of acute coronary syndromes, hypertension, arrhythmias, decreased cardiac contractile function, electrocardiographic (ECG) changes, thromboembolic events can be regarded as an expression of cardiotoxicity (CTX). However, the most frequent and clinically impacting manifestation of CTX, feared by both oncologists and cardiologists is the development of left ventricular dysfunction (LVD), leading to a hypokinetic cardiomyopathy. This form of cardiomyopathy has been linked to a 3.5-fold increased mortality risk compared to idiopathic cardiomyopathy [1].

Conventional chemotherapeutics, such as anthracyclines (AC), antimetabolites, and cyclophosphamide, can induce myocardial cell injury, leading to acute or chronic LVD. Additionally, many targeted therapies, in particular monoclonal antibodies and tyrosine kinase inhibitors (TKIs), human epidermal growth factor receptor 2 (HER 2) targeting drugs, such as trastuzumab, pertuzumab, Vascular Endothelial Growth Factor (VEGF), VEGF receptors (bevacizumab, sunitinib, sorafenib, etc), and Abl kinase activity (imatinib, nilotinib, dasatinib) possibly lead to cardiac dysfunction. Anti-cancer related cardiomyopathy usually begins with asymptomatic diastolic or systolic dysfunction and may progress until congestive heart failure (HF), possibly leading to symptoms onset and, finally, to death [2].

Moreover, cancer therapies may be associated with a variety of rhythm disturbances but most notably can prolong the QT interval, potentially leading to ven-

tricular arrhythmias. The use of some medications in supportive care during cancer therapy (eg, antiemetics, antidepressants), in combination with cancer treatments and also electrolyte disturbances, can lead to QT prolongation.

Valvular dysfunction, pericardial diseases, myocardial fibrosis and defects in the conduction system can also occur, especially as a consequence of radiation therapy. In fact, radiotherapy is associated with microvascular, macrovascular and endothelial injury: HF can develop as an acute radiation myocarditis, or, more frequently, as a restrictive or dilated cardiomyopathy (Fig. 24.1). Notably, radiation-associated cardiac injuries are especially important in young patients with curable malignancies, in whom the risk of developing clinically significant late CTX is high.

Definition

Several definitions for cancer-therapy related CTX have been proposed. Currently, expert consensus from the American Society of Echocardiography and the European Association of Cardiovascular Imaging defines CTX as a decline of the left ventricular ejection fraction (LVEF) greater than 10 % points with a final LVEF <53 %.

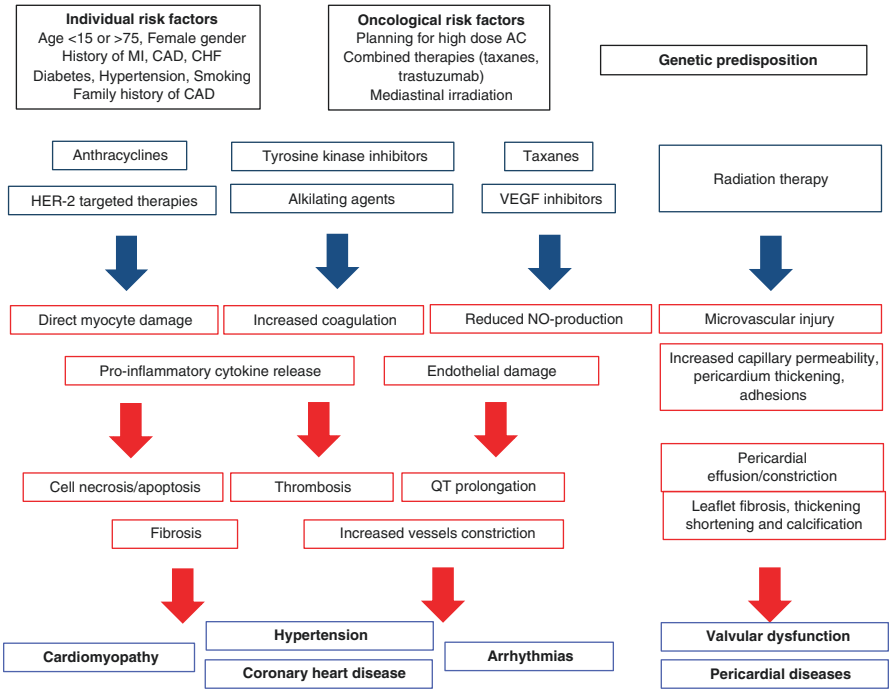

Fig. 24.1 Pathophysiology and clinical presentation of anticancer treatment related cardiotoxicity. *MI* myocardial infarction, *CAD* coronary artery disease, *CHF* congestive heart failure, *AC* anthracyclines, *VEGF* vascular endothelial growth factor, *NO* nitric oxide

This decrease should be confirmed by repeated cardiac imaging. LVEF assessment should be repeated two to three weeks after the evidence of the decrease in LVEF [3]. Previously, the Cardiac Review and Evaluation Committee supervising trastuzumab trials defined CTX as a decrease in LVEF that is either global or more severe in the septum and decline in LVEF of at least 5 to <55 %, with accompanying signs or symptoms of HF, or a decline of at least 10 to <55 % without HF signs or symptoms [4]. An other definition has been proposed by National Cancer Institute [5] and is based in severity into grades 1–5: from asymptomatic elevations in biomarkers or abnormalities on imaging (grade 1), to symptoms on exertion (grade 2 and 3), overt HF (grade 4) and finally, death (grade 5).

However, the existing definitions include arbitrary cutoffs and are not guided by clinical outcomes: development of uniformly accepted definition of CTX are of pivotal importance.

Classification

Time of onset of CTX is variable. In the past, three types of CTX were described, according to the timing of cardiac symptom occurrence, and to its clinical course: acute, occurring after a single dose or course of AC-containing chemotherapy, with clinical manifestations developing within two weeks from the end of drugs administration; early-onset chronic, developing within one year; and late-onset chronic, developing years after the end of treatment. However, this classification dates back to the early 90s, and is based on small retrospective studies reporting HF symptoms occurrence in childhood cancer survivors' populations (Fig. 24.2) [6, 7]. The clinical relevance of such a classification, however, is unclear, particularly when applied to adult populations.

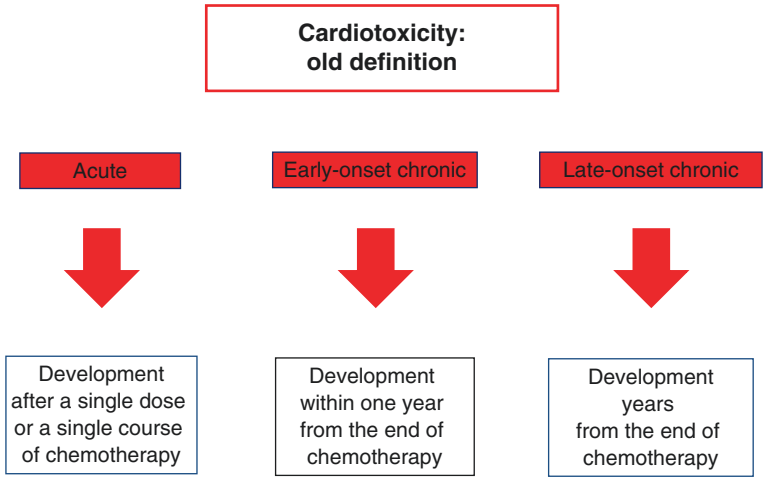

Fig. 24.2 Old classification of cardiotoxicity

More recent studies suggest that drug-induced CTX is a continuum starting with myocardial cell injury, followed by asymptomatic, progressive LVD that, if disregarded and not treated, leads to overt HF (Fig. 24.3) [8, 9].

The distinction between different forms of CTX depends therefore, on the definition we give to it, and on our ability to identify early subclinical cardiac damage. So, if we look at HF symptoms, our diagnosis may take several years, and we will define this CTX as "late". If we look at LVEF reduction, it may take months and we will designate it as "early." Finally, if we look at pre-clinical myocardial cell damage, using a biomarker, like troponin (Tn) for instance, we will identify CTX during or soon after chemotherapy, and we will define it as "acute". In other words, we are possibly observing different stages of evolution of the same phenomenon and not three distinct diseases [8].

Anticancer Agents: Pathophysiology

Over the last few years, some authors proposed to classify CTX on the basis of the type and extent of structural abnormalities and degree of reversibility [10]. Two types of CTX have been described: type I (model: anthracyclines) is considered irreversible and dose related; type II (model: trastuzumab) includes reversibility

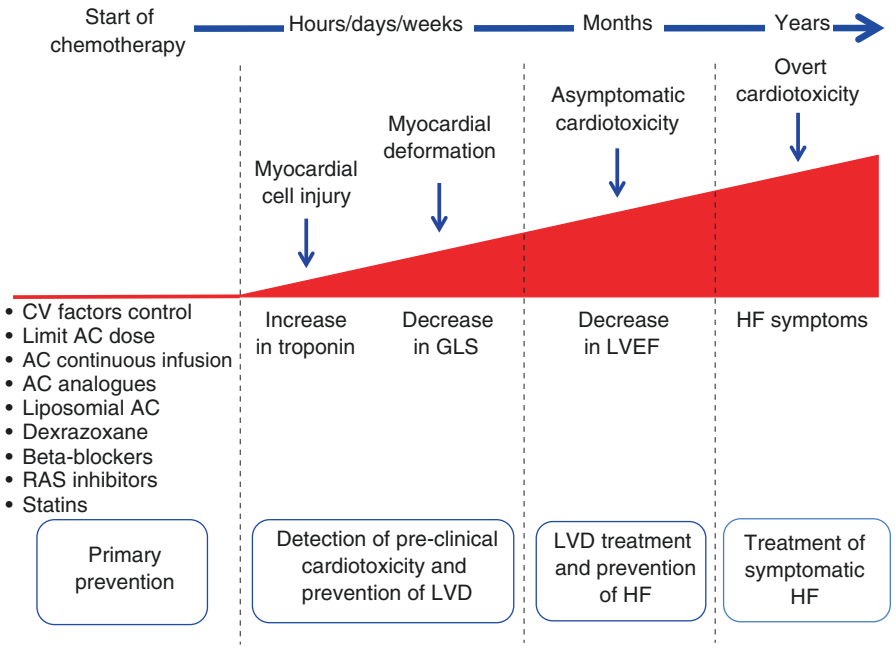

Fig. 24.3 Schematic representation of cardiotoxicity progression and management: the continuum phenomenon hypothesis. *GLS* Global longitudinal strain, *LVEF* left ventricular ejection fraction, *LVD* left ventricular dysfunction, *HF* heart failure (Modified from Cardinale et al. [9])

with cessation of treatment in most cases, lack of dose-relationship, and absence of ultrastructural abnormalities. However, this distinction seems overly simplified. In the real world AC and trastuzumab are rarely administered alone; generally, patients are treated with a cocktail of drugs with possibly different, synergistic, toxic effects.

Although several drugs have been demonstrated to be potentially cardiotoxic, the drugs most commonly associated with CTX are AC, trastuzumab, which belongs to the class of monoclonal antibodies against human epidermal receptor-2, taxanes, tyrosine kinase inhibitors and VEGF inhibitors. Other possibly cardio-toxic drugs are antimetabolites (5-fluorouracil, capecitabine, methotrexate), akylating agents (cyclophosphamide, cisplatin) and proteasome inhibitors (bortezomib).

Anthracyclines

Anthracyclines are antibiotics used for the treatment of many solid and hematologic cancers in both the neoadjuvant (before definitive surgery) and adjuvant (following definitive surgery) setting, as well as in metastatic patients. The mechanisms of action of AC include intercalation into nuclear DNA to impair protein synthesis, production of reactive oxygen species, and inhibition of topoisomerase II to inhibit DNA repair. AC-related CTX is generally irreversible and dose related with myocyte injury [11, 12]. However, recent studies demonstrated that an early detection of the disease and a prompt HF therapy allow for recovery of LVEF [8].

HER2-Targeted Cancer Therapies

Human epidermal growth factor receptor 2 (HER2/ERbB2) can be overexpressed in cancer cells (especially in breast cancer). Trastuzumab, a humanized anti-HER2 monoclonal antibody targets the extracellular domain of this oncoprotein and has been shown to be useful in both the metastatic and the adjuvant setting. HER2/ERbB2 is expressed on myocytes, as well, and plays a protective role in oxidative myocyte homeostasis. The binding of cancer drugs to HER2 receptors may disrupt this cardioprotective pathway, resulting in CTX [13]. Trastuzumab-related CTX is usually considered reversibile and not dose-related. However, since 2007, its reversibility is subject of debate [14, 15].

Microtubular Polymerization Inhibitors, Vascular Endothelial Growth Factor (VEGF) Inhibitors and Tyrosine Kinase Inhibitors

Taxanes (paclitaxel and docetaxel) bind to and inhibit disassembly of microtubules, interrupting cell division. Taxanes interfere with the metabolism and excretion of AC, thus increasing their cardio-toxic effect. VEGF inhibitors exert their action by

inhibiting VEGF-mediated angiogenesis. Small molecule tyrosine kinase inhibitors (sunitinib and sorafenib) are non-selective inhibitors of VEGF receptors. Mechanisms leading to CTX include reduced nitric oxide production in the wall of arterioles, increased endothelin-1 production, and capillary rarefaction resulting in the reduction of effective capillary beds, and VEGF-mediated suppression of nephrin. These agents have been linked to hypertension and ischemia induced by endothelial dysfunction [16].

Risk Factors

Several risk factors for CTX have been identified. Some of them are related to the patient: age at the time of first therapy administered, cardiovascular diseases (coronary artery disease, peripheral vascular disease), hypertension, dyslipidemia, smoking, diabetes, obesity, chronic kidney disease, post-menopausal state. Interestingly, recent studies suggest that genetic variation could modulate the risk of CTX after cancer treatment: in fact genetic polymorphisms may predispose to CTX even at lower AC doses [17].

Others risk factors are related to treatment strategy: cancer therapy combination, bolus administration, dose concentrations, prior treatment with AC, prior or concomitant mediastinal irradiation.

Different risk scores have been proposed. These risk models are based both on cancer therapy and patients' risk factors [18–21]. Currently, however, there is no consensus model. Although many aspects of CTX need to be better elucidated, the severity and the incidence of this complication demand a more accurate prediction of the risk in a preclinical and early clinical stage. The identification of high-risk patients, deserving a more aggressive approach – that may include a closer cardiac monitoring and the initiation of a cardioprotective treatment – would allow the avoidance of restrictions in indications and dose of anticancer agents, and withdrawal the drug when the cardiac damage is already clinically evident, avoiding a reduction in the effectiveness of the anticancer treatment.

Diagnosis

The detection of drug-related CTX is based on regular assessment of cardiac function by LVEF, measured through transthoracic echocardiography or radionuclide multi-gated acquisition (MUGA) [3]. However this approaches has several limitations [22].

In fact, LVEF calculated by conventional echocardiography has low sensitivity for the detection of small changes in left ventricular function, due to several factors. These factors include geometric assumptions of left ventricle, inadequate visualization, image quality, lack of consideration of subtle regional wall motion

abnormalities, and intra- and inter-observer variability of the measurement. Of note, changes in loading conditions are frequent during chemotherapy and may affect the LVEF calculation. On the other hand, MUGA is able to detect only significant changes in cardiac function, and requires exposure to radioactivity.

Magnetic Resonance Imaging is now considered the gold standard for the evaluation of cardiac volumes and function of the left ventricle, but it is limited by low availability and high costs. Finally, endomyocardial biopsy provides histological evidence of CTX but it is not currently used in clinical practice because of its invasiveness.

Over the last few decades, the use of cardiac biomarkers has been investigated as a possible new tool aimed at the early identification, assessment and monitoring of drug-induced CTX [23]. This approach, based on biomarkers assessment is minimally invasive, low-cost, and easily repeatable.

Most of the existing data regarding use of cardiac biomarkers refer to troponins, directly reflective of cardiomyocyte integrity, and natriuretic peptides, released by the heart in response to volume expansion and increased wall stress [24].

Troponins are very useful markers in diagnosis and risk stratification of patients with suspected and proved acute coronary sindrome [25]. Beyond this well-know and recognized setting, troponins have also been evaluated in other clinical contexts, including cardioncology. Increase in troponins are observed in patients receiving both conventional and newer anti-cancer drugs. Many studies have demonstrated that troponin elevation is predictive of cardiac dysfunction, as well as of its severity after anticancer therapy (Table 24.1) [22–38]. In fact, several authors observed a strict relationship between maximal elevation of Tn and the degree of LVEF reduction. According to current guidelines [39], determination of TnI at baseline and periodically, during anticancer therapy is very useful to schedule a close surveillance of cardiac function in selected high-risk patients. On the other hand, high negative predictive value of this marker allows to safely identify patients at low risk, who can be excluded from the programs of long-term cardiac monitoring, leading to a subsequent lowering of costs.

Recently, a new generation of highly sensitive assay has been developed. It is able to detect very low amounts of Tn. This is of particular interest in the cardioncological setting [40]: in most patients, in fact, troponin values are just slightly above the cut-off (Table 24.1) [41–44].

Natriuretic peptides are hormones involved in the maintenance of cardiovascular homeostasis. Clinical utility of natriuretic peptides has been demonstrated, particularly in diagnosis, prognosis and evaluation of treatment efficacy in patients with HF [45]. The role of natriuretic peptides assessment in cardioncological setting has been investigated since the late 1990s [46]. Several authors demonstrated an association between persistent elevations of Brain Natriuretic Peptide (BNP) and reduced cardiac tolerance to anticancer cardio-toxic drugs. Indeed persistently elevated B-type natriuretic peptide levels correlate with echocardiographic parameters of myocardial dysfunction (Table 24.1) [46–51]. To date, few studies are available on the role of natriuretic peptides in patients treated with new therapies (targeted therapy, anti-angiogenic therapies) [49].

Table 24.1 Studies demonstrating biomarkers as predictors of anticancer drug-induced cardiotoxicity

Author	Number of pts	Cancer type	Anti-cancer drugs	Type of biomarkers	Timing of assessment
Lipshultz et al. [26]	15[a]	ALL	AC	TnT	Before CT; 1–3 days after each dose
Cardinale et al. [27]	201	Various	HD CT	TnI	Before, 0–12–24–36–72 hours after CT
Auner et al. [28]	30	Hematological	HD Cycl	TnT	Before, 1–14 days after CT
Cardinale et al. [29]	211	Breast cancer	HD CT	TnI	Before, 0–12–24–36–72 hours after CT
Sandri et al. [30]	179	Various	HD CT	TnI	Before, 0–12–24–36–72 hours after CT
Cardinale et al. [31]	703	Various	HD CT	TnI	Before, 0–12–24–36–72 hours after CT
Lipshultz et al. [32]	158[a]	ALL	AC	TnT	Before, daily for 7 days during induction therapy, end CT
Specchia et al. [33]	79	Hematological	AC	TnI	Before, weekly for 4 times duirmg CT
Kilickap et al. [34]	41	Various	AC	TnT	Before, 3–5 days after 1st and last dose
Lee et al. [35]	86	Hematological	AC	TnI	Before each dose
Schmidinger et al. [36]	74	Renal carcinoma	Sunitinib/ sorafenib	TnI	Before, bimonthly during CT
Cardinale et al. [37]	251	Breast cancer	TRZ	TnI	Before and after each cycle
Morris et al. [38]	95	Breast cancer	AC+taxanes +TRZ/LAP	TnI	Every 2 weeks during CT
Sawaya et al. [41]	43	Breast cancer	AC+taxanes +TRZ	HS-TnI	Before, after 3 and 6 months during CT
Sawaya et al. [42]	81	Breast cancer	AC+taxane +TRZ	HS-TnI	Before, after 3 and 6 months during CT
Ky et al. [43]	78	Breast cancer	AC+taxanes +TRZ	Hs-TnI	Before, after 3 and 6 months during CT

(continued)

Table 24.1 (continued)

Author	Number of pts	Cancer type	Anti-cancer drugs	Type of biomarkers	Timing of assessment
Putt et al. [44]	78	Breast cancer	AC+taxanes +TRZ	Hs-TnI	Before , after 3, 6, 9, 12, 15 months during CT
Suzuki et al. [46]	27	Hematological	AC	BNP	Before and after CT
Soker and Kervancioglu [47]	31[a]	Hematological	Doxorubicin	NT-proBNP	At least 1 month after CT
Sandri et al. [48]	52	Various	HD CT	NT-proBNP	Before, 0–12–24–36–72 hours after CT
Knobloch et al. [49]	48	Breast cancer	TRZ	NT-proBNP	Before and after each cycle
Mavinkurve-Groothuis et al. [50]	122[a]	Various	AC	NT-proBNP	5 years after CT
Romano et al. [51]	71	Breast cancer	AC	NT-proBNP	Before, 24 h after each cycle.

AC anthracycline-containing chemotherapy, *ALL* acute lymphoblastic leukemia, *CT* chemotherapy, *H* hours, *HD* high-dose, *Cycl* cyclophosphamide, *LAP* lapatinib, *TnT* troponin T, *TnI* troponin I, *TRZ* trastuzumab, *NHL* Non-Hodgkin limphoma, *HS* ultra-sensitive, *BNP* Brain natriuretic peptide, *NT-proBNP* N-terminal Brain Natriuretic Peptide
[a]pediatric population

Monitoring

Several groups have published recommendations and consensus statements in the adult cancer population, but evidence-based guidelines for monitoring of CTX are not available yet.

The European Society of Cardiology HF guidelines recommend LVEF evaluation before and after chemotherapy. The initiation of standard therapy for HF and discontinuation of chemotherapy is recommended if LVD occurs [52].

A position statement from the American Society of Echocardiography and European Association of Cardiovascular Imaging recommends baseline evaluation – with LVEF assessment and Tn measurement – for patients undergoing chemotherapy with AC and trastuzumab. Follow-up is recommended at the completion of therapy and 6 months later for patients treated with AC. For patients treated with trastuzumab it is recommended every 3 months during therapy, at completion, and again 6 month later [3].

For patients receiving AC and/or trastuzumab in the adjuvant setting, ESMO Clinical Practice Guidelines recommend serial monitoring of cardiac function at baseline, 3, 6 and 9 months during treatment, and then at 12 and 18 months after the initiation of treatment. Monitoring should be repeated during or following treatment

as clinically indicated. Moreover, the same guidelines suggest measurement of Tn at each cycle of AC-chemotherapy coupled with a prompt treatment with enalapril and a close cardiac monitoring in patients showing an increase in the marker (Fig. 24.4) [39].

At present, however, an agreement regarding the better strategy for cardiac monitoring, both through biomarkers and/or imaging, is still lacking.

Treatment

Although the development of left ventricular dysfunction during or after anticancer therapy is a growing problem, and may compromise both cardiological and oncological outcomes in cancer patients, at present, no clear guidelines for the treatment of this form of cardiomyopathy are available yet. In fact, existing recommendations focus mainly on continuation/withdrawal/resumption of anticancer therapy – according to LVEF values assessed during anticancer drug administration – without suggesting the best pharmacological treatment of cardiac dysfunction. Evidence

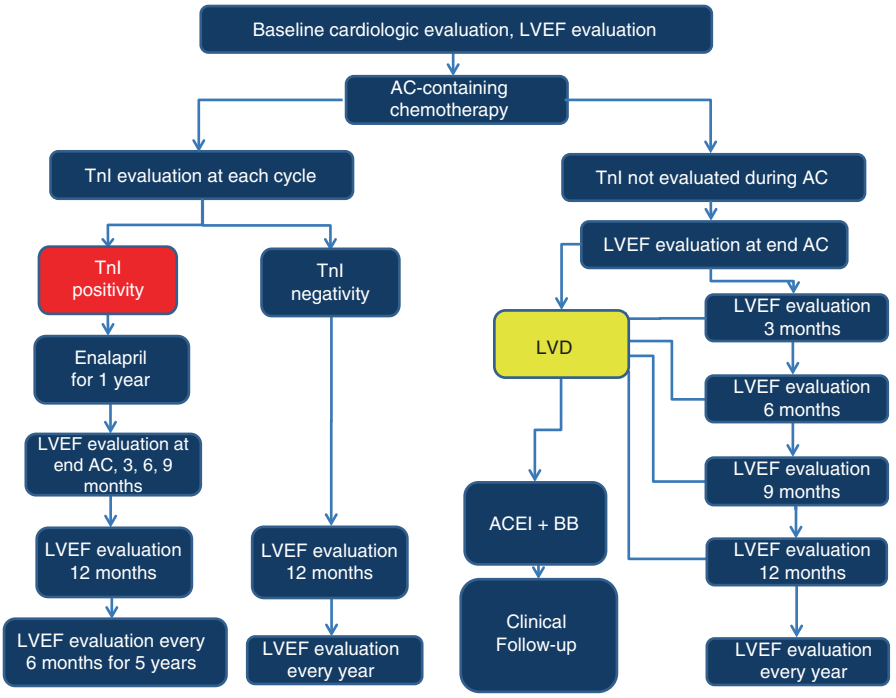

Fig. 24.4 Proposed algorithm for monitoring and management of patients treated with anthracycline-containing chemotherapy according to ESMO guidelines. *LVEF* left ventricular ejection fraction, *AC* anthracycline, *ACEI* angiotensin-converting enzyme inhibitors, *BB* beta-blockers (Modified from Curigliano et al. [39])

based recommendation are still lacking, since these patients have always been excluded from large randomized trials evaluating the effectiveness of modern HF therapy.

A large, recent study aimed at evaluating the quality of cardiac care in cancer patients documented that chemotherapy-related LVD is diagnosed late after primary cancer diagnosis in routine clinical practice, and is inappropriately treated with poor adherence to current guidelines [53].

Most of existing data are related to AC and trastuzumab treatment. Evidence supporting the use of angiotensin-converting enzyme inhibitors (ACEI) and beta-blockers (BB) is limited to case series and retrospective studies from 2010 or older [10, 54–57].

More recently, the effectiveness of ACEI and BB were prospectively assessed. In patients with AC-induced LVD, enalapril combined – when tolerated – with carvedilol was initiated at the time of LVEF impairment detection and was uptitrated to the maximal tolerated dose. The time elapsed from the end of chemotherapy to the start of HF therapy was a crucial variable for the recovery of cardiac function. This suggests that a prompt initiation of HF medications after the detection of asymptomatic or symptomatic AC-induced cardiomyopathy can lead to the achievement of LVEF recovery and events reduction [58], demonstrating that this form of cardiomyopathy is also treatable when therapy is commenced early – i.e. at a still reversible phase (Fig. 24.5).

In a very recent prospective study involving a large, unselected population treated with AC, a close monitoring of LVEF by echocardiography after chemotherapy completion, allowed for early detection of almost all (98 %) cases of CTX during the first 12 months. Prompt treatment with enalapril and BB (carvedilol or

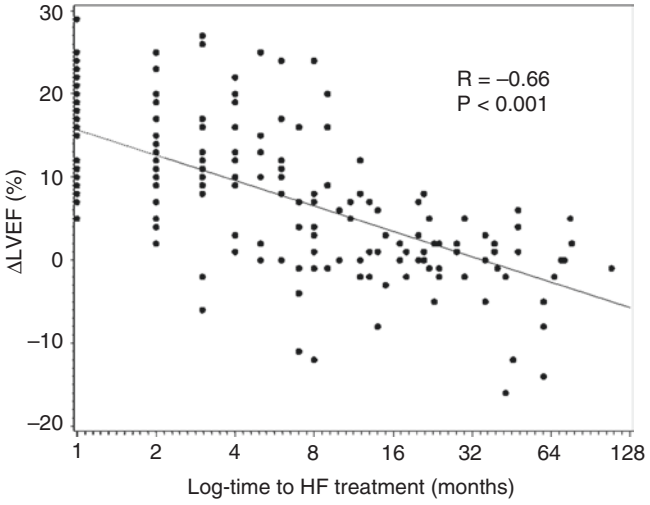

Fig. 24.5 Relationship between maximal left ventricular ejection fraction (LVEF) changes during the follow-up period and log time elapsed from chemotherapy and start of treatment. *HF* heart failure (Modified from Cardinale et al. [58])

bisoprolol), led to the normalization of LVEF in most cases (82 %). However, a small percentage (11 %) of patients who recovered had a full recovery of cardiac function – i.e. a final LVEF equal to baseline, before starting chemotherapy suggesting that strategies aimed at preventing the development of LVD appear more effective than interventions aimed at counteracting an already existing LVD, which can be progressive and irreversible (Fig. 24.6) [8].

Prevention

The best treatment of antineoplastic drug induced CTX is its prevention. In fact, several preventive strategies aimed at reducing risk have been proposed. Prevention may be extended to all patients scheduled for potential cardiotoxic therapy (primary prevention), or could be addressed in selected high-risk patients, showing preclinical signs of CTX, in order to prevent the development of asymptomatic LVD that may progressive led to overt HF (Fig. 24.4).

Primary Prevention

As primary prevention, the evaluation of the cardiovascular risk profile should be considered in order to select the best therapeutic approach for each patient (drug type and administration schedule). Pre-existing cardiovascular risk factors should

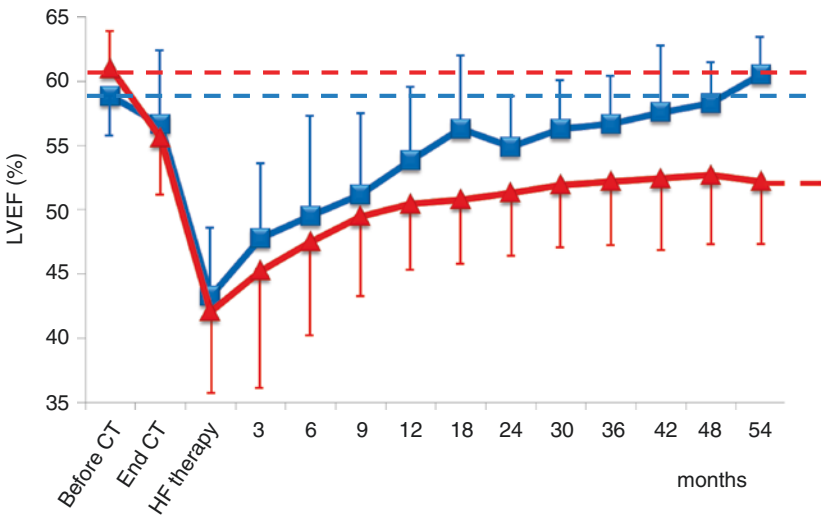

Fig. 24.6 Left ventricular ejection fraction (LVEF) in patients with cardiotoxicity and with partial (triangle) or full (square) recovery with heart failure therapy. *CT* chemotherapy, *HF* heart failure (Modified from Cardinale et al. [8])

be carefully evaluated and possibly corrected, in patients scheduled for anticancer treatment. Control of blood pressure, glucose and cholesterol levels are mandatory. Positive health-promoting behavior, including lifestyle factors (healthy diet, cessation of smoking, weight control, and regular exercise) should be strongly advised by both cardiologists and oncologists. In particular aerobic exercise is considered a promising non-pharmacological strategy to prevent or even treat chemotherapy-induced CTX. In fact, exercise training has been shown to reduce CTX risk in patients undergoing AC therapy and to improve quality of life [59]. Modulation of CTX by exercise training is probably related to different mechanisms: reduction of ROS formation, reduction of expression of pro-apoptotic signaling, and preservation of cardiomyocyte proliferation, triggering the AMP-activated-protein-kinase pathway [60].

Pharmacological strategies aimed at reducing the direct toxic effects of anticancer drugs are suggested. First, limitating the maximal cumulative dose of AC to 450–550 mg/m2. It should be considered, however, that this strategy could interfere with the success of anti-cancer treatment; moreover a variability in tolerance of AC dose exists among different patients. Administration of AC through infusion rather than through bolus is an other strategy to limit direct cardiotoxic effect. Continuous infusion limits peak dose; on the other hand, time of exposure to the drug is prolonged. Recently, AC analogues with a lower cardiotoxic effect have been developed: in particular liposomal formulations selectively target anticancer drugs directly to the tumoral tissue, preventing side effects in healthy tissue [61]. In fact, liposomes cannot escape the vascular space where capillaries have tight junctions, including the heart. So, the tendency to accumulate in myocardial tissue is reduced. Conversely, they exit the circulatory system in areas where capillaries are disrupted by tumor growth, resulting in high concentrations in tumoral tissue.

Another strategy of primary prevention is adding cardioprotectant agents to anticancer drugs. In particular dexrazosane has been shown to be a useful cardioprotective agent against AC. Efficacy of dexrazosane relies on two mechanisms: iron chelation and prevention of the binding of AC to DNA topoisomerase II. Among AC, Doxorubicin, in particular, is a strong inhibitor of Top2: it acts through the formation of a covalent complex. Dexrazoxane changes Top2's configuration and prevents AC from binding to the Top2 complex, as demonstrated by Lyu [62]. However, the doubt that dexrazosane might interfere with the anticancer efficacy of AC, and increase the risk of the occurrence of secondary malignancies, and its myelosuppressor effect [63] justifies its use only in patients in whom CTX risk is expected to be high. In particular, it is recommended as a cardioprotectant only in patients with metastatic breast cancer who have already received >300 mg/m2 of doxorubicin [64]. Other cardio-protective agents like coenzyme Q10, carnitine, nacetylcysteine, the antioxidant vitamins E and C, erythropoietin, the endothelin-1 receptor antagonist bosentan, the lipid-lowering agent probucol, and statins have been investigated. Preliminary evidence shows that these agents may have cardioprotective effects, but their utility in preventing CTX requires further investigation.

Finally, the use of cardiovascular drugs as cardioprotective agents, as a primary prevention strategy in addition to anti-cancer therapy has been investigated. It

should be noted that most of the existing data are related to animal and in-vitro models, and few studies performed in the clinical setting are available. Four groups of agents – BB, angiotensin antagonists, statins, and aldosterone antagonists – have proven to be cardioprotective (Table 24.2) [66, 67, 69, 73–75, 77–80, 83–85].

The first evidence showing cardio-protective effects of BB emerged from an in vitro study [65]. This effect was confirmed in a small randomized study in which prophylactic use of the drug prevented LVD and reduced mortality in a population of AC-treated patients [66]. More recently, a retrospective analysis observed that the continuous use of BB during cancer treatment was associated with a decreased incidence of HF over a 5-year period [67]. Cardioprotective effects of BB are probably related to antioxidant action (carvedilol) [68], or NO-dependent vasodilatory properties (nebivol) [69], rather than beta-blocker activity.

Experimental data have recently demonstrated that the cardiac renin-angiotensin system (RAS) could play a significant role in the development and progression of anti-cancer drug induced CTX, [70] thus suggesting the possible beneficial effect of drugs blocking RAS. Different studies performed on animal models conducted over the last few decades and have shown that administration of ACEI in addition to AC therapy, blunted LVEF decrease and cardiac remodeling, and significantly reduced mortality [71]. Furthermore, other authors demonstrated that doxorubicin cannot induce cardiac injury in angiotensin II type I receptor gene knockout mice [72]. A cardioprotective role of angiotensin receptor blocker (ARB), has been demonstrated, as well: valsartan [73] and telmisartan [74] prevent increases in natriuretic peptides, alterations of echocardiographic parameters and prolongation in QTc interval, in small populations of cancer patients treated with AC. Co-administration of BB and ACEI has also been evaluated. In fact, the efficacy of carvedilol, in combination with enalapril, to prevent chemotherapy induced LVD was explored in the OVERCOME trial [75]. Patients with various hematologic malignancies receiving intensive high-dose chemotherapy were randomized to the intervention group (enalapril plus carvedilol) or the control group (no intervention). After 6 months-follow up, no changes in LVEF were observed in the intervention group, while a significant decrease in the control group was present.

Many studies have shown anti-oxidative and anti-inflammatory pleiotropic effects of statins. Pre-treatment with statins blunted AC-induced toxicity by reducing oxidative stress and enhancing expression of antioxidative enzyme mitochondrial superoxide-dismutase2 in an animal model [76]. Few clinical data are available, at present. In a retrospective observational study, patients treated with AC, who had already received statins for alternative indications, uninterrupted statin use was associated with a marked reduction of the risk for HF and cardiac-related mortality compared with controls [77]. Interesting data are emerging from prospective studies. In a small clinical trial, 40 patients without pre-existing cardiovascular diseases or LVD, undergoing chemotherapy were randomized into statin- or control-group: LVEF was unchanged among patients treated with atorvastatin, while a decrease was observed in controls [78]. Consistently, Chotenimitkhun found [79], in a prospective observational study, that persons already receiving statin therapy experienced less deterioration in echocardiographic parameters, than those individuals not

Table 24.2 Drugs showing cardioprotective effects against anticancer agents-induced left ventricular dysfunction

Author	Number of pts	Cancer type	Anti-cancer drug	Follow-up duration	Intervention drug
Beta-blockers					
Kalay et al. [66]	50	Various	AC	6 months	Carvedilol
Kaya et al. [69]	45	Breast cancer	AC	6 months	Nebivolol
Seicean et al. [67]	318	Breast cancer	AC, TRZ	5 years	Beta-blockers
Pituskin et al. [85]	99	Breast cancer	CT, TRZ	12 months	Bisoprolol
ACEI					
Cardinale et al. [80]	114	Various	HD CT	12 months	Enalapril
Pituskin et al. [85]	99	Breast cancer	CT, TRZ	12 months	Perindopril
ARB					
Nakamae et al. [73]	40	NHL	AC	7 days	Valsartan
Cadeddu et al. [74]	49	Various	AC	18 months	Telmisartan
Gulati et al. [83]	120	Breast cancer	AC,TX,TRZ	1.5–16 months	Candesartan
Aldosterone antagonists					
Akpek et al. [84]	83	Breast cancer	AC	6 months	Spironolactone
ACEI + beta-blockers					
Bosh et al. [75]	90	Hematological	AC	6 months	Enalapril/carvedilol
Statins					
Acar et al. [78]	40	Hematological	AC	6 months	Atorvastatin
Seicean et al. [77]	67	Breast cancer	AC	5 years	Statins
Chotenimitkhun et al. [79]	51	Various	AC	6 months	Atorvastatin/simvastatin

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *HD CT* high-dose chemotherapy, *LVEF* left ventricular ejection fraction, *NHL* non Hodgkin lymphoma, *Tx* taxanes, *TRZ* trastuzumab

receiving statins. Additional prospective randomized control trials are needed to further delineate the effects of statins on clinical outcomes in the cardioncological setting.

Prevention in High-Risk Patients

A different prevention strategy is based on the identification of patients at high CTX risk or with preclinical signs of CTX, in order to start an appropriate treatment to prevent the development of HF. According to this strategy, cardioprotective therapy is limited to a selected and restricted number of patients.

In this scenario early identification of patients with preclinical signs of CTX is a very relevant tool. The usefulness of serological biomarkers of myocardial damage, and Tn in particular, in diagnosis and risk stratification in the cardioncological setting has been widely demonstrated. Recently, the importance of Tn in selecting patients for prophylactic cardioprotective therapy has emerged. In particular the usefulness of Tn in this context was investigated in a randomized trial enrolling patients treated with high-dose AC [80], in whom serial measurement of Tn and serial assessment of LVEF was performed. Patients showing an early increase of TnI were randomized either to receive enalapril (ACEI group) or not (Control group). Patients receiving enalapril did not experience a change in LVEF during the follow-up period; moreover a lower incidence of cardiac events was observed. On the other hand, patients who increased TnI and were not receiving enalapril, experienced a reduction in LVEF and a worsening of echocardiographic parameters. Similar results were observed in patients treated with developing molecular targeted therapies [81]: among patients developing an increase of Tn values during treatment with new anti-VEGF monoclonal inhibitors and tyrosine kinase inhibitors, normalization of TnI values was obtained with BB and aspirin administration.

Conclusion

Given the survival improvement in anticancer therapy treated patients, early recognition of CTX is of pivotal importance. Patients with cancer, with either preexisting cardiac disease or increased cardiac risk, require individualized risk stratification strategies. Patients who develop cardiovascular complications during or after anticancer therapy, and, in particular, those developing LVD often require modifications or withdrawal of life-saving cancer therapies, with profound implications on clinical outcomes.

In this complex scenario, close monitoring of patients undergoing anticancer drugs is now recommended in order to detect CTX early: evaluation of Tn levels and assessment of myocardial deformation indexes, in addition to LVEF are useful tools for the early identification of preclinical signs of CTX. This strategy, aimed at

preventing the development of LVD appears strategically more effective than interventions aimed at counteracting existent LVD or overt HF, which can be progressive and irreversible in most cases.

Future Directions

Ongoing trials are exploring the usefulness of cardiovascular drugs as cardioprotective agents. The International Cardioncology Society (ICOS)-ONE trial is the only randomized study to compare a primary prevention approach with prevention in selected high-risk patients, in patients treated with AC. The primary objective of the ongoing trial is to assess whether enalapril started concomitantly with AC therapy can prevent CTX more effectively than when enalapril is prescribed to selected patients showing an increase in Tn. (NCT01968200). The SAFE (Cardiotoxicity Prevention in Breast Cancer Patients Treated with AC and/or trastuzumab) trial is assessing whether the use of ramipril or bisoprolol, or their combination can prevent the development of HF in women receiving neoadjuvant or adjuvant AC-containing chemotherapy, with or without trastuzumab.

Early identification of preclinical CTX could be provided by echocardiographic techniques, in particular tissue Doppler analysis and strain rate imaging. A recent study observed that early subclinical changes in cardiac function, as assessed by strain rate imaging during and after chemotherapy preceded a decrease in LVEF [82]. According to a recent consensus statement peak systolic global longitudinal strain (GLS) would appear to be an accurate measure. In particular a 10–15 % early decrease in GLS by speckle-tracking echocardiography (STE) during therapy seems to be the most useful parameter for the prediction of CTX, defined as a drop in LVEF or HF onset [3]. However, larger, randomized trials are needed to better evaluate this approach. An ongoing trial is assessing usefulness of carvedilol for the prevention of CTX in patients showing a decrease in GLS (NCT02177175).

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Chapter 25
Iron Deficiency in Heart Failure

Ewa A. Jankowska, Marcin Drozd, and Piotr Ponikowski

Background

Iron deficiency (ID) represents the most prevalent nutritional deficiency worldwide, with an estimated population of two billion affected globally [1, 2]. Its prevalence is particularly high in women, children and elderly, patients with chronic disorders, subjects with low economic status and developed countries [2–6]. From the population perspective, ID has several unfavourable consequences, including higher health and economic costs, poor pregnancy outcome, impaired school performance, decreased productivity, high morbidity and mortality [2].

ID itself should be distinguished from ID-related anaemia (IDA). Although untreated ID can result in anaemia as a consequence of more advanced and longer lasting ID, ID itself reveals several clinical unfavourable effects. This co-morbidity is particularly common in elderly patients with chronic diseases. The majority of evidence, including clinical trials in the context of ID correction relate to patients with chronic kidney disease (CKD) [7–9], but in recent decades heart failure (HF) has been identified as a disease which is commonly accompanied by ID, both with and without anaemia [10, 11].

Importance of Iron in Physiology

Iron is critical for optimal functioning of both haematopoietic and non-haematopoietic cells, mainly for the maintenance of cellular energy metabolism as a component of respiratory chain proteins in mitochondria and other enzymes crucial for these

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M. Dorobanțu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_25

energetic reactions [12, 13]. Hence, it is not surprising that iron is particularly needed for tissues with high energy demand (such as: myocardium, skeletal muscles) and high mitogenic activity (such as: haematopoietic cells of all lines). Contrary to traditional approach, the consequences of ID in patients with HF are attributable not only to ID-related anaemia, immunodeficiency, coagulopathy, but are also related with abnormal functioning of skeletal muscles and myocardium [13].

Pathogenesis of Iron Deficiency in Heart Failure

Pathogenesis of ID in HF is remains enigmatic.

As in general, iron is not actively excreted from the body, the pathogenesis of ID is associated with reduced iron intake, increased iron losses and the abnormal iron distribution to these body compartments where it is not available for body metabolism. There is scarce evidence that ID can be due to inadequate dietary iron intake [14, 15], low gastrointestinal bioavailability of iron (also as a consequence of intestinal interstitial oedema, the use of drugs lowering gastric pH such as omeprazole or H2 receptor-antagonists and food ingestion reducing iron absorption such as calcium, tannins, oxalates, phytate, phosphates, antiacids) [16, 17]. Iron loss may be increased in the course of gastrointestinal disorders (peptic ulcer, esophagitis, gastritis, duodenitis), menstrual blood loss, excessive blood sampling, to name but a few. Importantly, although anticipated, all aforementioned pathomechanisms have not been confirmed to be present in patients with HF, hence still remain hypothetical.

It has been hypothesized that the pathogenesis of ID in the course of HF resembles the pathomechanisms seen in the course of chronic kidney disease (CKD). Patients with CKD demonstrate mainly the so-called functional ID, namely due to inflammation and related high circulating hepcidin iron is present in the body but trapped in reticuloendothelial cells and therefore not available for metabolic needs [13, 18–21]. Importantly, until now, the links between inflammation and depleted iron have not been demonstrated in patients with HF. Moreover, patients with HF both in chronic [22] and acute settings [23] demonstrate extremely low (but not high) circulating hepcidin, which suggests that ID seen in the course HF is the consequence of depleted iron stores in the body (the so-called absolute ID).

Definition of Iron Deficiency in Heart Failure

According to haematologists, bone-marrow aspiration with the assessment of iron stores in bone marrow is the ‘gold standard’ method to assess ID [24–28], but this examination is invasive, not widely accessible and unsuitable to assess ID in a daily clinical practice, particularly in the context of cardiovascular diseases. Therefore, the biomarker-related approach is more suitable here for diagnosis of ID in patients

with HF. Specific biomarkers reflecting stored and utilized iron (described below) are recommended for the assessment of iron status in these patients.

Circulating ferritin is a reliable surrogate of iron stored predominantly in hepatocytes and reticuloendothelial cells. Moreover, ferritin belongs to acute phase proteins and its production is increased due to concomitant inflammation [27, 29]. Therefore, relatively higher values of serum ferritin (namely <100 μg/L) indicate the presence of absolute ID in HF. The lower serum ferritin, the more depleted iron stores in the body. It should be emphasised that in a general population, absolute ID is diagnosed when serum ferritin is <30 μg/L [27, 28, 30] or even when serum ferritin is <12–15 μg/L according to some authors [31].

Another type of ID reflects the situation when, despite adequate stores, iron is restricted for metabolic needs, and is called functional (relative) ID, and is associated with higher levels of ferritin (between 100 and 299 μg/L) with low transferrin saturation (Tsat) (the latter indicating the reduced pool of utilized iron). Tsat is the percentage of transferrin which binds iron, and is calculated as a ratio of serum iron and TIBC × 100 % (TIBC, total iron binding capacity—by transferrin) [13].

It should be emphasised that neither serum iron nor serum transferrin alone are reliable for the assessment of iron status in patients with HF.

The 2016 ESC/HFA guidelines on HF management emphasize the need to screen all patients with HF for the presence of ID based on serum ferritin and Tsat, regardless of haemoglobin level in order to detect reversible/treatable causes of HF and co-morbidities interfering with HF [32]. The following definition of ID is recommended to be used by the 2016 ESC/HFA guidelines: serum ferritin <100 μg/L, or ferritin between 100 and 299 μg/L and Tsat <20 %) [32]. This definition has been used in CKD [29] and also in major clinical trials in HF with intravenous iron supplementation [10, 11].

There are also attempts to apply novel iron biomarkers in order to improve the accuracy of the definition of ID in the clinical setting of HF. Recently, we have proposed a new pathophysiological definition of ID based on the combined assessment of low serum hepcidin (reflecting depleted iron stores more accurately than ferritin) and high serum soluble transferrin receptor (sTfR) (reflecting depleted iron within metabolizing cells) [22, 23]. TfR is the membrane entrance pathway for iron import into all cells; it is upregulated when intracellular metabolic needs for iron are not met in order to facilitate the iron entrance to the cells and later shed in excess to the circulation [23].

Prevalence and Clinical Consequences of Iron Deficiency in Heart Failure

ID is a prevalent co-morbidity in patients with HF. When applying the aforementioned definition of ID, the prevalence of ID in a general population ranges between 37 and 74 % [12, 23, 33–42]. The prevalence of ID is higher in anaemic vs. non-anaemic patients: 43–78 % [12, 23, 33–35, 38, 39] vs. 15–65 % [12, 23, 33–35, 38]

and in decompensated vs. stable ones: 65–74 % [23, 42, 43] vs. 33–65 % [12, 33–41, 44]. Also, the following characteristics can be considered as factors of higher risk for ID in the population of patients with HF: female gender [33, 35, 43], advanced NYHA class [33, 35], high plasma N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) [33, 35] high serum high-sensitivity C-reactive protein (hsCRP) [33].

So far, only Nanas et al. investigated the prevalence of ID based on the assessment of iron stores in bone marrow, and reported ID in anaemic HF patients to be approx. 73 % [45].

ID is related with impaired aerobic performance expressed as lower peak oxygen consumption VO2 (peak VO2), higher ventilatory response to exercise (VE-VCO2 slope) in patients with HFrEF and HFpEF [12, 41, 46], reduced submaximal exercise capacity as expressed as a shorter 6MWT distance in patients with HFrEF and HFpEF [41]. Importantly, we have demonstrated that the impact of ID on both peak VO2 and VE-VCO2 slope in patients with stable HFrEF is independent of and much stronger than the effect of anaemia on these parameters [46].

ID is also accompanied by poor health related quality of life (HRQoL) expressed for example by Minnesota Living with Heart Failure Questionnaire in patients with HF (MLWHFQ) [36, 47].

In a cohort of patients with HF (including both HFpEF and HFrEF), ID appeared to be an independent predictor of all-cause mortality, regardless of the presence of anaemia [12, 23, 33–35, 39, 48]. Moreover among these patients, ID was associated with an increased risk of composite endpoint: mortality and nonfatal cardiovascular events (hospitalization for congestive HF, acute coronary syndrome, severe arrhythmia or stroke) [38] as well as death or heart transplantation [33].

Iron Supplementation in Heart Failure

The majority of evidence on oral iron supplementation comes from studies in patients with CKD and IDA. In patients with IDA and non-dialysis CKD randomized studies showed the inferiority of oral versus IV iron as slower and less efficient stimulation of erythropoiesis [49–55], and also more adverse events with oral iron in comparison to IV iron have been shown [54]. Similar results were found in patients with IDA and juvenile chronic arthritis [49], postpartum IDA [56, 57], and inflammatory bowel disease [58]. There is no prospective study investigating safety and efficacy of oral iron supplementation in patients with HF. Recently, only Niehaus et al. [59] in a retrospective observational study demonstrated that oral iron supplemented in patients with HFrEF (LVEF <45 %) and ID-related anaemia (haemoglobin level between 9.7 and 12.0 g/dL) over 164 days resulted in a moderate increase in serum ferritin, Tsat and haemoglobin level, but no clinical benefits were reported. It remains unclear if oral iron supplementation could be an option for patients with HF, as after over 5 month of oral treatment serum ferritin remained still far below normal values.

It should be noted that the previously used parenteral iron preparations were toxic and administered as an iron oxyhydroxide complex [60, 61], which generated a lot of non-transferrin bound iron, induced oxidative stress and led to numerous adverse events, such as: hypotension, nausea, vomiting, abdominal and lower back pain, peripheral oedema and a metallic taste [62] [21]. These side-effects have been circumvented due to the introduction of compounds containing iron in a core surrounded by a carbohydrate shell, which eliminated the vast majority of adverse reactions and side effects [63]. Until now, only five new parental formulations have been used in the field of HF. Iron sucrose (ISC) was investigated in seven studies (136 treated patients in total) [64–70]. Iron dextran, iron isomaltose and ferric gluconate were used only in small single-centre non-comparative studies with only 40, 20, 13 treated patients respectively [71–74].

Ferric carboxymaltose (FCM) was used in 2 multi-centre, randomized, placebo-controlled, double-blind trials (454 treated patients in total) [11]. In the FAIR-HF study, the Ganzoni formula [75] was used to calculate the required cumulative FCM dose, whereby the cumulative iron deficit [mg] = bodyweight [kg] × (target haemoglobin – actual haemoglobin) [g/dL] × 2.4 + iron storage depot [mg]. In patients weighing <35 and ±35 kg, the target haemoglobin should be 13 and 15 g/dL, respectively, and the iron storage depot should be 15 mg/kg and 500 mg, respectively. The calculated cumulative iron dose should be rounded down to the nearest 100 mg in patients weighing ≤66 kg and up to the nearest 100 mg in those weighing >66 kg [10, 76]. The dosing frequency was 200 mg of FCM weekly until iron repletion was achieved (the correction phase) and then every 4 weeks during the maintenance phase, which started at week 8 or week 12, depending on the required iron-repletion dose. In the CONFIRM-HF study, FCM was administered according to a fixed scheme based on the subject's weight and haemoglobin value at screening and administered at weeks 0 and 6. Further FCM doses could be administered at weeks 12, 24, and 36 if ID was still present, but importantly more than 75 % of treated patients required a maximum of 2 doses [11]. This new dosage pattern appeared to be convergent with a total iron dose administered in all, anaemic and non-anaemic patients, in the FAIR-HF study [77].

The effects of FCM in patients with HF have already been tested in two major clinical trials [76, 78]. In the FAIR-HF study, 304 ambulatory patients with symptomatic HF with LVEF ≤40 % (NYHA II) or ≤45 % (NYHA III), with ID (serum ferritin <100 ng/mL or ferritin 100–300 ng/mL when Tsat <20 %), and haemoglobin between 9.5 and 13.5 g/dL were randomized in a 2:1 ratio to receive FCM 200 mg iron i.v. or saline i.v. weekly until iron repletion (correction phase), then monthly until week 24 (maintenance phase) (based on the Ganzoni formula described above). Primary endpoints were self-reported PGA at week 24 and NYHA class at week 24, adjusted for baseline NYHA class [76], both of which improved in the FCM arm as compared to a saline arm. The improvement in aforementioned characteristics were seen in both anaemic and non-anaemic patients, even though the clinical improvement in non-anaemic patients was not accompanied by an increase in haemoglobin level [77]. The treatment with FCM resulted also in an increase in the distance of the 6-min walk test and quality-of-life assessments. The rates of death, adverse events, and serious adverse events were similar in the two study groups [10].

In the CONFIRM-HF study, ambulatory patients with HF in NYHA class II-III with LVEF ≤45 %, BNP >100 pg/mL or NT-proBNP >400 pg/mL, with ID (defined as in the FAIR-HF study) and haemoglobin level <15 g/dL were randomized 1:1 to treatment with FCM or placebo for 52 weeks (doses as described above). FCM was administered in a single dose as an undiluted bolus injection of up to 1000 mg at week 0 and 6 up to iron repletion. Further FCM doses were administered at weeks 12, 24, and 36 if ID was still present [78]. Treatment with FCM increased the 6MWT distance at week 24 (primary endpoint). The treatment effect of FCM was consistent in all clinical subgroups and was sustained to week 52. Throughout the study, an improvement in NYHA class, PGA, QoL, and Fatigue Score in patients treated with FCM was demonstrated with a statistical significance confirmed from week 24 onwards. Treatment with FCM was associated with a reduction in the risk of hospitalizations for worsening HF at week 52. The number of deaths and adverse events were similar in both study groups [11].

In other small studies with intravenous iron in patients with HFrEF also the following beneficial effects of this therapy were found regarding echocardiography parameters (an increase in LVEF, a reduction in LVSD, LVDD, LVPW, IVS thickness, left ventricular mass index; left ventricular end systolic volume, an improvement in S′, E', a decline in E/E', a reduction in peak systolic strain rate) [64–67, 71] and some biomarkers (a reduction in plasma NT-proBNP and CRP [65].

Recently, few meta-analyses have been published based on studies with intravenous iron supplementation performed in patients with HF and ID [79–83]. The most recent one included five trials in patients with systolic HF (LVEF of ≤45 %) (509 patients received intravenous iron therapy (majority with FCM) compared with 342 controls), with at least a single-blind randomization without a concomitant therapy with erythropoiesis-stimulating agents (ESAs) [83]. It has been shown that intravenous iron therapy in patients with systolic HF and ID reduced the risk of the combined endpoint of all-cause death or cardiovascular hospitalization, the risk of the combined endpoint of cardiovascular death or hospitalization for worsening HF, and the risk of HF hospitalization, but without an effect on either all-cause or cardiovascular mortality (which may be due to a low number of reported and relatively short follow-up) [83]. Also, this intervention resulted in an improvement in exercise capacity (an increase in 6MWT distance), an alleviation of HF symptoms (a reduction in NYHA class) and an improvement in HRQoL as assessed using not only questionnaires specific for HF (KCCQ score and MLHFQ score) but also those reflecting patients' general medical condition (EQ-5D score and PGA) [83]. In a subgroup of anaemic subjects, intravenous iron therapy reduced the risk of combined all-cause death or cardiovascular hospitalization, combined cardiovascular death or hospitalization for worsening HF, and the risk of HF hospitalization, whereas in the subgroup of non-anaemics, this intervention reduced the risk of combined all-cause death or cardiovascular hospitalization, and borderline reduce the risk of HF hospitalization [83].

All the aforementioned evidence resulted in the formulation of the following recommendation regarding the administration of intravenous iron in patients with HF in 2016 ESC/HFA guidelines on HF management [32]: "Intravenous FCM

should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 μg/L, or ferritin between 100 and 299 μg/L and transferrin saturation <20 %) in order to alleviate HF symptoms and improve exercise capacity and quality of life (Class of recommendations IIa, Level of evidence A)".

Future Directions

Although ID is prevalent in HF, it origin still remains unknown. Moreover, evidence on the prevalence along with clinical and prognostic consequences of ID in patients with HFmrEF/HFpEF is scarce. Although it has been demonstrated that intravenous iron supplementation in iron deficient patients with HFrEF improves exercise capacity and quality of life and alleviates HF symptoms, it has not been shown if this therapy could also improve clinical outcomes (reducing the risk of HF hospitalizations, cardiovascular hospitalizations, cardiovascular and/or all-cause deaths). The clinical importance of oral iron therapy in patients with HF remains equivocal. Also, the effects of pharmacological correction of IF in patients with both acute HF and patients with HFmrEF/HFpEF have not been tested yet.

Acknowledgement: The preparation of the manuscript was supported by the National Science Centre (Poland) grant allocated on the basis of the decision number DEC-2012/05/E/NZ5/00590.

Conflict of Interest: Wroclaw Medical University received an unrestricted grant from Vifor Pharma. E.A.J. reports grants and personal fees from Vifor Pharma and personal fees from Fresenius. M.D. reports personal fees from Fresenius. P.P. reports personal fees from Vifor Pharma and AMGEN.

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Chapter 26
The Kidney and Electrolytes Imbalances in Heart Failure

Jozine M. ter Maaten and Adriaan A. Voors

Introduction

Heart and kidney are closely related in heart failure and the relationship between these two organs has been well described. Despite the fact that this relation was already mentioned in the Lancet in 1868, the paramount of studies and knowledge regarding cardiorenal interaction originates from the first decade of the twenty-first century (Fig. 26.1) [11]. Traditionally a decline in ejection fraction was considered the main determinant of poor outcome in heart failure. This shifted when a landmark trial found that impaired renal function was a stronger predictor of mortality than impaired cardiac function (ejection fraction and New York Heart Association class) in patients with chronic heart failure [28]. The strong independent prognostic value of renal dysfunction in patients with heart failure has been confirmed in a great number of further studies. In this chapter the incidence, underlying pathophysiology of cardiorenal interaction, electrolyte imbalances and consequences for treatment will be discussed.

Epidemiology

Both the incidence of heart failure and chronic kidney disease have been steadily increasing due to aging and better treatment. Also, heart failure and chronic kidney disease often co-exist. In a large meta-analysis including 1,076,104 heart failure patients, chronic kidney disease was present in 32 % of these patients [13]. The incidence of chronic kidney disease in patients that present with acute heart failure is

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M. Dorobanțu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_26

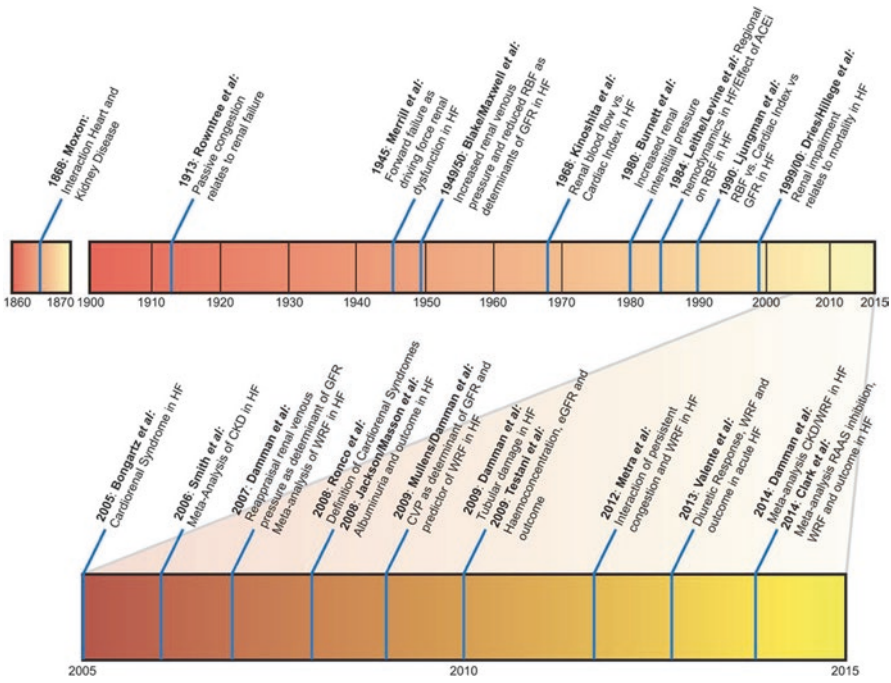

Fig. 26.1 History of research in cardiorenal interaction. Reprinted from Oxford University Press. Damman and Testani [11]

even greater than in patients with chronic heart failure. Overall, in almost 50 % of patients with heart failure, some degree of renal dysfunction is present. Yet, renal dysfunction is not only common in patients with established heart failure, it has also been identified as a risk factor for new onset heart failure. In a large community cohort renal dysfunction was associated with new onset heart failure with a preserved ejection fraction (HFpEF) [70]. Additional studies identified renal dysfunction as both a predictor for HFpEF and heart failure with a reduced ejection fraction (HFrEF).

Renal function is not static over time and is for instance influenced by heart failure therapies and disease progression. Therefore worsening of renal function, most often defined as an increase in creatinine ≥0.3 mg/dL, is also of interest in heart failure patients. Of 49,890 patients included in the previously mentioned meta-analysis, 23 % had worsening renal function over time [13]. This percentage was similar in patients with acute heart failure versus chronic heart failure.

Pathophysiology

Normal Physiology of the Kidney

The kidney of a healthy individual consist of approximately one million nephrons and collecting ducts. A nephron is the functional unit of the kidney and contains the glomerulus which is connected to the collecting duct of a tubule. The glomerulus

exists of a network of capillaries that have a high hydrostatic pressure. The total of glomerular capillaries and epithelial cells is termed Bowman's capsule. The connecting tubule has several segments, namely proximal, Henle's loop, and distal. These tubules are merged in collecting ducts that empty in the bladder. The most important function of the kidney is maintaining a stable fluid and electrolyte balance [26].

The rate at which different substances are excreted in the urine results from three renal processes, glomerular filtration, reabsorption and secretion, respectively. The urine excretion rate is the resultant of the filtration rate minus the reabsorption rate plus the secretion rate. The total glomerular filtration is determined by multiple factors, such as the number of functional nephrons, the balance of hydrostatic and colloid osmotic forces and the product of the permeability and filtering surface area of the capillaries [26]. In a healthy adult the average glomerular filtration rate is approximately 125 ml/min. Twenty percent of the plasma flowing through the kidney is filtered through the glomerular capillaries. Selective reabsorption from tubular fluid to blood and selective secretion from peritubular capillary blood to tubular fluid both occur in the tubules. Thus the kidney regulates fluid and electrolyte (sodium) balance highly selectively.

Intrinsic feedback mechanisms keep the glomerular filtration rate relatively stable, despite changes in blood pressure [26]. This autoregulation maintains renal blood flow at a constant rate by affecting arteriolar flow through the glomerulus. Additionally, through tubuloglomerular feedback sodium chloride concentration in the distal tubule is sensed by macula densa cells. This mechanisms protects the kidney against hyperfiltration, as an increase in sodium chloride concentration in the ascending loop of Henle stimulates vasoconstriction of the afferent arteriole, as well as reduces renin release from the arterioles [52]. Renin stimulates the formation of angiotensin I, which has to be converted to angiotensin II. Angiotensin II constricts the efferent arterioles and as such restores glomerular filtration rate in a setting of low sodium chloride concentration.

The Kidney in Heart Failure

Several mechanisms in heart failure contribute to the development or maintenance of concomitant renal failure. First, decreased cardiac output results in decreased organ perfusion. This cardiac output can be the result of either decreased systolic or diastolic function, or both. In patients with chronic heart failure changes in cardiac output of around 25 % have been shown to result in a reduction of renal blood flow of more than 50 % [20]. Based on the dependence of the glomerular filtration rate on renal blood flow, this would be expected to result in a decrease in glomerular filtration rate. However because of the above described autoregulation the kidney is able to maintain a stable glomerular filtration rate, despite changes in renal blood flow. This adaptive mechanism has been shown in several studies, in which despite a decline in renal blood flow, glomerular filtration rate remained stable. In patients with heart failure this autoregulatory mechanism is however impaired by treatment with angiotensin-converting enzyme inhibitor or angiotensin receptor blockers.

These medications block the autoregulatory function of the kidney, resulting in a more linear relation between renal blood flow and glomerular filtration rate. In retrospective analysis in patients with acute heart failure however no significant association was found between renal function and cardiac output. Therefore cardiac output may not be the primary driver of renal dysfunction in acute heart failure.

Another consequence of impaired cardiac output is the initiation of several counter regulatory mechanisms that result in sodium and water retention by the kidney. This ultimately gives rise to a vicious circle of decreased organ perfusion, venous pressure and congestion. Experimental animal studies have demonstrated that an isolated increase in central venous pressure results in direct impairment of renal function. In patients with chronic heart failure increased central venous pressure was associated with a decrease in glomerular filtration rate [17, 19]. In patients with acute heart failure higher central venous pressure was associated with an increased risk of worsening renal function [42]. Additionally increased abdominal pressure may also lead to impaired renal function [43]. The mechanism of increased central venous and abdominal pressures leading to renal dysfunction can be explained as follows. Increased central venous pressure leads to increased renal pressure. This in turn increases renal interstitial pressure resulting in tubular collapse and negligible pressure gradients over the glomerulus causing a halt to passive filtration. Also, both a reduction in cardiac output and increased central venous pressure cause increased neurohormonal activation through activation of the renin-angiotensin-aldosterone system and sympathetic nervous system activation [52]. Angiotensin II release leads to both afferent and efferent vasoconstriction and stimulates sodium retention in the proximal tubule. Additionally, it stimulates release of aldosterone which further increases sodium reabsorption in the collecting duct. Adenosine is released in response to increased renal workload and high sodium concentration in the distal tubule. Release of adenosine further reduces renal blood flow and activates tubuloglomerular feedback which results in a reduction in glomerular filtration rate. As most of these mechanisms are maladaptive in the setting of heart failure, all of these further contribute to sodium reabsorption and renal insufficiency [28]. Some of the factors may be reversible and in these cases glomerular filtration rate may be restored. However, in contrast lost nephrons cannot be developed or restored.

Renal function encapsulates more than just glomerular function, and tubular function is also of great importance as this plays a major role in sodium regulation and diuresis. The proximal tubule reabsorbs up to 80 % of the filtered electrolytes. The loop of Henle also reabsorbs several electrolytes and is responsible for the kidney's ability to generate a concentrated or diluted urine. Finally, the distal tubule consists of three segments, the distal convoluted tubule, the connecting tubule and the collecting duct. In heart failure, tubular injury is associated with poor clinical outcome [14, 16]. However, compared to patients with (acute) kidney injury, elevations in tubular injury markers are only moderate. This might suggest that structural tubular injury is relatively uncommon in heart failure, and rather external factors such as congestion, renin-angiotensin-aldosterone system activation, insufficient oxygen availability and intrinsic adaptations might be among the causative factors in heart failure.

Classification of Heart Failure and Renal Failure

The interaction between heart and kidney is often termed 'cardiorenal syndrome' [51]. As this is not a static or one way process, a cardiorenal classification system has been proposed (Table 26.1). Briefly, dysfunction of the heart or kidney may lead to deregulation of the other. Of main interest in patients with heart failure are cardiorenal interaction type 1 and 2. However, chronic kidney disease, or worsening renal function may also lead to a deterioration or onset of cardiac symptoms.

Worsening Renal Function

Renal function can be dynamic and may change over time. In nephrology, an acute worsening of renal function, or acute kidney is usually diagnosed using the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage renal disease), or KDIGO (Kidney Disease: Improving Global Outcomes) criteria. These criteria incorporate both an increase in serum creatinine and changes in urine output, over a short (pre-specified) period of time. In heart failure research the most commonly used definitions for worsening renal function only takes changes in creatinine into account. This is usually defined as an increase in serum creatinine >0.3 mg/dL and/or a 25 % increase, over varying time periods. Several studies have shown that worsening of renal function is associated with an increased risk of all-cause mortality [14, 18]. Recently, it has however been suggested that not all worsening renal function is similarly detrimental [11]. In patients with kidney disease an increase in creatinine is a direct consequence of the disease, while in heart failure these changes are more often indirect. If during treatment the clinical status of a heart failure patients improves while its creatinine level rises; the subsequent worsening renal function in this setting might be beneficial. This is true during treatment with

Table 26.1 Different subtypes of cardiorenal interaction

Type	Description
Cardiorenal interaction type 1 (acute)	Rapid worsening of cardiac function leads to acute kidney injury
Cardiorenal interaction type 2 (chronic)	Chronic abnormalities in cardiac function cause progressive kidney disease
Cardiorenal interaction type 3 (acute renocardiac interaction)	Abrupt and primary worsening of kidney function leads to acute cardiac dysfunction
Cardiorenal interaction type 4 (chronic renocardiac interaction)	Chronic kidney disease contributes to decreased cardiac function, ventricular hypertrophy, diastolic dysfunction and/or increased risk of cardiovascular events
Cardiorenal interaction type 5 (secondary)	Both cardiac and renal dysfunction due to acute or chronic systemic disorders

intravenous diuretics in acute heart failure patients and similarly during initiation of renin-angiotensin-aldosterone system-blocking therapies despite an initial worsening of renal function, receiving this treatment was still associated with improved outcome. Therefore increases in serum creatinine that occur in parallel with improvement in symptoms may be considered as pseudo-worsening renal function. This important distinction should trigger the clinician to re-evaluate changes in creatinine based on the patient's response to therapy, and will prevent withdrawal of necessary and potentially life-saving therapies.

Markers of Renal Function

Renal function can be assessed using several markers and metrics, that assess different aspects of the kidney, such as glomerular or tubular function (Fig. 26.2) [60].

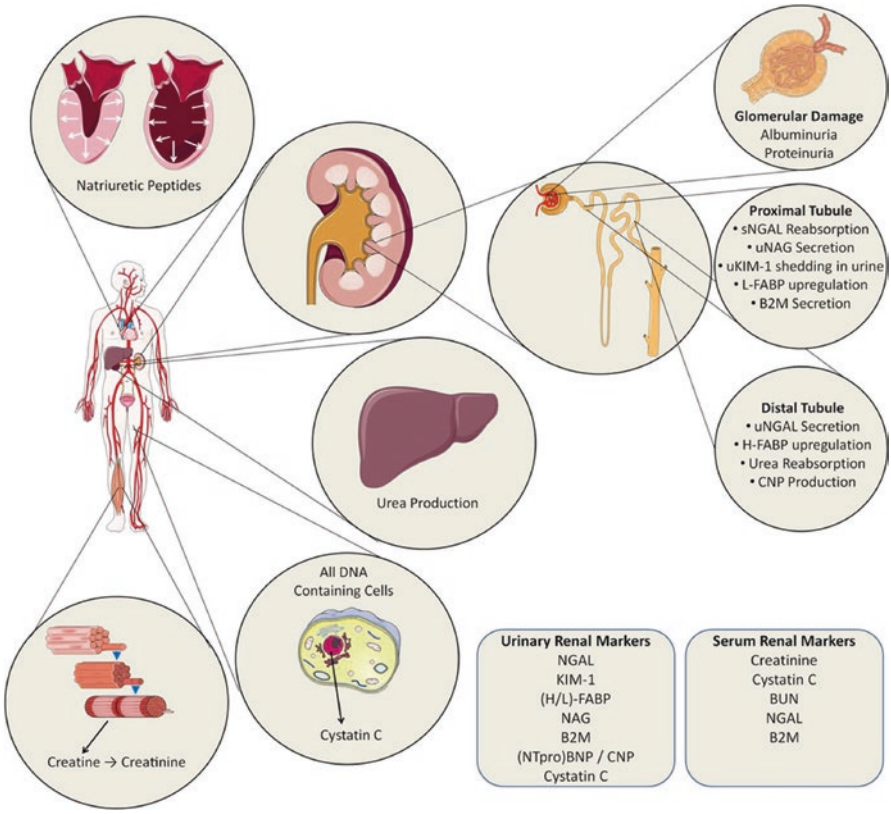

Fig. 26.2 Schematic overview of sources of renal biomarkers. Reprinted from Oxford University Press. van Veldhuisen et al. [60]

Glomerular Filtration Rate and Creatinine

Glomerular filtration rate, the rate at which substances are filtered by the kidney, is the most commonly used method to assess renal function. If a substance is freely filtered and is not reabsorbed or secreted by the tubules then the glomerular filtration rate is equal to the concentration of the substance in the urine multiplied by the urine volume, divided by the concentration of the substance in the plasma. The golden standard of measuring glomerular filtration rate using radioactive labeled markers like iothalamate or inulin clearance, is not regularly performed is it is time-consuming, patient-unfriendly and expensive. Therefore simpler methods using serum creatinine have been developed to estimate glomerular filtration rate. Serum creatinine is a reflection of the regular break down of skeletal muscles. Due to the fact that creatinine undergoes some active tubular secretion after being freely filtered by the glomerulus, it provides a slightly imperfect (over) estimation of glomerular filtration rate. Also other factors such as body composition, age, and gender influence the relation between creatinine and glomerular filtration rate. Therefore several methods have been developed to estimate glomerular filtration rate. The most commonly used creatinine-based equation is the simplified Modification of Diet in Renal Disease (sMDRD) [37, 38]. The sMDRD includes four variables, namely age, gender, race and serum creatinine. The full MDRD equation, that also takes into account blood urea nitrogen and albumin, outperforms the sMDRD, yet as this requires more variables it is less commonly used. Most recently the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was introduced, which includes age, race, serum creatinine, and has an option to also include cystatin C [36]. A small study comparing these glomerular filtration rate equations to the golden standard measurement in chronic heart failure patients showed that the CKD-EPI equation more accurately estimates glomerular filtration rate than the sMDRD equation [68].

Glomerular filtration rate is the most used method to assess the association of renal function and outcome in heart failure patients. A great number of studies have shown that lower glomerular filtration rate, or the presence of chronic kidney disease (usually defined as a glomerular filtration rate <60 ml/min/1.73 m^2) is independently predictive of an increased risk of mortality. This association is present in both acute and chronic heart failure, as well as in heart failure with a preserved and reduced ejection fraction.

Cystatin C

Cystatin C is a small protein that is freely filtered by the glomerulus and is therefore considered an incredibly suitable biomarker to asses glomerular filtration rate. However cystatin C unfortunately also undergoes some tubular reabsorption. The CKD-EPI equation that includes cystatin C is considered the best method to assess glomerular filtration rate. Elevated levels of cystatin C have

been associated with poor outcome in heart failure [15, 35, 54]. Both increases in cystatin C and creatinine have been used in heart failure studies to assess worsening renal function. One study assessed the level of agreement between these two and found that the correlation between the changes over time in these biomarkers was modest [21]. This suggests that both markers may be influenced by different external factors and more reliable markers of renal function and changes therein are still needed.

Blood Urea Nitrogen

Blood urea nitrogen (BUN) is a strong prognostic marker in heart failure. The rate of urea excretion is determined mainly by its glomerular filtration and tubular reabsorption, which takes place in the proximal tubule and in the distal tubule under influence of arginine vasopressin. Blood urea nitrogen is therefore not only closely related to renal function but is also a marker of tubular function and neurohormonal activation of both the sympathetic nervous system and the renin-angiotensin-aldosterone system. The BUN/creatinine ratio has traditionally been used to differentiate between prerenal dysfunction and intrinsic renal parenchymal disease. In the setting of a prerenal problem, such as dehydration, significant renal neurhormonal activation causes a disproportionate reabsorption of BUN compared with the level of creatinine [29]. Multiple studies showed that increased BUN/creatinine ratios identify heart failure patients with worse outcomes [8].

Albuminuria and Proteinuria

The total rate of urinary protein excretion in the normal adult should be less than 150 mg/day. Higher rates of urinary protein excretion imply an increase in glomerular permeability. In non-heart failure populations, such as diabetic nephropathy, this is most commonly caused by high intraglomerular pressure leading to leakage and damage to the glomerular membrane. In heart failure on the other hand underlying mechanisms are probably different as intraglomerular pressures are relatively low, and processes such as endothelial damage, inflammation, and venous congestion are more likely to play a role. Albuminuria is assessed using the urinary albumin to creatinine ratio and divided in micro-albuminuria (30–299 mg/g creatinine) and macro-albuminuria ($\geq$300 mg/g creatinine). Albuminuria is common in chronic heart failure with up to 30 % of patients having micro-albuminuria and 10 % macro-albuminuria. In two retrospective analyses of large heart failure trials, albuminuria was associated with an increased risk of poor outcome [40]. Of note, a recent study showed that the risk of death associated with proteinuria in heart failure was restricted to patients

with an elevated BUN/creatinine ratio, suggesting that other factors, such as neurohormonal activation, might contribute to the negative effect of proteinuria [7].

Tubular Markers

In heart failure the kidneys are prone to tubulointerstitial damage due to reduced tissue perfusion and hypoxia. As tubular function is difficult to assess, several markers assessing tubular injury, mainly originating from chronic kidney disease trials, have been studied in heart failure [58].

Neutrophil Gelatinase-Associated Lipocalin (NGAL)

Neutrophil gelatinase-associated lipocalin (NGAL) is a protein that is secreted by a number of organs and is normally found in plasma. Plasma NGAL levels are increased in sepsis, inflammation and malignant disease. In a setting of acute kidney injury NGAL levels both in plasma and urine can rise 1000 fold or more over a short period of time. Interestingly, urinary levels of NGAL seem to be unaffected by plasma levels, as plasma NGAL is freely filtered by the glomerulus, but completely reabsorbed by the tubules. In acute kidney injury, urinary NGAL levels are therefore thought to be completely derived from the kidney itself and result from tubular production and secretion. Both urine and plasma NGAL have been studied in heart failure mainly to determine its prognostic value to identify acute kidney injury. In chronic heart failure, urinary NGAL levels were found to be higher compared with matched controls, however there was no association with worsening renal function. In acute heart failure plasma NGAL levels were generally higher in patients who develop worsening renal function, whereas urine NGAL levels did not differ. In acute heart failure, plasma NGAL was however found to be a strong predictor of outcome [39, 59]. Recently the results of a trial studying the usefulness of NGAL in predicting worsening renal function showed that plasma NGAL does not predict worsening renal function better than creatinine. Additionally, plasma NGAL was not found to be a predictor of adverse outcome. Current evidence does not provide clear information on the position and use of NGAL in the treatment of heart failure patients.

N-Acetyl-β-D-Glucosaminidase (NAG)

N-acetyl-β-D-glucosaminidase (NAG) is an enzyme that is found in cells of the proximal tubule and elevated urinary concentrations of NAG are thought to be a markers of proximal tubular damage. Urinary NAG has been studied extensively in

a number of patient populations, such as patients with chronic kidney disease, diabetic nephropathy and coronary artery disease. In chronic heart failure urinary NAG levels were found to be elevated compared with controls and associated with poor outcome, independent of glomerular filtration rate. In acute heart failure urinary NAG levels were not elevated in patients who developed worsening renal function and were not useful in determining risk of worsening renal function. In a small proof of concept study, urinary NAG levels varied with the initiation and withdrawal of diuretic therapy, suggesting that NAG might be used to monitor response to diuretic treatment or hemodynamic changes [69].

Kidney Injury Molecule 1 (KIM-1)

Kidney injury molecule 1 (KIM-1) is a protein that is undetectable in healthy kidneys or urine. It is highly upregulated after hypoxic tubular injury, which leads to expression of high levels of urinary KIM-1. Elevated urinary KIM-1 levels were found to be associated with heart failure hospitalizations in the general population. Experimental studies have shown that urinary KIM-1 levels are associated with tubulointerstitial damage, fibrosis, and inflammation. In chronic heart failure patients, urinary KIM-1 levels were found to be increased compared with matched controls, and associated with outcome. Also, urinary KIM-1 levels were predictive of an increased risk of worsening renal function in chronic heart failure patients. Data on urinary KIM-1 in acute heart failure are scarce and conflicting results have been described. One study investigated the value of plasma KIM-1 in heart failure and found it was not associated with urinary KIM-1 and was not a strong predictor of outcome [22]. Interestingly, similarly to urinary NAG, urinary KIM-1 levels were susceptible to diuretic-induced volume changes, suggesting that urinary KIM-1 might be sensitive to small hemodynamic and renal alterations [69].

Treatment in Heart Failure Patients with Concomitant Renal Dysfunction

The 2016 heart failure guidelines recommend treatment with angiotensin converting enzyme (ACE) inhibitors, and beta-blockers for symptomatic heart failure patients with a reduced ejection fraction [50]. Addition of a mineralocorticoid antagonist (MRA) is recommended for patients who remain symptomatic despite treatment with an ACE-inhibitor and beta-blocker. As these therapies potentially influence renal function or expose heart failure patients with renal dysfunction to an increased risk of adverse events, these patients are less likely to receive guideline recommended therapies. This may not always be justified as will be outlined below.

Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Most randomized clinical trials studying the effect of ACE-inhibitors largely excluded heart failure patients with renal dysfunction. Yet interaction or retrospective analyses in the small subgroups with renal impairment showed that the relative risk reduction achieved by ACE-inhibitors was equal compared to patients with normal renal function [4, 12]. As the risk of poor outcome is greater in heart failure patients with renal impairment, the absolute benefit of ACE-inhibitor treatment in this patient group might even be higher. In patients with severe renal dysfunction (glomerular filtration rate <30 ml/min/1.73 m^2) no conclusive data is available.

The heart failure guidelines only recommend prescribing angiotensin receptor blockers (ARBs) as an alternative in patients intolerant to an ACE-inhibitor. For both losartan and candesartan, there was no significant interaction between renal function and the beneficial effect of ARB treatment in patients with moderate renal dysfunction. There are no studies investigating the effect of ARBs in heart failure patients with severe renal dysfunction.

The addition of an ARB to ACE-inhibitor therapy, or dual renin-angiotensin-aldosterone system blockade, showed consistent benefit in patients with moderate renal dysfunction, compared to those without. The combination of ACE-inhibitor/ARB is only advised for symptomatic heart failure patients who are unable to tolerate a MRA and are already receiving beta-blocker treatment.

For all of the therapies above caution should be observed with regard to renal function and electrolytes, as these treatments can potentially cause worsening renal function or hyperkalemia. It should be noted that an initial moderate elevation of creatinine after introduction of an ACE-inhibitor or ARB should be expected. This elevation is free of adverse prognostic value as to the contrary several studies suggest that this initial rise in creatinine actually identifies patients who benefit the most from treatment. Of note, as ACE-inhibitors are predominantly cleared by the kidneys, starting with a lower dose is recommended in patients with renal dysfunction. ARBs on the other hand are mainly eliminated by the liver and as such adjustment of the dose is not necessary.

Beta-Blockers

Similar to the ACE-inhibitor trials, most trials in heart failure that studied beta-blockers excluded patients with severe kidney dysfunction, despite the lack of evidence of an effect of beta-blockers on renal function. Several large subgroup analyses from important clinical trials studying the effect of beta-blockers in heart failure showed clear mortality and morbidity benefit associated with beta-blockers therapy in patients with moderate renal dysfunction [10]. There is limited data available on the effect in heart failure patients with severe renal dysfunction; however

improved outcome is also suggested in this subgroup [12]. Also, none of the recommended beta-blockers in the guidelines (bisoprolol, carvedilol, metoprolol, and nebivolol) are dependent on renal elimination, as all are eliminated by the liver.

Mineralocorticoid Receptor Antagonists

Mineralocorticoid receptor antagonists (MRAs) are recommend as add-on therapy in heart failure patients who remain symptomatic despite treatment with an ACE-inhibitor and beta-blocker. Initially these drugs were considered contra-indicated in patients with renal dysfunction because of the risk of hyperkalemia. Indeed, several registries showed that the incidence of hyperkalemia increased after the introduction of spironolactone. However, both studies with spironolactone and eplerenone found that the treatment benefit persisted in heart failure patients with moderate renal dysfunction [12, 47, 48, 61]. Again, no data is available in heart failure patients with severe renal failure. Patients should be monitored closely in terms of renal function and electrolytes (potassium) after initiation of a MRA as this might lead to life-threatening tachycardia's.

Angiotensin Receptor Neprilysin Inhibitor

The most recent heart failure guidelines added a recommendation for angiotensin receptor neprilysin inhibitors (ARNIs), where these are recommended as a replacement for an ACE-inhibitor to further reduce the risk of heart failure hospitalization and death in heart failure patients that remain symptomatic despite optimal treatment with an ACE-inhibitor, beta-blocker and an MRA [50]. The beneficial effect of treatment with an ARNI in heart failure patients was consistent among subgroups based on glomerular filtration above or below 60 ml/min/1.73 m^2, with no significant interaction [41]. In patients with heart failure with a preserved ejection fraction treatment with an ARNI was associated with preservation of renal function [63]. This study was not designed to study the effect of treatment on outcomes. Based on the limited available information, treatment with an ARNI seems to be relatively safe in patients with concomitant renal dysfunction, yet more data is warranted to be able to definitely conclude this.

Diuretics

Diuretics are the first-choice treatment to alleviate signs and symptoms associated with fluid overload in patients with acute heart failure. Diuretics increase sodium and water excretion by inhibiting specific transporters in the tubule. Loop diuretics

act on the sodium-chloride-potassium co-transporter in the thick ascending loop of Henle, causing decreased sodium and chloride reabsorption from the urine [55]. According to the heart failure guidelines the dose of loop diuretic should be limited to the smallest amount necessary to provide adequate clinical effect and modified according to previous renal function and previous doses of diuretics [50]. In patients with renal dysfunction, due to a loss of nephrons, higher doses of diuretics are required to overcome this and elicit the desired response [5]. Conflicting data is available on the effect of high dose diuretics, where some studies showed an association with poor outcome, whereas others did not. It might be hypothesized that diuretics could potentially even improve renal function and outcome in the setting of renal venous congestion. Furthermore, in patients with an adequate decongestive response, high dose diuretics might be free of adverse outcome [55]. No randomized data is available on the outcome benefit of treatment with loop diuretics in acute heart failure. In patients with a decline in renal function, low-dose dopamine is often suggested as a method to overcome this, despite the fact that this was not shown to be effective in randomized trials. Finally in patients with diuretic resistance, combination therapy with two classes of diuretic drugs might improve diuretic efficiency [55]. As this could potentially lead to severe adverse events, such as renal failure, hypovolemia and electrolyte imbalance, this should only be used under careful monitoring.

Electrolytes in Heart Failure

In heart failure both underlying pathophysiological mechanisms, as well as treatment may cause several electrolyte imbalances. An overview of these can be found in Table 26.2.

Sodium

Sodium and accompanying anions (predominantly chloride and bicarbonate) are the most important determinants of plasma and extracellular fluid osmolality. Interest in sodium in heart failure populations originated decades ago, as most hospitalizations for heart failure are attributed to sodium and fluid overload causing signs and symptoms, such as dyspnea. Neurohormonal activation of the renin-angiotensin-aldosterone system and increased anti-diuretic hormone production leads to elevated sodium absorption by the kidneys. This in turn leads to volume retention to maintain normal osmolality. The 2016 ESC heart failure guidelines recommend monitoring of plasma sodium levels daily during hospitalization for acute heart failure as not only neurohormonal influences inherent to the disease itself, but also therapies such as diuretics influence sodium levels [50].

Table 26.2 Electrolyte imbalances in heart failure

Electrolyte imbalance	Prevalence in HF	Related to prognosis	Cause	Treatment
Hyponatremia	+++	+++	Most commonly depletional	Depending on the cause either diuretics, hypertonic saline or tolvaptan
Hypernatremia	0	0	External causes such as diarrhea or mannitol	Slowly correct hypernatremia by administering fluid
Hypokalemia	+	+	Neurohormonal activation or treatment with diuretics	Potassium supplements or a diuretic drug that inhibits potassium excretion
Hyperkalemia	+++	+++	Treatment with ACEi, ARBs or MRAs	Administration of intravenous calcium, insulin with glucose, sodium bicarbonate, or novel potassium binders
Hypochloremia	++	++	Not specifically known; possibly dilutional, due to neurohoromonal activation or diuretic induced	Chloride repletion with for instance lysine chloride
Hyperchloremia	0	Unknown	Causes underlying metabolic acidosis	Treat underlying causes

Abbreviations: *ACEi* angiotensin converting enzyme inhibitors, *ARBs* angiotensin receptor blockers, *MRAs* mineralocorticoid receptor antagonists

Hyponatremia

Hyponatremia is most often defined as a serum sodium <135 mEq/L (mmol/L) and is a common finding in heart failure patients. Incidence rates of hyponatremia as high as 20 % at admission have been described in the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry, that enrolled 47,647 patients with acute heart failure [23].

Hyponatremia has been associated with poor outcome in a large number of heart failure studies. It is not only associated with an increased risk of mortality, but also with increased rehospitalization rates, length of stay, complications and costs [9, 31, 53].

For the treatment of hyponatremia it is important to distinguish between dilutional and depletional hyponatremia [62]. In the case of dilutional hyponatremia, this is the consequence of impaired fluid excretion, rather than excess sodium wasting/excretion. Several mechanisms in heart failure, such as increased release of anti-diuretic hormone and decreased distal flow contribute to increased water retention. In heart failure, activation of the sympathetic nervous system and renin-angiotensin-aldosteron system and release of antidiuretic hormone cause excess retention of sodium and

water (Fig. 26.3). These mechanisms are an adequate response elicited by baroreceptors, however in the long run these response become maladaptive and contribute to disease progression. On the other hand depletional hyponatremia, which is caused by actual sodium losses, is relatively rare in heart failure, yet can be caused by loss of sodium into third spaces or be loop diuretic-induced. Loop diuretics are administered in over 90 % of patients hospitalized for acute heart failure and aim to establish a negative sodium balance by blocking the sodium-potassium-chloride co-transporter in Henle's loop. This will initially elicit pronounced water excretion, however due to neurohormonal activation and long term exposure adaptation occurs and the effects will diminish, creating a situation in which hyopnatremia may develop. Differentiation between dilutional and depletional hyponatremia can be made by measuring urine osmolality, which should be suppressed in patients with depletional but not in patients with dilutional hyponatremia. Alternatively, a fluid challenge may help differentiate; however in dilutional hyponatremia this may exaggerate fluid overload and is therefore considered harmful. In this setting

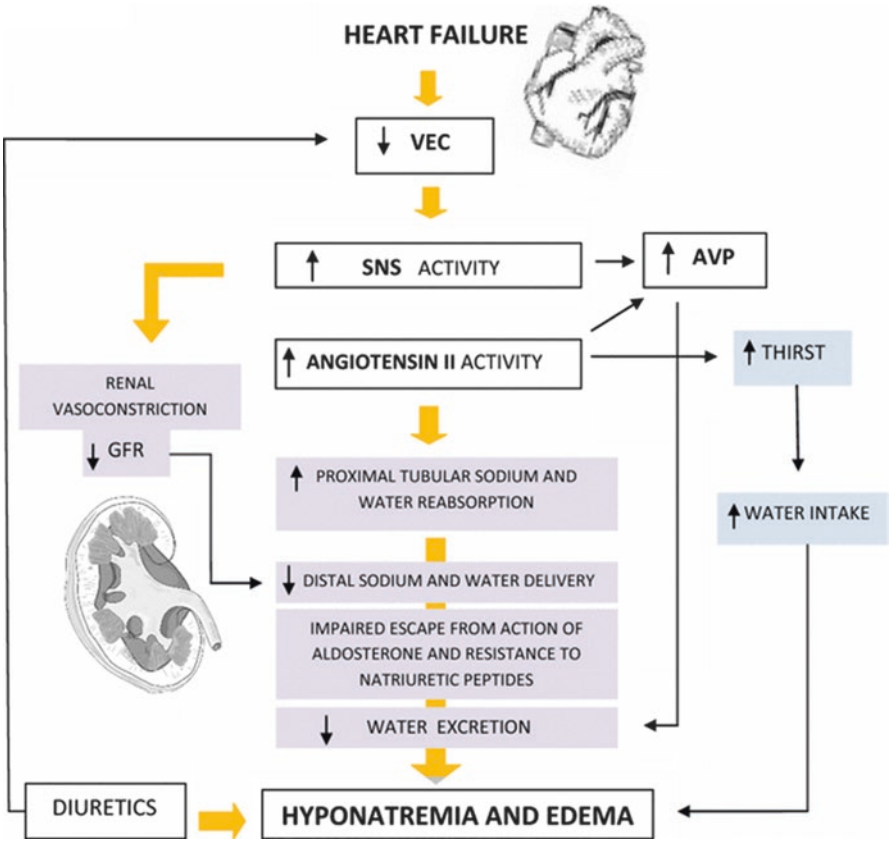

Fig. 26.3 Hyponatremia in heart failure. Reprinted with permission from Springer Open. Urso et al. [57]

administration of loop diuretics is the best revenue to restore sodium concentration. Several small, non-randomized studies have demonstrated that the addition of hypertonic saline to intravenous high dose loop diuretic resulted in an increase in sodium levels and pronounced diuresis [44, 67]. Although counter-intuitive, administering hypertonic saline to heart failure patients with over fluid overload is thought to mobilize extravascular fluid into the intravascular space which results in increased cardiac output, renal blood flow, and greater diuresis and natriuresis. The use of hypertonic saline is however still controversial as most experience comes from a limited number of studies all performed by one group of investigators.

Tolvaptan is a vasopressin V_2 receptor blocker that promotes free water excretion by prevention of aquaporin-2 channel availability in the collecting ducts of the nephron. Tolvaptan is effective at increasing sodium concentrations in heart failure patients with hyponatremia. In the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) trial the effect of tolvaptan on both short- and long term outcome in patients hospitalized for acute heart failure was studied [32]. Hyponatremia was not an inclusion criterion in this trial. No effect was found on mortality or readmission rates, however in a subanalysis in patients with hyponatremia at baseline (serum sodium<134 mEq/L) treatment with tolvaptan resulted in an increase in sodium concentration and was associated with more favorable in-hospital and suggested improved survival [27].

Initiation or uptitration to guideline recommended doses of angiotensin converting enzyme blockers or angiotensin receptor blockers have also been demonstrated to be effective in correcting dilutional hyponatremia.

Additionally, both in acute and chronic heart failure, sodium restriction might be considered. Even though this is often recommended, data supporting efficacy are scarce and the available data is conflicting. Moreover no studies comparing different doses of sodium intake are lacking and the optimal (lowest) dose of sodium is not known.

Hypernatremia

Hypernatremia, most often defined as a serum sodium >145 mEq/L (mmol/L) is seldom observed in heart failure patients. One study showed that in patients with chronic kidney disease and congestive heart failure both hyponatremia and hypernatremia were independently associated with higher mortality [34].

Potassium

Potassium is essential for a healthy nervous system and regular heart rhythm. Total body potassium is 3500 mmol of which 98 % can be found intracellular. Normal distribution of potassium is maintained by insulin and beta adrenergic catecholamines; both increase cellular potassium uptake. Aldosterone regulates the overall

potassium storage by influencing excretion of potassium by the kidneys, which is influenced by hyperkalemia.

Most of the drugs recommended in the guidelines for the treatment of heart failure potentially affect potassium levels. Renin-angiotensin-aldosterone system inhibitors increase the risk of hyperkalemia. Diuretics on the other hand may cause hypokalemia due to renal potassium losses. Use of potassium sparing diuretics (mineralocorticoid receptor antagonists (MRAs)/aldosterone antagonists) in contrast potentially gives rise to hyperkalemia. Optimal potassium levels have not been clearly defined in patients with heart failure. Yet both hypo- and hyperkalemia are common in heart failure and have been associated with poor outcome.

Hypokalemia

The cut off point for hypokalemia in heart failure has not been well defined, most commonly used however is a serum potassium level<3.5 mEq/L (mmol/L). Neurohormonal activation, as well as treatment with diuretics contributes to the development of hypokalemia in heart failure patients. The effects of hypokalemia on cardiovascular mortality and morbidity have been shown in several studies in different populations. In heart failure a propensity-matched study in chronic systolic and diastolic heart failure patients showed that a serum potassium <4 mmol/L was associated with increased mortality, with a trend towards increased hospitalization [1].

Hypokalemia may lead to muscle weakness, renal abnormalities and cardiac arrhythmias, as low potassium affects the myocardial resting membrane potential, repolarization, relative refractory times, and conduction velocity. The arrhythmias that can be observed are, amongst others, bradycardia, atrioventricular block, and ventricular tachycardia or fibrillation. Correction or repletion of potassium levels is therefore of great importance. This can be achieved using different strategies. First of all, potassium can be restored by administering potassium supplements. Caution should be observed using intravenous supplements as supplemental potassium administration is the most common cause of severe hyperkalemia in hospitalized patients. Secondly, potassium levels can be corrected by using a diuretic drug that inhibits potassium excretion, such as amiloride, triamterene, spironolactone, or eplerenone. Of these spironolactone is most commonly used. Again, this strategy can cause severe and life threatening hyperkalemia, and potassium levels should be monitored closely. The risk of hyperkalemia is greatest in patients with concomitant diabetes or renal dysfunction.

Hyperkalemia

On the other hand hyperkalemia is also a common problem in heart failure patients [30]. Definitions for hyperkalemia vary across trials and clinical practice and are subdivided in moderate and severe hyperkalemia. Moderate hyperkalemia is most commonly defined as a serum potassium >5.5 mEq/L (mmol/L), whereas severe

hyperkalemia is defined as a serum potassium > 6.0 mEq/L (mmol/L). Hyperkalemia is a well-known risk factor for arrhythmias and sudden death. There is even some evidence suggesting that a serum potassium >5.0 mEq/L (mmol/L) is associated with an increased risk of cardiovascular events in patients with heart failure and chronic kidney disease.

Since the introduction of ACE-inhibitors, ARBs and in particular MRAs the incidence of hyperkalemia has risen significantly with some studies also showing increased incidences of sudden cardiac death. Treating hyperkalemia is therefore of the utmost importance. Several treatment options exist, such as the administration of intravenous calcium, insulin with glucose, sodium bicarbonate, calcium polystyrene sulphonate or sodium polystyrene sulphonate. All of these treatments may induce significant side-effects or result in hypokalemia. Additionally, none of these treatments have been studied in a randomized manner in heart failure patients. Recently, two novel potassium binders, patiromer and ZS-9, have been introduced [2, 46]. Both of these were effective in significantly lowering potassium levels in patients with heart failure. This allowed patients to receive treatment with (higher) doses of RAAS-inhibition as the potassium levels were no longer a limitation to receive this treatment or even increase doses. Further studies will have to show whether this actually translates in survival benefit.

In current clinical practice however, potassium levels will have to be monitored closely, especially during initiation and uptitration of RAAS inhibitor therapy. All cases will have to be managed and reviewed individually where optimal treatment with guideline recommended doses remains one of the primary goals.

Chloride

Chloride has a great number of functions in the body, and deregulation of chloride results in a wide range of abnormalities [3]. The concentration of chloride is mainly determined by the gastrointestinal tract and the kidneys. Chloride is absorbed in the intestine, which is controlled by a variety of endocrine, paracrine, neuronal and immunological factors. Excretion of chloride is mainly regulated by the kidneys. A large amount of chloride is filtered, with 99.1 % being reabsorbed along the tubule, mainly proximally [3].

Chloride plays an import role in salt sensing, and seems to be the predominant driver in the kidneys ability to sense volume overload. Several studies from the 80s showed that chloride containing solutions in contrast to non-chloride containing solutions elicited a response from the kidney [6, 33, 64]. Additionally, chloride has been shown to reduce renin release where non-chloride containing sodium salts did not affect renin levels. The role of chloride in the kidney however also extents to the regulation of diuretic targets as multiple studies showed that sensing of hypochloremia by a specific serine-threonine kinase causes upregulation of the sodium potassium chloride co-transporter [45, 49]. Binding of chloride to these kinases causes decreased availability of both the sodium potassium chloride co-transporter and

sodium chloride co-transporter and through this reduces renal salt reabsorption. As such chloride potentially influences the targets and possibly efficacy of both loop and thiazide diuretics. Based on this data chloride may play a key role in the regulation of volume retention in heart failure and response to diuretic treatment.

Hypochloremia

Recent studies have shown that hypochloremia, defined as chloride<96 mEq/L (mmol/L), was present in approximately 13 % of heart failure patients and was a strong, independent predictor of mortality in both acute and chronic heart failure [24, 25, 56]. In these studies, chloride was a stronger predictor of outcome than sodium. One study additionally found that low serum chloride at acute heart failure hospital admission was strongly associated with multiple markers of impaired decongestion, such as diuretic response, hemoconcentration, worsening heart failure and residual congestion [65]. In clinical practice assessment of chloride might provide the clinician with information regarding decongestive responsiveness and outcome.

Taking these observations into account, chloride might also be a target for therapy, for instance through supplementation. For this application a suitable ligation such as lysine chloride should be used, rather than for instance potassium chloride which may give rise to additional or different problems such as hyperkalemia [66]. Further studies will have to show whether chloride is a modifiable risk factor and might be used to improve decongestive response and ultimately possibly also outcome.

Hyperchloremia

Hyperchloremia is usually defined as a serum chloride >107 mEq/L (mmol/L) and is most commonly associated with metabolic acidosis. Data on hyperchloremia or metabolic acidosis in heart failure are scarce and are mainly associated with other underlying conditions such as diabetes leading to ketoacidosis, diarrhea, or thiamine deficiency.

Future Directions
In the treatment of heart failure patients, treating physicians need to be aware of concomitant renal dysfunction and adjust treatment accordingly. Ultimately, a personalized approach towards treating heart failure patients might lead to more specific recommendations concerning specific subgroups of patients, such as patients with renal dysfunction in which certain medications may only be approved for specific subgroups. Finally, future research will have to show whether modulation of electrolytes or renal biomarkers may proof to be a target for therapy.

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Part VI
Prognostic Factors and Rehabilitation in Heart Failure

Chapter 27
Prognostic Factors and Risk Scores in Heart Failure

Eva Prescott

Prognostic Factors and Risk Scores in Heart Failure

Even in the current era with the development and implementation of several pharmacological and other interventions that have drastically improved prognosis in heart failure patients, prognosis remains severe with 1-year mortality rates up to 42 % in community studies and as high as 75 % in trials [1]. In clinical care of heart failure patient, risk is continuously assessed to guide treatment, e.g. NYHA class and left ventricular ejection fraction are used to guide choice of pharmacological treatment and device implantation. Similarly, disease progression with increased symptoms and signs of congestion will guide toward intensification of treatment, including heart transplantation and LVAD. Knowledge of future risk can on the one hand help the clinician to take informed decisions on stepping up care while on the other hand identification of low risk in a patient can help reduce both patient anxiety and intensity of follow-up. Studies show, however, that clinicians do not accurately predict risk and that there is clear trend to substantially overestimate risk [2]. This may result in inappropriate treatment and in overutilization of critical care resources. Thus, optimally, management of patient with heart failure should be based on an objective assessment of prognosis of the individual patient.

Several studies have assessed prognosis in terms of mortality and progression to transplantation and assist device and have identified a very large number of variables associated with prognosis in heart failure. These include demographics and data derived from patient history, presence of comorbidity and findings from physical examination, routine laboratory tests, e.g. plasma sodium and renal function, a number of biomarkers including neurohormones and cytokines, ECG

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M. Dorobanţu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_27

derived variables such as QRS width, atrial fibrillation and heart rate variability, variables derived from imaging, mainly echocardiography and cardiac MRI, and variables derived from exercise testing. A comprehensive list of risk factors and risk markers identified in heart failure is provided in Table 27.1 [3].

Table 27.1 Prognostic variables in chronic heart failure

Prognostic variables in chronic heart failure: list of the more commonly described variables shown to be related to outcome
Demographics, symptoms, etiology, co-morbidity, lifestyle and physical examination
Age, sex, ethnicity
NYHA class
Ischaemic aetiology, history of myocardial infarction
Diabetes mellitus, renal dysfunction, depression, COPD, cerebrovascular disease, PAD
Smoking and physical activity
BMI, signs of congestion, increased jugular venous pressure, third heart sound, low systolic blood pressure, higher heart rate
Routine laboratory tests
Serum sodium
Liver enzymes, bilirubin
Serum creatinine/creatinine clearance/eGFR BUN/urea and markers of tubular injury
Urinary albumin creatinine ratio
Serum albumin
Uric acid
Haemoglobin
(NT)-pro BNP
Medication
Dosage of diuretics
Treatment with statin
Treatment with betablocker/ACE inhibitor/ARB/MRA
Neurohormones, cytokines, and related factors
Plasma renin activity/Angiotensin II Aldosterone/Catecholamines/(Big) endothelin-1/ Adrenomedullin
Natriuretic peptides/ Vasopressin/Co-peptin Cytokines sST-2
Galectin-3 Collagen markers
ECG derived variables
QRS width
LV hypertrophy
Atrial fibrillation
Complex ventricular arrhythmias
Heart rate variability
Imaging
Echo: LV internal dimensions and fractional shortening/Wall motion index/Ejection fraction/ Global longitudinal Strain/Left atrial size/Restrictive filling pattern/short deceleration time/ Right ventricular function/Mitral regurgitation
Chest X-ray: Cardiothoracic ratio/congestion

Table 27.1 (continued)

CMR: Inflammation (contrast-enhanced CMR), iron content (in thalassaemia: CMR) Amyloidosis (contrast kinetics in CMR)
Ischaemia and viability imaging, arrhythmogenic substrates
Exercise test/haemodynamic variables
VO_2peak/heart rate recovery/oxygen uptake efficiency slope
VE/VCO_2slope
6-min walk distance
Cardiac index
LV end-diastolic pressure/pulmonary artery wedge pressure (normal <12 mmHg)

Risk Scores in Chronic Heart Failure

Prognosis in heart failure populations vary remarkably in different studies. One-year mortality rates have been reported to vary between 5 and 75 % in randomized clinical trials and between 11 and 42 % in community studies [4]. In such heterogeneous populations it is not possible for single patient parameters to accurately predict prognosis. To provide more objective and precise risk stratification different risk models incorporating a varying number of demographic, clinical, biomarkers, imaging and functional capacity characteristics have been developed. It is relatively easy to develop a risk model from a cohort of patients with chronic heart failure and numerous such studies have been published. Initial models were based on single centre data with relatively small study populations and few risk parameters while the more recently developed models are derived from pooling of multiple datasets either from randomized controlled trials or from collaborating registries. A key point in the usefulness of such models is that they are tested in different sets of patients, i.e. validated externally, and shown to predict well. This is however, relatively rarely done. A review published in 2003 provided a comparison of 10 heart failure risk scoring systems published in the preceding 20 years only one of which has since been validated and significantly used in clinical practice. Since 2003 more than 30 more risk models have been developed. A recent paper carefully and systematic reviewed the literature and identified 20 different studies reporting prognostic risk score models on heart failure populations [5], five of which had been validated externally. These five were the Heart Failure Survival Score published in 1997 [6], the Seattle Heart Failure Model from 2006 [7], the model proposed by Frankenstein et al. in 2011 [8], the PACE risk score from 2012 [9] and the SHOCKED score from 2012 [10] (please see Table 27.2 for an overview). Other recent risk scores based on large populations of patients with chronic heart failure include the HF-Action study (n = 4402) [11], the MAGGIC study (n = 39,372) [12] , the GISSI-HF study (n = 6875) [13] and the I-PRESERVE trial, which only included patients with heart failure with preserved ejection fraction (HFpEF) (n = 4128) [14].

Table 27.2

First author/name of study	Year published	N model derived	Study population	HFrEF/HFpEF	Externally validated	Patient characteristics – AGE/gender/ LVEF/NYHA/Ischemic origin
Aaronson [6]/HFSS	1997	268	Ambulatory patients with advanced HF, one centre, US	HFrEF, LVEF<40, age<70	Yes	Mean age 50, 80 % male, mean LVEF 20, mean NYHA 2.8, 45 % ischemic origin
Lee [33]/EFFECT	2003	2624	Patients admitted to hospital with HF in Canada	HFrEF and HFpEF	Yes	Mean age 76, 50 % male, 53 % LVEF<40 %, NYHA class and ischmic origin not reported
Levy [7], SHFM	2006	1125	Multicentre trial in US and Canada	HFrEF, LVEF<30 and NYHA IIIb-IV	Yes	Mean age 65, 76 % male, mean LVEF 21 %, mean NYHA 3.6, 64 % ischemic origin
Pocock [19], CHARM	2006	7599	Inernational multicentre trial	HFrEF and HFpEF	No	Mean age 65, 68 % male, mean LVEF 39 %, 55 %>NYHA II, 70 % ischemic origin
Senni [20], CMV-HF	2006	292	One institution in Italy, observational	HFrEF and HFpEF	No	Mean age 71, 62 % male, 13 % LVEF<20 %, 25 % <NYHA II,
Vazquez [21], MUSIC	2009	992	Consecutive ambulatory CHF patients enrolled from eight centres in Spain	HFrEF or HFpEF	No	Mean age 65 years, 72 % male, mean LVEF 37 %, 22 %>NYHA II, 46 % ischemic origin
Myers [22], CPX-SCORE	2008	710	Observational cohort from 4 centres in US and Italy	HFrEF	No	Mean age 56 years, 80 % male, mean LVEF 33 %, mean NYHA 2.4, 49 % ischemic origin
Huynh [23]	2008	282	One centre, data from clinical trial, US, age>70	HFrEF	No	Mean age 79, 37 % male, mean LVEF 42 %, mean NYHA 2.3, 55 % ischemic origin
Wedel [56], CORONA	2009	3342	Multicentre trial	HFrEF	No	Mean age 73, 75 % male, mean LVEF 31 %, 63 %>NYHA II, 100 % ischemic origin

Leyva [24], DSC Index	2009	148	One centre, HF patients LVEF<=35 % undergoing CRT, UK	HFrEF	No	Mean age 67, 77 % male, mean LVEF 23 %, mean NYHA 3.2, 62 % ischemic origin
Frankenstein [8]	2011	636	One centre, Germany	HFrEF	Yes	Mean age 56, 81 % male, mean LVEF 28 %, 41 %>NYHA II, 32 % ischemic origin
Komajda [14], I-PRESERVE	2011	4128	Multicentre trial	HFpEF	No	Mean age 72, 40 % male, mean LVEF 59 %, 79 % >NYHA II, 25 % ischemic origin
Subramanian [25], VEST score	2011	963	Multicentre trial	HFrEF	No	Mean age 61 years, 77 % male, Mean LVEEF 21 %, 88 % >NYHA II, 57 % ischemic
Kramer [9], PACE	2012	905	Observational cohort of ICD patients from 3 centres	Patients receiving ICD, 68 % CHF	Yes	Mean age 65, 78 % male, mean LVEF 31 %, 27 % > NYHA II, 59 % ischemic
Bilchick [10], SHOCKED	2012	17,991	Patients receiving ICD for primary prevention	HFrEF	Yes	Median age 72.5, 87 % male, 32 % LVEF<20 %, 40 %>NYHA II, majority ischemic origin
O'Connor [11], HF-Action	2012	2331	Multicentre trial with 82 centres in US, Canada and France	Ambulatory patients with HFrEF, LVEF<=35	No	Mean age 59 years, 72 % male, mean LVEF 25 %, 37 %>NYHA II, 51 % ischemic etiology
Agostoni [26], MECKI	2012	2716	13 centres in Italy	HFrEF	No	Mean age 60, 84 % male, mean LVEF 30.8, mean NYHA 2.2, 46 % ischemic origin
Pocock [12], MAGGIC	2012	39,372	International multicentre observational cohort studies and clinical trials	HFrEF and HFpEF	No	Mean age 67, 67 % male, mean LVEF 32 %, 44 %>NYHA II, 52 % ischemic cardiomyopathy

(continued)

Table 27.2 (continued)

First author/name of study	Year published	N model derived	Study population	HFrEF/HFpEF	Externally validated	Patient characteristics – AGE/gender/ LVEF/NYHA/Ischemic origin
Hermann [27]	2012	114	One centre, UK	HFrEF	No	Mean age 63 years, gender distribution not reported, mean LVEF 29 %, mean NYHA 2.6, ischemic origin not reported
Scrutinio [28]	2012	802	On centre, Italy	HFrEF	No	Mean age 64, 79 % male, mean LVEF 28 %, mean NYHA 2.5, 50 % ischemic
Senni [4]	2013	2016	8 European registries/ surveys	HFrEF and HFpEF	Yes, C-statistic 0.83	Median age 69 years, 64 % male, mean LVEF 35 %/34 %>NYHA II
Barlera [13], GISSI-HF	2013	6975	Multiple centres across Italy	HFrEF	No	Median age 67 years, 80 % male, mean LVEF 33 %, 37 % >NYHA II, 50 % ischemic
Collier [29], EMPHASIS-HF	2013	2737	International multicentre trial	Mild HFrEF, only NYHA II	Yes, on CHARM, C-statistics 0.64	Patients with LVEF<35 % and NYHA II were included in a multicentre trial. Mean age 68 years, 78 % male, mean LVEF 26 %, all NYHA II, 69 % ischemic
Myers [35]	2013	2625	Multicentre in US and Italy	HFrEF and HfpEF	No	Mean age 56, 75 % male, mean LVEF 36, mean NYHA 2.4, 35 % ischemic
Lupon [31], BCN bio-HF calculator	2014	864	One centre, observational, ambulatory patients	HFrEF and HFpEF	No	Mean age 68 years, 72 % men, mean LVEF 36 %, 27 %>NYHA II, 52 % ischemic
Chyu [34], UCLA risk score	2014	1569	Patients referred for heart transplantation and management	HFrEF	Internal validation	Mean age 53 years, 70 % male, LVEF 28 %, 68 %>NYHA II, 39 % ischemic origin

Table 27.2 (continued)

% beta blocker/ACE	Variables tested	Events/Median follow-up	Outcome	Variables in final model	Available online	Risk score model
No information /88 % ACE	80 clinical characteristics	82 (31 %) events at 1 year	Death or transplant	In order of importance: Ischemic cardiomyopathy, resting heart rate, LVEF, (low) mean blood pressure, IVCD, peak VO_2 and serum sodium.	No	Three strata of risk score had 1-year mortality of 7 %, 28 % and 57 %, respectively
No information	22 parameters of demographics, vital signs, laboratory tests and comorbid conditions	282 (11 %) 30-day mortality and 862 (33 %) 1-year mortality	30-day and 1-year all-cause mortality	Age, lower SBP, respiratory rate, sodium<136 mEq/L, hemoglobin, BUN, cerebrovascular disease, dementia, COPD, hepatic cirrosis, cancer	No, nomogram provided	5 strata risk score: 1-year mortality risk 7.8 % for lowest risk group vs 78.8%for highest risk group
0 % beta-blocker, 99 % ACE	29 demographic, clinical, medical history and laboratory data variables	289 (26 %) 1-year mortality	All-cause mortality	Predictors in order of importance: diuretic dose, systolic blood pressure, lymphocytes, hemoglobin, etiology, LVEF, cholesterol, uric acid, allopurinol, sodium <138, statin, NYHA, age, gender	www.Seattleheartfailuremodel.org	6 strata defined from sum score with 1-year mortality rate ranging from 2 to 86 %
Information on beta-blocker not given, Randomized to candesartan/ placebo	>40 demographic, clinical and medication. No laboratory data included	1831 (24 %) deaths during 3.2 years follow-up	All-cause mortality	Predictors in order of importance: Age, LVEF, BMI, sex, NYHA, smoking, BBB, cardiomegalia, prior HF admission, diastolic BP, time HF diagnosis, previous MI, pulmonary crackles/edema, edema, heart rate, mitral regurgitation, atrial fibrillation, rest dyspnea, candesartan (vs placebo)	No	2-year mortality by deciles of risk score ranging from 3.6 to 30 %

(continued)

Table 27.2 (continued)

% beta blocker/ACE	Variables tested	Events/Median follow-up	Outcome	Variables in final model	Available online	Risk score model
65 % beta blocker, 86 % ACE/ARB	22 demographic, clinical and laboratory variables	61 (21 %) died after 1 year	All-cause mortality at one year	Predictors included in index: Age, anemia, hypertension, COPD, complicated diabetes, moderate to severe kidney dysfunction, metastatic cancer, no Beta blocker, no ACE/ARB, NYHA iii/IV, LVEF <20 %, severe valvular heart disase, atrial fibrillation	No	4 strata of risk score ranging from 4 % 1-year mortality to 98 % 1-year mortality
68 % beta-blocker, 90 % ACE/ARB	20 demographic, clinical, echocardiographic, ecg and laboratory variables	267 (27 %) died during 44 month follow-up	All-cause mortality	Predictors in order of immportance: LA size>26 mm/m2, NT-proBNP>1000 ng/L, troponin positive, LVEF<35 %, non-sustained VT or frequent VPBs, eGFR<60 ml/min, prior vascular event, sodium<138 meq/L	Nomogram provided	In low risk sub-group 5 % mortality, in high risk sub-group 20 % mortality
53 % beta-blocker, 75 % ACE	5 CPET results, age-adjusted	111 (16 %) died during 2.4 years follow-up	All-cause mortality	Predictors in order of importance: VE/VCO2>34, heart rate recovery < 6 beats at 1 min, OUES>1.4, PetCO2<33 mmHg and peak VO_2<14,	No	Sum score from CPET superior to individual CPET components. Sum score: 0.4 % 1-year mortality for score <5, 27 % mortality for score>15
Not reported	Baseline demographic, medical history, clinical characteristics and laboratory data	43 (15 %) died during 6 month follow-up	All-cause mortality	In order of importance: BUN>=30 mg/dL, PAD, systolic BP<120 mmHg, sodium<135 mEq/l	No	4 risk groups with 6-month mortality risk ranging from 3.7 to 67 %

77 % beta-blocker, 92 % ACE/ ARB	27 demographic, clinical and biomarkers included	934 (28 %) died during follow-up	All-cause mortality	Model in order of importance: NT-proBNP, age, diabetes, LVEF, lower BMI, CABG, male sex, atrial fibrillation, NYHA, Apo-A1, creatinine, PAD, heart rate, MI	No	Lowest decile mortality risk 1.5, highest decile 39.5 per 100 pt. years
Beta-blocker 55 %, ACE/ ARB 92 %	16 risk factors including CMR measures of myocardial scarring and dyssynchrony before implantation	37 (25 %) died from CVD during 2.5 years follow-up	Cardiovascular mortality	In order of importance: Posterolateral scar location, dyssyncroni and creatinine	No	Event rate according to DSC index low: 4 %, medium: 30 % and high: 71 %
78 % beta blocker, 94 % ACE/ARB,	More than 11 parameters on demographics, medical histry, lab values and exercise test	151 (24 %) died during 3.2 years if follow-up	All-cause mortality	Beta-blocker, NT-proBNP and 6MWT	No	a simple model based on 6MWT and NT-proBNP stratified into three groups with 2-year mortality ranging from 5 to 40 %.
No information	58 baseline demographic, clinical and biological variables	881 (21 %) died during	All-cause mortality or cardiovascular hospitalization	Model for all-cause mortality in order of importance: NT-proBNP, age, diabetes, LVEF, heart rate, neutrophil count, recent hospital admission for HF, QOL, COPD, GFR, ischemic etiology, MI	No	3 year mortality rate in highest septile of risk score 37 %, in lowest 2.7 %
No information	23 basic variables and cytokines	172 (18 %) died during 1-year follow-up	All-cause mortality	BUN, LVEF, lymphocytes, CT ratio. (+ serial measures of cytokines: TNF, IL6 and their receptors)	No	Serial measurement of biomarkers improves risk prediction
No information	13 parameters	125 (14 %) died during 3.2 years follow-up	All-cause mortality	Age>70, LVEF<20 %, creatinine>=2.0, PAD	No	5 risk prediction groups with 1-year mortality risk ranging from <2 to 18 %

(continued)

Table 27.2 (continued)

% beta blocker/ACE	Variables tested	Events/Median follow-up	Outcome	Variables in final model	Available online	Risk score model
80 % beta-blockers, 74 % ACE/ ARB	Approx 20 parameters tested	37 % died during mean 4.4 years follow-up	All-cause mortality	In order of importance: CKD, age >75, COPD, diabetes, NYHA>2, LVEF<20 (all dichotomized)	Nomogram provided	Risk score quintiles ranging from 1-year mortality <5 to 23 %
95 % beta blocker, 74 % ACE inhibitor, 40 % ICD	48 candidate parameters: demographics, medical history, lab values, exercise test values and quality of life indices	387 (17 %) died and 1555 (67 %) experienced primary endpoint during 2.5 years of follow-up	All-cause mortality or hospitalization	For composite end point: Exercise duration, symptom stability, BUN and male sex. For mortality outcome: Exercise duration, urea nitrogen (BUN), male sex, low BMI	No	Risk score decile ranging from 21 % to 68 % probability of composite end point, from <1 to 14 % mortality risk.
81 % beta-blocker, 93 % ACE/ ARB	34 variables including 17 derived from CPET	19 % died during mean 2.9 years follow-up	Cardiovascular death/ urgent transplant	Hemoglobin, sodium, kidney function, LVEF, VO_2peak and VE/ VCO_2slope	www.cardiologicomonzino.it/Inglese/News/Pages/UserNewsHome.aspx	MECKI risk score <5 % 3-year mortality 5 %, score >15 %, 3-year mortality 40 %
34 % beta-blocker, 69 % ACE/ ARB	31 clinical variables tested	15,851 (40 %) died during 2.5 years follow-up	All-cause mortality	Age, LVEF, NYHA, serum creatinine, diabetes, not prescribed beta-blocker, lower sysstolic BP, lower BMI, time since diagnosis, current smoking, COPD, male gender and not prescribed ACE/ ARB	www.heartfailurerisk.org	6 risk groups from Risk score with 3-year mortality ranging from 11 % in lowest to 71 % in highest risk group

4 % beta-blocker, 91 % ACE	3 metabolic-immunological parameters and LVEF, pVO_2 and NYHA	31 (73 %) died during 2 years follow-up	All-cause mortality	Peak VO_2<14 ml/kg/min, uric acid>565 umol/l, LVEF<22, cholesterol<5.27 mmol/l, sTNF-r1>1016 pg/l,	No	Not reported
73 % beta-blocker, 92 % ACE/ ARB	20 parameters including 4 measures of renal function	301 (38 %) during 3.5 years follow-up	All-cause mortality	Age, ischemic CMP, anemia, LVEF, renal function	No	Addition of renal function overall significantly improved the model but not in a subgroup adjusting for NT-proBNP
71 % beta-blocker, 88 % ACE/ ARB	16 clinical, laboratory and echocardiographic parameters	11.2 % died during 1 year follow-up	All cause mortality/ urgent heart transplant	(in order of importance: Age, NYHA III-IV, LVEF<20 %, no RAS inhibitors, Severe valve heart disease, atrial fibrillation , no beta blocker, CKD, diabetes with target organ damage, anemia, (no) hypertension	www.3chf.org	One-year mortality rate ranging from <5 % in the three lowest deciles to almost 50 % in the highest decile
No information	39 clinical, laboratory, echocardiography and ECG parameters	1969 (28 %) died during 3.9 years follow-up	All-cause mortality	A final reduced model included in order of importance: age, NYHA, eGFR, LVEF, COPD, Gender, SBP, diabetes mellitus, hemoglobin, uicemia, aortic stenosis, BMI. In a subgroup with biomarkers, NT-proBNP and hs-cTnT were the strongest predictors of outcome	A nomogram for calcualation of risk is provided	Not reported

(continued)

Table 27.2 (continued)

% beta blocker/ACE	Variables tested	Events/Median follow-up	Outcome	Variables in final model	Available online	Risk score model
87 % beta-blocker,	38 clinical, laboratory, echocardiography and ECG parameters	During 2.1 years follow-up	Cardiovascular death or hhospitalization for heart failure	Age, male sex, lower SBP, lower eGFR, diabetes, prior hospitaliation for HF, lower haemoglobin, prior MI/CABG, lower BMI and higher heart rate	No	Categorized in low medium and high risk with 7.6, 19 and 39.4 events per 100 patient years, respectively
66 % beta-blocker, 56 % ACE	Age, gender, BMI, LVEF, HF pathogenesis and 5 CPET derived variables	290 deaths during 2.4 years follow-up	Cardiac-related mortality or death/transplantation/LVAD	After adjustment for age, sex, BMI, LVEF and etiology, 5 CPET variables (VO_2peak, HRR, VE/VCO2, OUES, PetCO2) were individual predictors of outcome	No	Using a weighted summed score derived from 5 CPET variables, 1-year mortality rate was 1.2 % in the lowest group (score <=5) and 12.2 % in the highest group (score>15)
88 % beta-blocker, 90 % ACE/ARB	23 variables tested	305 deaths (%) during mean follow-up of 3.4 years	All-cause mortality	Age, sex, NYHA, LVEF, sodiu, eGFR, hemoglobin, loop diuretica dose, beta-blocker, ACE/ARB and statin and the biomarkers hs-cTNT, ST2 and NT-proBNP	www.BCN BioHFcalculator.cat	One-year motality ranging from <1 to 40 % by deciles of risk score
79 % beta-blocker, 79 % ACE/ARB	39 variables tested	248 (15.8 %) mortality at one year	All-cause mortalty, urgent transplant or LVAD	4-variables in final model: NT-proBNP, peak VO_2, NYHA class, and use of ACE/ARB	No	Quartiles of risk score ranging from 1-year mortality risk of 5 to 70 %

Abbreviations: *LVEF* left ventricular ejection fraction, *BUN* blood urea nitrogen, *SBP* systolic blood pressure, *NYHA* New York Heart Association, *IVCD* intraventricular conduction delay, *CPET* cardiopulmonary exercise test, *PAD* peripheral arterial disease

The strategies used in developing the models have differed as have the resulting predictive factors included in the risk prediction models. The earliest study, the Heart Failure Survival Score (HFSS) was published in 1997 and is based on follow-up of only 268 ambulatory patients with heart failure [6]. Mean LVEF was 20, mean NYHA class 2.8 and peak VO_2 was 14.6 indicating quite advanced heart failure. 80 invasive and non-invasive clinical parameters were tested and the resulting model included the following 7 variables: ischemic cardiomyopathy, resting heart rate, LVEF, QRS duration >=120 ms, mean resting blood pressure, peak VO_2 and serum sodium. Based on an individually calculated HFSS risk score, patients were divided into three risk strata: low, medium and high risk. The odds of an outcome event at 1 year for the low-risk stratum were 5 times lower than for the medium strata and 21 times lower than for the high risk strata, with corresponding 1-year survival rates of 93, 72 and 43 %.

Probably the most widely used and validated risk prediction score is the Seattle Heart Failure Model (SHFM) [7]. This prediction model was based on 1125 patients with heart failure from the Prospective Randomized Amlodipine Survival Evaluation (PRAISE1) study and validated in 4 other studies. These patients also had very advanced heart failure reflected in mean NYHA of 3.6 and mean LVEF of 21 %. Notably, none of the patients received beta-blocker treatment. The final model based on multivariable analysis included age, gender, NYHA class, LVEF, ischemic aetiology, SBP, diuretic dose, allopurinol use, statin use and laboratory data: sodium, uric acid, haemoglobin, leucocyte count and cholesterol. Based on an individually calculated risk score, which was then grouped into 6 risk score groups, the model had excellent discriminatory powers with 1-year survival ranging from 95 to 20 % in the lowest to the highest risk groups. A web-based calculator of the SHFM is available at www.Seattleheartfailuremodel.org. In addition to being derived from patients with very advanced heart failure, the model was also developed on a population of heart failure patients which may today be regarded as historical in terms of pharmacological and device treatment (e.g., none of the patients were treated with beta-blockers). Further, the model did not include measures derived from a cardiopulmonary exercise test (CPET) or natriuretic peptides, which have both consequently been shown to be strong predictors of outcome in heart failure populations.

A risk score model for recipients of ICDs for primary prophylaxis has been developed based on more than 17,000 Medicare beneficiaries. Patients were followed for all-cause mortality after their ICD implantation [10] and the model was tested in a large validation cohort from a national registry. Patients included had systolic heart failure, 40 % had LVEF below 20, 80 % were male and mean age was 72.5. Mortality rate over a median of 4 years follow-up was 37.5 %. The resulting simplified risk score included 7 dichotomized variables: Age >75, NYHA>2, LVEF<20, COPD, diabetes, atrial fibrillation, CKD, with CKD being the strongest risk factor. A sum score could be calculated based on these 7 variables and a nomogram for this is provided in the paper. When dividing the population into quintiles based on the risk score, the 3-year mortality rate ranged from 12 % in the lowest quintile to 58 % in the highest.

The largest study-population to date to form the basis of a risk score was derived from 21 cohort studies including 6 randomized controlled trials and 24 other patient registries trials collated in the Meta-Analysis Global Group in Chronic Heart failure (MAGGIC) [12]. The study comprises almost 40,000 patients, both patients with reduced and preserved LVEF. The patients included in the study for score derivation had a mean age of 67, 67 % were male, mean LVEF was 32 % and 44 % were in NYHA class III or IV. The study population was more contemporary than the SHFM but only 34 % were treated with a beta-blocker and 68 % with an ACE inhibitor or ARB. The final risk prediction model included 13 variables: age, gender (with males having 11 % higher mortality risk), BMI (with a 3.5 % reduction in risk per 1 kg/m^2 increase in BMI up to 30 kg/m^2), smoking (with 15 % higher mortality risk in current smokers), systolic BP (with 12 % reduced mortality risk per 10 mmHg increase), diabetes (with 42 % higher mortality risk in patients with diabetes), NYHA class, LVEF (with 42 % risk reduction per 5 % increase in LVEF up to LVEF of 40 %), COPD (associated with 23 % higher mortality risk), heart failure duration (19 % higher risk after 18mo duration of heart failure diagnosis), creatinine (with 4 % increase in risk per 10 umol/L increase in creatinine), and beta-blocker and ACE/ARB treatment (both associated with reduced risk). An integer score ranging from 0 to 52 points was derived and a chart for use in individual patients is offered. When grouped according to the integer score into six groups, the 3-year mortality risk ranged from approximately 10 % in the lowest quintile to 70 % in the highest decile. The risk score is accessible from the website www.heartfailurerisk.org.

An overview of risk scores developed on larger samples of patients with chronic heart failure in recent years is provided in Table 27.2. This table summarizes the most widely used, the most recent and the largest risk prediction studies [4, 6–33]. The variables most often recurring in the risk scores are LVEF, NYHA class, co-morbidity such as renal dysfunction, diabetes and COPD, ischemic origin of chronic heart failure, low blood pressure and sodium. In all of the studies that have included CPET data, variables derived from the test have been strong predictors of prognosis. The same is true for studies including NT-proBNP. Several risk scores have included medication in the model. Use of beta blockers or ACE-inhibitor/ARB has been predictive in most of these studies with higher risk on those not treated with these evidence based medications. It is likely that this is due to reverse causality, i.e. that most of the patients not treated in these more contemporary populations are patients who do not tolerate these drugs because of co-morbidity and more advanced heart failure.

It is evident that the number of risk scores has increased rapidly in recent years. A recent study summarized the 64 identified such studies based on 48 populations. The study confirmed the huge variation in the study population the risk scores are derived from and also found that the predictive abilities of the model were greater when using mortality as outcome. Despite the great variation between study populations and variables included in the models, some variables were found to be most consistent predictors of outcome. These were age, renal function, blood pressure, blood sodium level, left ventricular ejection fraction, sex, brain natriuretic peptide level, New York Heart Association functional class, diabetes, weight or

body mass index, and exercise capacity. Interestingly, the variables with the highest ratio of being included in the final model were exercise tolerance and NYHA class, which were found to be predictors in 85 and 88 % of the studies in which they were included, respectively. NT-proBNP, age, renal function and (low) blood pressure in were predictive in 70–80 %.

Several of the studies have developed risk scores that are available as nomograms and/or online risk calculators to calculate individual patient risk. Both HFrEF and HFpEF are represented in several of the risk scores with some but not all providing stratified analyses. The only study which includes only HFpEF is the iPRESERVE [14]. In the risk model derived from this study age was a stronger predictors and the model also underscores the importance of co-morbidities in prognosis in HFpEF.

Overall, the risk prediction models have performed relatively well in internal validation. The studies that have been validated externally have, however, shown relatively poor prediction properties of the models with C-statistics showing mostly moderate prediction abilities ranging from 56 to 81 [5]. The proportion of patients on beta blocker medication in the populations on which the risk scores were developed as well as the populations used to validate the risk scores has varied widely and this was shown to be correlated with the C-statistics: The larger the proportion on beta-blocker medication, the poorer the model discrimination (C-statistic). The same was seen for other important prognostic factors percentage of patients with ICD and progressive study year [5]. Moreover, most of the risk models were developed on populations that are not representative of the populations that they are applied to: They are derived from younger, mostly male populations and mostly from among patients participating in clinical trials, with all the selection mechanisms inclusion in clinical trials is associated with. More recent and larger studies do not indicate that models are necessarily improving or that they are easily transferred between populations and provide precise risk estimation. These risk models should therefore be continuously updated as treatment and pathophysiological characteristics of the heart failure population evolves. They do, however, provide a risk stratification enabling to classify patients in low, moderate and high mortality risk groups.

Cardiopulmonay Exercise Test and Prognosis in Heart Failure

In clinical practice, cardiopulmonary exercise testing (CPET) has mainly been applied in the context of selecting patients for transplantation and has beyond this not gained wide use in prediction of prognosis in heart failure patients. In only 7 of the 26 models shown in Table 27.2 was CPET derived values tested in the model. In all of these CPET remained a strong significant predictor of mortality. Measures such as exercise duration or peak VO_2 are highly correlated and integrate physiological information that includes peripheral adaptation to impaired cardiac output. Risk models that have incorporated CPET data include the Heart Failure Survival Score (HFSS) developed in 467 patients with HFrEF and included peak VO_2 [6] and the

MECKI score (Metabolic exercise and cardiac and kidney indexes) derived from 2716 HfrEF patients using peak VO_2 and VE/VCO_2slope selected from 18 CPET parameters [26]. Also the simple, sex-specific UCLA model, included VO_2peak as one of only four variables to predict death/urgent heart transplant/LVAD in patients with severe HF [34]. In the HF-action study different measures derived from the CPET have been tested against a composite as well as mortality outcome. VO_2peak, exercise duration and VE/VCO_2slope were all significant predictors but the stronger predictor was exercise duration [11]. Exercise duration requires more standardization of the protocol than the other two parameters which is a draw-back and the utility of exercise duration depends on a standardized protocol for comparison among cohorts. Thus, if VO_2peak is measured this is preferable as it is more easily standardized.

Traditionally VO_2peak has been the main measure derived from CPET but in recent years there has been a shift in focus to indices of ventilatory inefficiency to maximize the utilization of the information derived from the CPET. Most notable the minute ventilation carbondioxide production (VE/VCO_2) slope has been shown to be a strong predictor of outcome in heart failure patients and this measure has also been shown to be modifiable by exercise intervention. Other CPET measures tested for their prognostic abilities include end-tidal carbon dioxide pressure ($PetCO_2$), heart rate recovery and the oxygen uptake efficiency slope (OUES). All of these seem to identify different aspects of the impact of heart failure on prognosis. Their individual predictive abilities were tested in a prospective multicentre study including heart failure patients from 4 centres in the US and Italy [22]. A weighted risk score combining the CPET derived information on VE/VCO_2slope, heart rate recovery, oxygen uptake efficiency slope, $PetCO_2$ and VO_2peak remained significantly associated with mortality after adjusting for age, gender, BMI, LVEF and cardiomyopathy type. The model predicted similarly regardless of type of cardiomyopathy (ischemic versus non-ischemic) or severity of heart failure (LVEF). A summed risk score of <5 was associated with a 1-year mortality risk of 0.4 % while a summed risk score >15 was associated with a mortality risk of 27 %. The superior prediction by adding several CPET derived variables was later confirmed in a larger study [35].

Risk Prediction in Acute Heart Failure

Risk models predicting in-hospital mortality in patients hospitalized with heart failure have also been developed. The largest is the based on data from the American Heart Association, Get with the Guidelines-Heart Failure/GTWG-HF) program [36]. This was based on data from more than 39,000 patients admitted to 198 hospitals in the period 2005–2007 with a clinical diagnosis of heart failure. The data is thus based on heart failure with both reduced and preserved ejection fraction. Mean age of the population was 72 years, 50 % were male and almost 50 % of the population had LVEF<40. The prediction model was derived on 27,850 patients and

validated internally on 11,933 patients. Candidate variables to include in the model were demographic, medical history and laboratory results from admission. In-hospital mortality was 2.9 % and the variables associated with increased risk and included in the resulting prediction model were higher age, lower systolic blood pressure, higher blood urea nitrogen (BUN), higher heart rate, lower sodium and COPD in addition to non-black race. Unlike several of the prediction models described above, LVEF was not a predictor, nor was diabetes or ischemic etiology. Biomarkers such as NT-proBNP, inflammatory markers, measures of symptoms or functional capacity were not entered into the model. From the model a mortality risk score was derived which distinguished a 24-fold range of risk across deciles ranging from 0.4 % mortality in the lowest decile to 9.7 % in-hospital mortality in the highest decile. The C-index for the model in the internal validation was 0.75 and the model performed equally well in patients with preserved and reduced LVEF. An advantage of the model is that all of the predictors are routinely registered in these patients. The mortality risk score is available on www.americanheart.org. However, the model has not been validated externally and should therefore be used with some caution.

Use of Risk Scores in Clinical Practice

A recent critical appraisal of existing risk scores in heart failure concluded that despite the large number of risk scores developed, the use of comprehensive prognostic models in clinical practice remains limited [37]. If good, precise and easily applicable models are available to the clinicians, these should help the clinicians select patients that may respond to certain therapies and should also serve to guide the clinician to the intensity of the care provided. Patients with a low risk score may be best suited cared for by their GP in primary care once the specialist or the heart failure clinic have optimised pharmacological and non-pharmacological treatment, while patients at intermediate risk should receive continued regular follow-up by a specialized team and the highest risk patients need to be monitored more closely including offered palliative care when end-stage disease is approached and further treatment is futile.

Given that a large number of risk scores are available, why do most clinicians not routinely use such scores? The answer may be because they frequently do not help very much in the care of the individual patient. Only few treatment choices depend on exact risk stratification by a risk score. Further, the outcome in most risk scores is all-cause mortality. This is the most validated outcome and has the advantage of being comparable across studies. However, to the patient other outcomes are more important, mainly non-fatal events, hospital admissions and quality of life. Unfortunately, the models developed tend to perform considerably poorer when using other outcome than all-cause mortality [37]. While this may be naturally explained by patterns of hospital admission being dependent on factors that vary with health systems and differ from those that predict mortality, more work is

needed to improve these models. More importantly, however, studies indicating that use of any risk score model improves care of patients with chronic heart failure are clearly lacking.

Studies have indicated that a barrier to the more widespread use of cardiovascular prediction tools is that many clinicians find the risk calculation too time consuming and are not convinced of the added value of their use. While use of risk prediction models are not evidence based in terms of clinical outcomes, they may be more useful in clinical practice if the information derived from these models was automatically calculated. This might be through development of automatized data capturing systems and systems for visualizing and stratifying risk calibrated to the relevant patient groups. This might minimize the user burden and could facilitate the communication and interaction with the patient. To the extent that modifiable variables are included in the model of choice, the model may also be used to illustrate how individual patient risk may be reduced.

Obesity and the Obesity Paradox

The prevalence of overweight and obesity is increasing world-wide and has been termed the obesity epidemic. Through the resulting increased prevalence of diabetes, hypertension and higher risk of coronary heart disease, the obesity epidemic contributes to the increase in prevalence of heart failure. Overweight is associated with increased risk of heart failure also through more direct effects on the pathogenesis of heart failure. The mechanisms are thought to be several and are summarized in Fig. 27.1. Adiposity has effects on hemodynamics, left ventricular structure and left ventricle function that are partially adverse. Obese individuals have higher central blood volume, higher stroke volume through central and peripheral adaptations, higher heart rate and higher cardiac output. At the same time, obesity without hypertension has reduced systemic vascular resistance which facilitates the higher cardiac output and the adipose tissue has lower oxygen demand and the obese individual has lower blood flow per unit BMI. Obesity leads to left ventricular remodelling, in particular in the co-existence with hypertension. The remodelling is mainly seen as an increase in left ventricular mass with or without hypertrophy which may both be eccentric and concentric depending on the balance between increased cardiac output and the increased systemic vascular resistance in hypertension. These mechanisms may result in left ventricular dysfunction. However, it is rare to see systolic dysfunction in patients who are overweight, obese or even extremely obese in the absence of other causes of systolic dysfunction, primarily coronary heart disease. Obesity does, however, lead to subclinical systolic dysfunction as apparent in studies using more advanced echocardiographic imaging such as tissue Doppler or speckle tracking [38–40]. More commonly, overweight and obesity leads to diastolic dysfunction, both through left ventricle hypertrophy but also independently of this. One study found that the prevalence of diastolic dysfunction in healthy

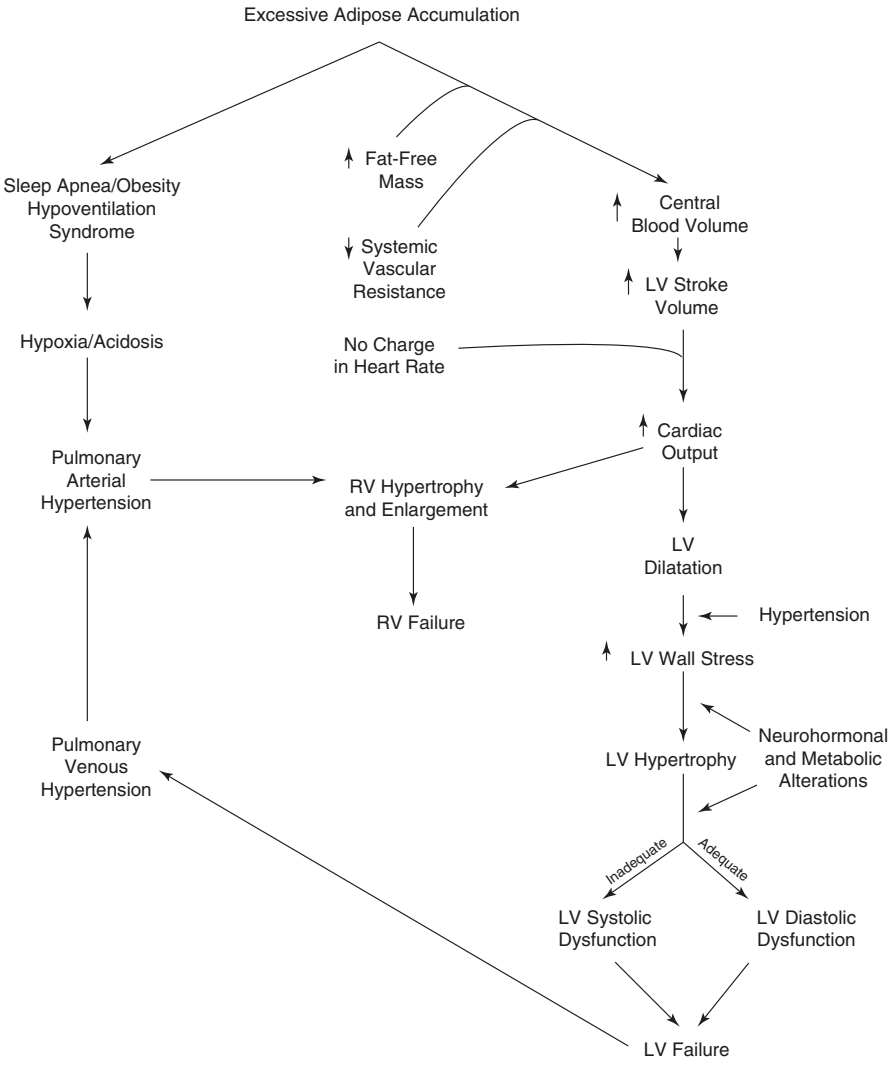

Fig. 27.1 A proposed model for the pathophysiology of obesity cardiomyopathy (Adapted from Alpert et al. [38] .Adapted from Reprinted from Alpert et al. [38], with permission from Elsevier)

individuals increased from 12 % in overweight (BMI 30–35) to 35 % in obese (BMI 30–35) and 45 % in very obese (BMI>35) [41]. Additionally, obesity has adverse effects on the left atrium and right ventricular function, partly through the co-existence of hypertension and increased left ventricular mass. Weight loss, in particular when leading to lowering of blood pressure, is associated with improvement in cardiac structure and function [38].

Given the higher risk of CVD in overweight and obese individuals and the mainly adverse effects of overweight on cardiac structure and function as described above it would be expected that overweight and obesity would also be associated with impaired prognosis in patients with established heart failure. However, this is not the case: overweight is consistently associated with lower all-cause and cardiovascular mortality in patients with heart failure. This unexpected finding of better survival in overweight and obese patients in clinical subpopulations has been termed 'The obesity paradox'. The paradox is not only seen for heart failure but also in many other disease conditions such as coronary heart disease, hypertension and atrial fibrillation as well as for non-cardiac conditions such as chronic obstructive pulmonary disease and renal disease.

After the association was first described two decades ago it has been confirmed in several prospective studies of heart failure populations. These studies were recently summarized in a systematic review and meta-analysis combining data from six studies, both clinical trials and observational studies and comprising heart failure with systolic dysfunction and with preserved ejection fraction [42]. The meta-analysis comprised 23,141 individuals, the majority male with a mean age ranging from 54 to 70. Follow-up was 1.5–4.1 years, NYHA class I-IV and the majority of the studies included HFrEF but one study included only HFpEF (I-PRESERVE). BMI was divided into underweight (<20 kg/m^2), normal weight (reference, BMI 20–24.9 kg/m^2), overweight (25–29.9 kg/m^2), obesity (30–34.9 kg/m^2) and severe obesity (BMI>=35 kg/m2). The outcomes studies were all-cause mortality, cardiovascular mortality and rehospitalisation. It was a uniform finding that the highest risk was seen in the underweight (mortality risk ratio (RR) 1.27 (1.17–1.37) compared to normal weight), followed by the normal-weight, and the lowest risk was seen in the overweight (mortality RR 0.78 (0.68–0.89)). Increasing levels of adiposity was not associated with further reduction of outcome (all-cause mortality RR 0.79 (0.65–0.97) and 0.75 (0.57–0.98) for obese and severely obese, respectively). There was significant heterogeneity between studies in the risk associated with obesity and severe obesity whereas the higher risk seen in underweight and normal weight was a homogenous finding. The overall associations are shown in Fig. 27.2, which also shows that hospital readmission showed a U-shaped relationship with lowest risk in the overweight and increased again in obese and severely obese heart failure patients.

The obesity paradox is poorly understood and continues to confound – hence the paradox. Several explanations have been offered that may each partially explain the surprise finding. Heart failure is a catabolic condition and it is not disputed that weight loss and low weight due to cardiac cachexia represents late stage disease and is associated with high mortality. It is difficult, however, to reconcile this with the optimal survival seen in overweight individuals. Another possible contributing factor may be lead time bias, i.e. the likelihood of earlier diagnosis in overweight patients because the cardinal symptoms of dyspnoea is apparent at an earlier stage. Indeed, in the meta-analyses reported above, overweight and obese heart failure patients were on average 4–7 years younger than their normal- and underweight counterparts. Heart failure is a catabolic state and overweight patients have a greater metabolic reserve, which may also give a survival benefit. It has also been suggested

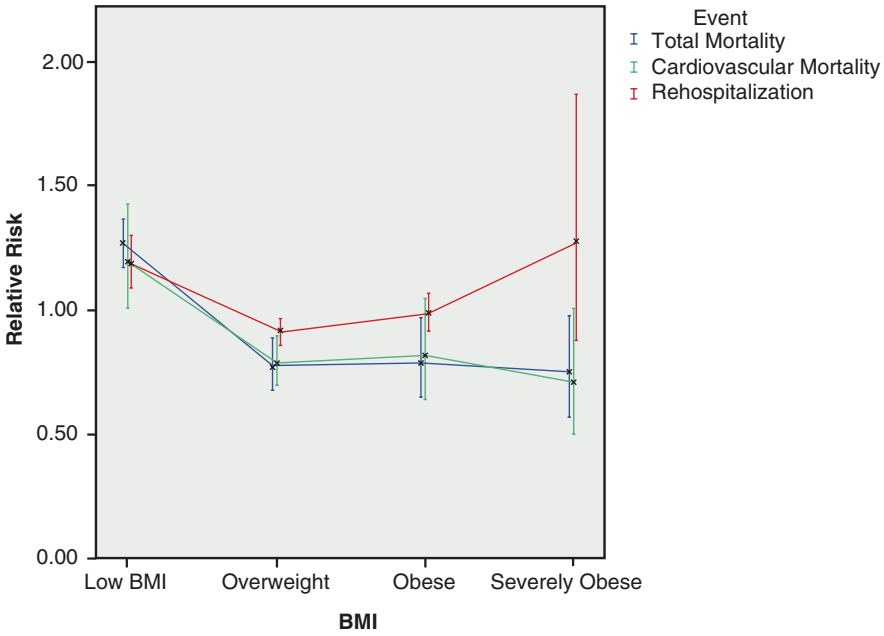

Fig. 27.2 Association between BMI and total mortality, cardiac mortality and hospitalization in heart failure patients. Results from metaanalysis of 16 studies with 3226 patients [42] (Reprinted from Sharma et al. [42], with permission from Elsevier)

that overweight individuals have protective cytokines. BMI is correlated with levels of soluble tumor necrosis factor alfa receptor level which may exert a protective role by partially neutralizing inflammation. Overweight and obese heart failure patients have higher levels of circulating lipoproteins that may bind and detoxify lipopolysaccharides and have a potential anti-inflammatory effect [42]. The use of BMI as the primary anthropometric measure of adiposity has been discussed as it does not distinguish between adipose tissue and fat-free mass. The lower mortality risk with higher BMI may also reflect beneficial effects of higher muscle mass. However, substitution of BMI for other anthropometric measures such as waist circumference and body fat have yielded similar associations. Interestingly, obese patients have an attenuated response to the renin-angiotensin-aldosterone axis which may lead to a better heart failure prognosis. Also, blood pressure is typically higher in overweight and obese patients and they may therefore tolerate higher dosage of evidence based medication, including beta-blockers, renin-angiotensin-aldosterone inhibitors and mineralocorticoid receptor antagonists.

With reference to the beneficial effect of exercise training and higher levels of fitness, it may also be argued that overweight and obese patients are in a permanent state of training due to the extra weight load they carry. In fact, one study stratifying heart failure patients by their exercise capacity from CPET found that overweight and obesity was only associated with improved survival in patients with low

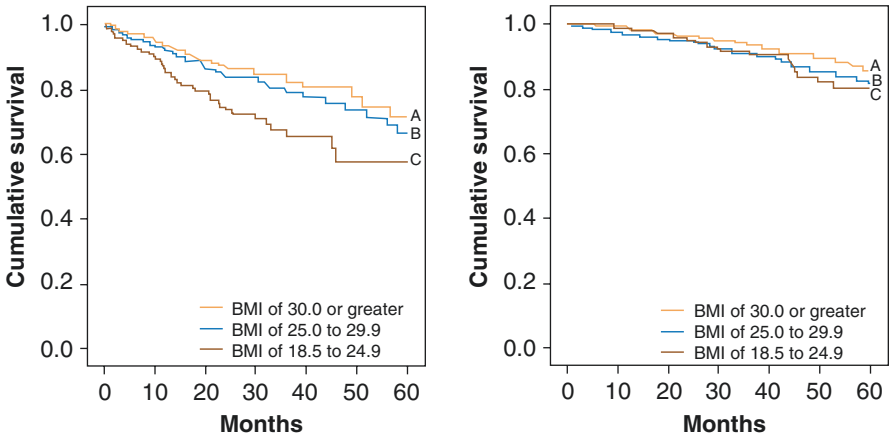

Fig. 27.3 BMI and cumulative survival stratified by low (*left*) and high (*right*) cardiorespiratory fitness [43] (Reprinted from Lavie et al. [43] with permission from Elsevier)

VO_2peak (<14 ml/(kg/min) whereas among patients who were more 'fit', degree of obesity was not associated with outcome [43] (Fig. 27.3).

Thus it remains unclear whether the lower mortality risk seen in patients who are overweight and obese is a true causal association or due to uncontrolled bias. The similar mortality ratios in overweight and obese individuals would indicate that the paradox is more a paradox of poorer survival in the normal and underweight than a protection conferred by adiposity. The poorer survival in the normal- and underweight may be due to more advanced disease. However, because of the uniformity of the finding, the insufficient understanding of the pathogenesis and the lack of intervention studies indicating beneficial effects of weight loss in patients with heart failure with morbidity or mortality outcomes, current guidelines do not provide firm recommendations for weight loss in heart failure patients who are overweight or even obese. Before weight loss can be recommended a better understanding of the mechanisms are needed and preferably also clinical trials showing that weight loss is beneficial in this patient group. However, in specific subgroups such as uncontrolled hypertension, severe obesity or diabetes, the balance may differ and weight loss can be recommended. Weight loss through exercise training with no loss of muscle mass may also be preferable. Conversely, weight increase through increased caloric intake is not recommended in patients who are not underweight or cachectic.

Depression and Prognosis in Heart Failure

Depression has been identified by the world health organization as one of the conditions responsible for the greatest loss of quality adjusted life years worldwide. With cardiovascular disease being the major cause of death, the co-existence of

depression with cardiovascular disease merits attention. Depression is associated with an increased risk of developing cardiovascular disease, rates of depression are higher among patients with cardiovascular disease and depression in patients diagnosed with coronary heart disease is associated with adverse outcome. It is unclear whether the association is causal but, regardless, the frequent concomitant presentation and consequences of undiagnosed depression has led to recommendations of screening for depression in patients with cardiovascular disease.

In heart failure the prevalence of depression is also increased. Studies indicate a prevalence of depression ranging from 9 to 54 % with a weighted mean of 22 % [44]. The prevalence of depression in the back-ground population is less than 10 % and the prevalence in patients with coronary heart disease is approximately 20 %. Thus the prevalence of depression among heart failure patients does not differ substantially from other cardiovascular disease groups. As the numbers indicate there is considerable heterogeneity in the registered prevalence in different studies, partly related to differences in depression scales used, whether diagnosis is through interview or questionnaire and the type of population studied. Prevalence is related to disease severity with an estimated prevalence of 11 % among asymptomatic heart failure patients and reaching 42 % among heart failure patients categorized in NYHA IV. As in both healthy populations and other cardiovascular disease populations, rates of depression are higher among women. Some symptoms of heart failure, e.g. fatigue, loss of appetite and sleeping disorder, are overlapping with heart failure symptoms and may confound association with adverse outcome. Depression is associated with disease severity as expressed in NYHA class and adjustment for disease severity as e.g. NT-proBNP did not affect the association [45, 46] .

A review of health care use and hospitalization among heart failure patients included 7 prospective studies of prognosis according to presence of depression. The data indicated a consistent pattern of increased health care use according to score on depression scales. Use of emergency room visits was twofold higher with depression, total health care costs 29 % higher and duration of hospital stays doubled [44]. A meta-analysis of mortality risk based on eight studies found a relative risk of 2.1 in heart failure patients with depressive symptoms or a depressive disorder. Despite variations as described above, this finding has been relatively constant. Unfortunately, the majority of studies of pharmacological treatment in patients with cardiovascular disease, including patients with chronic heart failure, have shown only moderate effect on depression symptom and in the two trials on chronic heart failure patients there was no effect [47]. However, the number of randomized trials of treating depression in patients with cardiovascular disease is limited and results heterogeneous. It is however, well documented that depression is associated with poorer compliance to pharmacological as well as other preventive medication and life-style changes [48]. Interestingly, while effect of pharmacological treatment is limited, exercise training seems to have beneficial effects on depression in patients with heart failure. A recent systematic review and meta-analysis of randomized controlled trials comprising 16 trials with a total of 3226 patients found that exercise training significantly reduced depression with a standardized mean difference

between those exercising and the controls of −0.38 (−0.55 to 0.21, $p < 0.00001$) [49]. Results were consistent across subgroups defined by age, ejection fraction, duration of training intervention and training modalities. Also cognitive behavioural therapy has been shown effective in treating depression in patients with heart failure in randomized trials [50, 51].

The American Heart Association recommends screening for depression in CVD patients [52] However, screening is only useful if it identifies patients who are not already diagnosed with depression and if it is followed by an adjustment in the way the heart failure patient is managed. While most other guidelines recognize the high prevalence of depression and the adverse outcome associated with the condition, the do not directly recommend systematic screening due to lack of evidence that this leads to improved outcomes in the population as such [53, 54], Guidelines from the European Society of Cardiology stress that the co-existence of depression may lead to poor adherence to treatment and social isolation and that there is a need of attention to consider the diagnosis in each heart failure patients, especially the elderly in whom the diagnosis of depression is often overlooked. There is no specific recommendation of how to diagnose or screen for depression in the cardiologic setting; several validated questionnaires are available. For pharmacological treatment of depression in heart failure patients, selective serotonin reuptake inhibitors are thought to be safe, whereas tricyclic antidepressants are not because they may cause hypotension, worsening heart failure, and arrhythmias [55].

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Chapter 28
Rehabilitation Therapy in Patients with Heart Failure

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Heart failure (HF) has proven to be a growing epidemic, with a significant socio-economic impact. In developed countries, 1–2 % of the adult population is diagnosed with HF, however prevalence is about 10 % in patients at age 70 [1].

Mortality and morbidity remain a major concern, despite a better understanding of the natural history of many cardiac conditions and the considerable progress in the management of patients with HF. Consequently, interest in cardiac rehabilitation has been renewed.

Cardiac rehabilitation programs have become an integral part in the standard of care in modern cardiology. Their objectives has shifted from an emphasis on individualized exercise therapy to secondary prevention strategies, including comprehensive management of risk factors, nutritional, psychological and behavioral strategies, all of which can impact patient outcomes.

As pioneers of cardiac rehabilitation, Levine and Lown have faced a strong opposition for supporting early mobilization patients. However, a growing body of evidence demonstrated the early benefits of physical activity, thus becoming an essential argument to convince skeptics [2].

In 1953, a study conducted by Morris revealed that bus drivers in London had a higher rate of events compared to ticket sellers [2]. This observation was attributed to the fact that ticket sellers climbed up and down the double-decker bus while drivers sat behind the wheel.

In 1968, Saltin et al. published a small study, highlighting the importance of physical exercise and the strong negative effects of prolonged bed rest [2].

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M. Dorobanţu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_28

The works of Braunwald, Sarnoff, Naughton and many others helped in providing a physiological basis for the benefits of exercise, which led to the development of cardiac rehabilitation programs from a multidisciplinary perspective. The main objective was to facilitate the recovery of cardiovascular patients, and to optimize their functional and psychological condition [3].

Since then, this approach proved to have indisputable benefits concerning morbidity and mortality and has been recommended by the majority of the professional cardiovascular societies as an important therapeutic tool in modern cardiology [4].

Cardiac rehabilitation is a multidisciplinary intervention program, adjusted for cardiac patients in whom the aim is to reach and maintain an optimal level of functioning by improving pathophysiological and psychological outcomes inherent to cardiac events. These long-term interventions include mainly training sessions, as well as psychological and educational support and allow for close monitoring and medical therapy adjustment [5].

From the perspective of the European Association of Cardiovascular Prevention and Rehabilitation, cardiac rehabilitation can be regarded as the clinical application of supervised prevention through a multidisciplinary, integrated and accessible approach, having set long term risk reduction and global monitoring of cardiac patients as main goals [6].

Enrollment of patients in a multidisciplinary management program to reduce the risk of hospitalization has been a class I recommendation since 2008, as stated in the European Society of Cardiology guidelines for the diagnosis and treatment of heart failure [7].

However, it is hardly implemented in daily practice. A study conducted in 673 hospitals from 43 European countries, showed that only 63 % reported implementation of heart failure management programs and, of these, only 42 % involved exercising. In Europe, less than 20 % of patients with HF are participating in cardiac rehabilitation programs designed for research [8].

In the past decade, the beneficial effects of cardiac rehabilitation programs for patients in NYHA functional class II–III with stable chronic HF have been confirmed in several randomized clinical trials.

Several reviews and meta-analyses of a number of small studies showed that physical conditioning and training improve exercise tolerance, quality of life and the hospitalization rate in patients with HF [9].

The most recent Cochrane review on physical training [10], which included 33 trials with 4740 patients, the majority of whom had heart failure with reduced ejection fraction (HFrEF), showed a decreasing trend in mortality at more than one year follow-up. Training reduced hospitalizations and improved quality of life compared to the control group [9].

Physical training has also demonstrated its benefits in patients with HF with preserved ejection fraction (HFpEF), obviated by an improvement in parameters such as increased oxygen consumption, and diastolic function (as evaluated echocardiographically).

Pathophysiological Basis of Physical Training

Most studies related to exercising in heart failure included patients with reduced EF. It is important to emphasize that there is a large number of heart failure patients with preserved ejection fraction and limited exercise capacity can be seen in this category of patients as well [11].

Physical therapy is complementary in chronic heart disease with left ventricular dysfunction and helps in reducing neurohormonal stimulation, production of proinflammatory cytokines and natriuretic peptides overexpression. Moreover, exercising improves peripheral vascular and muscular abnormalities by reducing systemic resistance, it improves endothelial dysfunction and restores the oxidative capacity with no consequent left ventricular remodeling.

Regardless of etiology, chronic HF begins as an insult to the heart's pump function, while disease progression causes peripheral organ damage and neurohormonal activation. As a general observation, heart rate (HR) is increased at rest and decreased on maximal exertion, leading to a reduction in chronotropic reserve, chiefly caused by beta-adrenergic receptor desensitization.HR recovery (adequate reduction in heart rate following exertion) is an indicator of the parasympathetic activity, which in heart failure is reduced. Physical therapy has been proven to reestablish cardiovascular autonomic tone, especially with a positive impact on sympathetic activity, seen including in patients who received beta-blockers [12, 13].

Excessive neurohormonal activation (sympathetic nervous system and renin-angiotensin system activation) is the main pathophysiological mechanism in advanced heart failure. Patients with excessive sympathetic activation have the poorest prognosis. More recently, proinflammatory cytokines and natriuretic peptides have been identified as markers in various stages of HF. Physical therapy reduces norepinephrineserum levels at rest and during exercise, decreasing central sympathetic discharge (as measured directly by microneurography) and improving vagal activity and, consequently, heart rate variability. Overall, physical therapy reestablishes a balance between sympathetic and vagal activity [14].

Moreover, in patients with HF, exercising causes a significant reduction in local cytokine tumor necrosis factor-alpha (TNF-alpha), interleukin-1-beta (IL-1-beta) and interleukin-6 (IL-6)expression, as well as increased nitric oxide (NO) synthesis in skeletal muscle [15, 16]. The local anti-inflammatory effects occurring during exercise can improve catalytic processes associated with HF progression. Numerous studies have shown a post-exercise reduction in natriuretic peptide overexpression, with a significant reduction of the brain natriuretic peptideprohormone and N-terminal brain natriuretic peptide levels [17].

In patients with HF, vascular abnormalities are involved in the impairment of the vasodilatory response. Impaired flow-dependent vasodilation within resistance arteries seems to be the main anomaly in the response to effort. Endothelial abnormalities and in flow-dependent vasodilation are the key pathophysiological phenomena responsible for the decreased vasodilatory response to exercise seen in HF. A significant improvement in endothelial relaxation has been demonstrated in

trained patients [18]. In addition, exercising improves both endothelial nitric oxide synthesis, endothelial-dependent vasodilation and skeletal muscle vascular relaxation in patients with HF [19].

Targets of Physical Training in Heart Failure

Physical training improves exercise capacity and quality of life, with no adverse effects on left ventricular remodeling. Furthermore, it reduces mortality and hospitalization rates in patients with mild-to-moderate chronic HF [20].

Hemodynamics

Exercise capacity is dependent on both central and peripheral mechanisms. The interdependence between the two mechanisms is explained by Fick's equation:

$VO_2 = [Q \times (CaO_2 – CvO_2)]$, where VO_2=oxygen consumption, Q = cardiac output, CaO_2=arterial oxygen concentration, CvO_2 = venous oxygen concentration.

Physical training improves left ventricular function and hemodynamics. The extent of these effects has been illustrated in a meta-analysis of randomized controlled trials related to physical training in chronic heart failure [21]. Aerobic training was correlated with a significant increase in left ventricular ejection fraction (LVEF) and left ventricular end-diastolic volume (LVEDV) [21], suggesting a training-induced reverse-remodeling [22]. In 2007, a meta-analysis of 14 studies (including 812 patients) demonstrated that moderate aerobic exercise significantly improves LVEF (*weighed difference* [WMD] = 2.59 %, 95 % confidence interval [CI] = 1.44–3.74 %) and LVEDV (WMD = −12.87 ml, 95 % CI = −19.95 ml up to −3.02 ml) compared to usual rehabilitation [21].

It was proposed that increased preload, improved myocardial contractility and increased vascular reserve combined can explain the improvement in LVEF observed after aerobic exercise. In line with these observations, training-induced reverse-remodeling seems plausible in clinically stable heart failure patients.

Improvement in LVEF has been comparable to the benefits seen with angiotensin-converting enzyme inhibitors (ACEI) and cardiac resynchronization therapy (CRT).

Some investigators suggested that interval training programs are associated with a higher increase in LVEF than the continuous or steady-state alternative [23].

Functional Capacity

Peripheral muscle abnormalities are a key factor for decreased exercise capacity in patients with HF. Muscle atrophy and structural changes occur frequently, particularly associated with malnutrition, deconditioning and cytokine toxicity. Muscle fiber distribution is also modified: the number of glycolytic type IIB fibers

increases on account of oxidative type I fibers loss. Mitochondrial density is low, in addition to a selective reduction in enzymes involved in the Krebs cycle [24].

Physical training leads to a significant increase in muscle aerobic capacity, with a dramatic increase in myofibrillar cross-sectional area and mitochondrial and capillary density. These changes also occur in low-intensity endurance training, significantly improving both peak VO_2 and ventilatory threshold. Moreover, an increase in exercise intensity (70 % of peak VO_2) seems necessary in order to achieve a significant redistribution and increase in type I fibers and a concomitant substantial decrease in type II fibers [24]. Improvement in aerobic metabolism post-training provides a means for the HF patient to perform daily activities more easily and more comfortably.

Numerous studies have shown that exercise training improves exercise tolerance, an observation supported by increasingly prolonged exercising, improvement in maximal oxygen consumption (peak VO_2 peak) or in NYHA functional class after one to 6 months of training [25]. These trials have been conducted in a single center, on a small lot of patients and with a short-term follow-up. None of these small trials had the capacity to examine mortality and morbidity.

Different meta-analyses have reported that physical training increases peak VO_2 with approximately 2 ml/kg/min [14, 18] or 17 % [19]. A post-training increase in aerobic metabolism allows patients to partake in daily activities more easily and more comfortably.

The results of the HF-ACTION (*Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training*), the largest multicentric randomized study, have been eagerly expected. HF-ACTION was designed to quantify the effects of physical training on clinical parameters and the safety of patients with stable systolic heart failure [21]. The effects of exercise have been studied on 2331 patients with heart failure, an LVEF <35 % and in NYHA functional class II–IV undergoing optimal medical therapy. Patients have been randomized 1:1, either in the physical training group (36 moderate intensity training sessions, supervised and followed by home training) [21], either in the classic rehabilitation group. After a mean follow-up of 30 months and adjustment of predefined prognostic predictors, the primary composite end-point of mortality and readmission was significantly reduced (−11 %, p = 0.03) in the physical training group. Increase in peak VO_2 was modest, though statistically significant (0.6 % versus 0.2 ml/min/kg) in the controlled program group. There was improvement in 6-minute walk distance in both groups, at 3 and 6 months, respectively. Improvement in 6-min walk distance attenuated at 12 months. Regardless, adherence to prescribed exercise regimens was reduced compared to predicted, and affected the increase in peak VO_2. Long-term and short-term optimization of adherence to physical exercise is one of the major objectives of cardiac rehabilitation, requiring specific strategies [26].

A recent post-hoc analysis concluded that HF-ACTION data demonstrated a clear association between improved exercise capacity and training volume, emphasizing once more the importance of compliance (n = 959) [26]. Moreover, a clear relationship between peak VO_2 and clinical results has been found. Investigators

have concluded that in the population studied in HF-ACTION, each 6 % increase in peak VO_2 (adjusted for other significant predictors) was associated with a 5 % lower risk of primary end-point (*hazard ratio* [HR] = 0.95; CI = 0.93–0.98; $p < 0.001$) and a 7 % lower mortality rate (HR = 0.93; CI 0.90–0.97; $p < 0.001$) [25]. Further supporting the relevance of the increase in exercise-induced aerobic capacity, another prospective study shows that the lack of improvement in peak VO_2 after a physical training program is a strong independent predictor for adverse cardiac outcomes [25].

The combination of aerobic training with resistance training has not proven superior to aerobic training alone in terms of peak VO_2 changes [25]. Evidence suggests that the beneficial effects of aerobic exercise on left ventricular volume diminish if resistance training is added to the rehabilitation program [21].

High-intensity interval training determines a higher increase in peak VO_2 than moderate continuous aerobic training (45 % versus 14 % increase) [23].

Regardless, patients with heart failure rarely use their maximum exercise capacity during their daily activities, the majority of these being under the anaerobic threshold. As a consequence, the majority of the studies are generally applicable and recommend training 3–5 h a week by cycling, walking or running [27]. This regimen is associated with a 25 % increase in VO_2 and ventilatory threshold and a 25 % increase in submaximal exercise duration (from 938 to 1429 s) [27, 28].

Maximal aerobic capacity is a strong and independent prognostic factor in patients with HF and determines the amount of daily activities a patient can perform independently. The latter translates directly to quality of life. In 2004, a systematic review of randomized controlled trials related to training in patients with congestive heart failure demonstrated an average increase of 2.16 ml/kg/min in maximal oxygen volume and an improvement in quality of life in 7 of the 9 studies. The HF-ACTION study included evaluation of training effects on the individual general state of health. A modest, but significant improvement in the general state of health was observed in the test group at 3 months, based on the KCCQ questionnaire results. This improvement persisted in time and the effect was similar in KCCQ sub-scales, that address physical limitations, symptoms, quality of life and social limitations [29].

Ventilatory Response

Exertional dyspnea is not only caused by increased pulmonary pressures, on the contrary, it is also linked to CO_2 volume, residual pulmonary space, pulmonary blood flow and peripheral muscle chemoreceptor stimulation. Both endurance and respiratory muscle training improves ventilator capacity. Mancini et al. [30] studied the effect of respiratory muscle training in a group of 14 HF patients.

Maximal ventilatory capacity increased from 48.6 to 76.9 l/min, with a concomitant increase in respiratory muscle power. Recently, other authors have reported an improvement in peripheral blood flow both at rest and during exercise following respiratory muscle training [31]. Furthermore, a significant improve-

ment in oxygen delivery efficiency was also reported. This new variable assesses the linear relationship between ventilation and exercise intensity, following 6 months of combined strength/aerobic training. The study included 35 patients with stable HF [32].

Cardiac Rehabilitation Phases

Cardiac rehabilitation consists of three phases of personalized care, all of which aim to facilitate recovery and to confer an additional strategy to prevent cardiovascular disease.

A. Phase I or the *hospital phase* begins during hospitalization, with early and progressive mobilization of the stable cardiac patient, in order to regain the required level of activity to perform daily activities and to ensure mobility independence. This is the phase that introduces the patient to the cardiac rehabilitation program, including the nature of their disease, treatment, risk factor management and follow-up planning.
B. Phase II consists of cardiac rehabilitation per se and continues in the outpatient institutionalized, non-institutionalized or hospital setting (the latter for complicated heart failure cases) and implies a complex approach, with supervised physical training, aggressive control of associated risk factors. Training programs are personalized and aim at improving physical conditioning.
C. Phase III is a *maintenance period* continued during the patient's lifetime, with further emphasis on physical abilities and supplementary reduction of risk factors. The patient is able to conduct activities independently or/and in specialized groups (cardiac patients clubs) in order to maintain and improve the level of fitness attained during the previous phase.

Modern and complete rehabilitation programs offer a comprehensive approach in order to alter disease course, to modify existing risk factors, as well as providing professional support in nutrition counseling, psychosocial management, and advice concerning physical activity and training [28].

The European Society of Cardiology (ESC) and European Association for Cardiovascular Prevention & Rehabilitation (EACPR) have established the main components of contemporary cardiac rehabilitation and secondary prevention programs comprised within guidelines that specifically address management and prevention of cardiovascular disease.

Scientific data clearly demonstrate that physical training improves exercise tolerance. When prescribed adequately, exercise training is the key component to cardiac rehabilitation. Meyers and collaborators showed that a one metabolic equivalent (MET) improvement in functional capacity reduces all-cause mortality by 12 % [33].

Physical training is recommended in patients with stable heart failure, in NYHA I–III functional classes. Data collected from clinical studies rule out exercising in

patients with acute HF, however early mobilization and a personalized training program following hospitalization can prevent disability progression. Investigators have described a transition phase between clinical stabilization and initiating physical activities [7].

Clinical stabilization and early mobilization help in attaining functional self-sufficiency prior to conducting symptom-limited stress testing and initiating physical activity. During this phase, gradual mobilization, respiratory training and small-muscle resistance training can be considered individually or in combination. Each exercise modality can be individually tested in heart failure patients through clinical tolerance and hemodynamic status. This phase can be extremely flexible in terms of temporal and modality development [7].

When clinical stabilization is achieved, screening for exercise training contraindications is required, including medical history, clinical examination, resting ECG, symptom-limited stress testing and echocardiography. If clinical status is unclear and/or previous studies are inconclusive, further investigation is required: 24-h Holter ECG monitoring, chest radiography or stress echocardiography [7].

Symptom-limited stress testing is used for risk stratification before initiating training. Exercise training prescription is based on stress testing results and includes the type, intensity, duration and frequency of exercise [34].

Finally, exercise modality selection depends on age, comorbidities, preferences and abilities, logistical restraints and availability of training equipment.

Identification of the appropriate level of training intensity is essential to obtain the desired benefits and maintaining reasonable risk control. There is no universal consensus on exercise prescription in patients with HF, therefore each approach should be personalized based on a careful clinical examination, including behavioral characteristics, personal goals and preferences [7].

Exercise training protocols vary, according to: *intensity*: aerobic and anaerobic, *type*: endurance, resistance and strength, *method*: continuous and intermittent/interval; *application*: systemic, regional and respiratory muscles, *control*: supervised and non-supervised, *location*: hospital, rehabilitation centers, home-based.

Exercise intensity is calculated based on the corresponding percentage value of functional capacity (peak VO_2) that in turn corresponds to the percentage value of the estimated maximal HR (220-age). The targeted HR can be determined through numerous other methods, such as the HR achieved during the maximal exercise point where symptoms of exercise intolerance develop. Therefore, exercise intensity can be classified into three categories utilizing maximum heart rate percentage in: light (<60 %), moderate (60–79 %) and vigorous (80 %) [35].

For submaximal tests, maximum HR is the HR where exercise-limiting symptoms develop: angina, dyspnea, tiredness. Training HR is calculated using maximum heart rate reserve (the difference percentage between maximum heart rate and resting heart rate). For example, by utilizing the maximum heart rate reserve method, exercise prescription for a 45-year old patient with a maximum HR of 170 bpm and a resting heart rate of 70 bpm, if the targeted exercise intensity is 60–80 % of capacity (60 % × 100 = 60, 80 % × 100 = 80, the sum between resting heart rate and heart

rate reserve depending on targeted exercise intensity corresponds to the targeted training HR: 130 bpm and 150 bpm, respectively).

Exercise intensity can also be estimated by using the perceived rate of exertion or the Borg scale. This is a validated method that many patients can easily learn [36, 37].

Borg scale – perceived rate of exertion			Exercise intensity (VO_2%)
Very, very light	8	9	
Very light	10	11	
Fairly light	12	13	Light intensity <60 %
Somewhat hard	14	15	Moderate intensity 60–79 %
Hard	16	17	Vigorous intensity >80 %
Very hard	18	19	
Very, very hard	20		

Physical Training Indications

Regular aerobic physical training is recommended in patients with heart failure in order to improve functional capacity, symptoms and to reduce hospitalization risk (class I recommendation, level of evidence A) [10].

The data available concerning cardiac rehabilitation refers to patients with stable heart failure in NYHA II–III functional class, in sinus rhythm with no limitation of exercise capacity [29].

The benefits of specialized cardiac rehabilitation programs that aim to improve the clinical status of outpatients with heart failure symptoms and reduced ejection fraction have been demonstrated. The beneficial impact of exercise can be seen early in low-intensity or high-intensity training after the first 3 weeks. Data available thus far are not sufficient to recommend cardiac rehabilitation in patients with heart failure in NYHA IV functional class [38].

Contraindications to Physical Training [7]

Physical training is contraindicated in the following situations:

- acute heart failure
- uncontrolled hypertension
- high grade atrioventricular block
- acute pericarditis or myocarditis
- symptomatic aortic stenosis
- severe obstructive hypertrophic cardiomyopathy
- acute systemic diseases

- intracardiac thrombosis
- dyspnea at rest 3–5 days previously
- significant ischemia during low-intensity effort (<2 METs, <50 W)
- uncontrolled diabetes mellitus
- recent embolism
- thrombophlebitis
- recent atrial fibrillation or flutter

Increased Risk for Training [7]

- >1.8 kg increase in body mass over the previous 1–3 days
- intermittent or continuous dobutamine therapy
- systolic blood pressure drop during effort
- heart failure NYHA IV functional class
- complex ventricular arrhythmias at rest or during effort
- resting heart rate >100 bpm
- comorbidities limiting exercise tolerance

Evaluation of Exercise Capacity Before Starting Physical Training

In heart failure patients, maximal or symptom-limited stress testing on cycle ergometer or treadmill with ventilatory gases analysis (cardiopulmonary exercise testing – CPET) is considered the basis to prescribing safe and efficient exercise regimens. It is essential to underline its importance in establishing prognosis (peak VO_2, VE/VCO_2 slope and oscillating breathing) [39], adjusting treatment (designing personalized physical training and establishing the indication for heart transplant [40]). These data cannot be derived from submaximal stress testing, such as the 6-min walk test [41].

With respect to safety, the HF-ACTION study provides a sound body of evidence. Out of 4411 tests, mortality rate was of 0:1000 tests, whereas the rate of non-fatal major cardiovascular events was 0.45:1000 tests (95 % CI = 0.11–1.81). No exercise related ICD discharge requiring hospitalization has been reported [42].

Training Modalities

Currently, there are no clear guidelines available for physical training prescription in heart failure, therefore there is a wide variety of approaches in these patients. Programs differ by type of exercise (endurance and resistance), intensity (aerobic

versus anaerobic), method (continuous versus interval training), setting (hospital/specialized center versus home), application (systemic, regional and respiratory) and control (supervised versus non-supervised) [39]. In order to optimize the benefits of physical training in patients with heart failure, a personalized program should be designed to address both peak aerobic capacity and the ability to continue submaximal exercise on long periods of time (quality of life and independence). To meet these requirements, three different modalities have been proposed in different combinations: (a) endurance or physical training (continuous and interval), (b) resistance training, (c) inspiratory muscles training.

Aerobic, Endurance Physical Training

Continuous aerobic training is typically recommended at a moderate-to-high intensity in steady-state energy yield conditions, which allows patients to perform prolonged training sessions of about 45–60 min duration. It is considered the most appropriate form of training, having demonstrated its efficacy and safety, while also being recommended by current guidelines [43]. Furthermore, it is well accepted because it is easy to perform and recommended as a core activity on a cycle ergometer or treadmill. In deconditioned patients, it is advisable to start at a low intensity, up to 10–15 min/week. If exercise tolerance is good, training duration is increased first each session, followed by an increase in the number of sessions per day, up to 20–30 min, 3–5 days/week, at a moderate-to-high intensity and with an indefinite program duration.

The gold standard method for exercise intensity assessment is the direct measurement of peak oxygen consumption (peak VO_2) through symptom-limited cardiopulmonary exercise testing. Training intensity is usually prescribed relative to peak VO_2 and VO_2 reserve (VO_2R). In the beginning, the recommended intensity is 40–50 % with gradual increase to 70–80 % of peak VO_2 [25].

Because the cardiopulmonary exercise testing is not routinely used in clinical practice, other indirect methods have been proposed, such as conventional stress tests or the 6-min walk test. Thus, heart rate (HR) or heart rate reserve (HRR = difference between peak heart rate and resting heart rate) and the rate of perceived exertion (RPE) are elements used to determine exercise intensity. For exercise training, an HRR between 40–70 % and a score of 10/20–14/20 on the Borg scale are recommended [41].

The HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) study was the largest randomized, multicenter study, designed to quantify the effects of physical training on clinical outcomes and safety in patients with stable systolic HF [21].

In this study, the exercise modalities were very clearly described, continuous aerobic training sessions were conducted at a moderate intensity (60–70 % of HRR). Interval aerobic and resistance training were prohibited in order to ease translation from clinical practice to everyday life.

HF-ACTION trial results recommended an exercise intensity at 70 % of heart rate reserve, 3 days a week for 6–8 weeks [44].

Intermittent or aerobic interval training (AIT) at intensities up to 95 % of maximal HR provides the best hemodynamic results [40] and is recommended to improve exercise capacity. This observation was revealed by a small randomized trial where the study population consisted of 27 patients with HF post-myocardial infarction (age 75.5 ± 11.1 years) (LVEF 29 %). Investigators have shown that interval training led to improvement in aerobic capacity (improvement in peak VO_2 46 % vs 14 %, $p < 0.001$), LV reverse remodeling, endothelial function and quality of life. Recently, the same group of investigators has published the results on AIT safety in cardiac patients (though not exclusively with HF) [45].

It was concluded that the risk of a cardiovascular event is low after high- and moderate-intensity exercise conducted in a cardiovascular rehabilitation setting.

Compared to continuous training protocols, patients switch between moderate-to-high exercise (50–100 % of FC max) at short intervals (10–30 s) with long recovery periods (60–80 s) that involve a small or no load.

High-intensity programs are recommended in patients who exercise on the treadmill. Each session includes: a 4-min high-intensity exercise (90–95 % of maximal exercise capacity) separated by 3-min intervals of low-intensity exercise, plus 5–10 min of warm-up [46]. If exercising is performed on the cycle ergometer, a training period of 30 s is recommended, with a gradual 25 W increase load every 10 s, followed by a recovery period of 50 s at an intensity of 20 % of maximal exercise capacity [47].

Resistance/Strength Training

Functional alterations in skeletal muscle are considered an important determinant of exercise intolerance in chronic HF. In addition, aging is associated with a continuous decline in skeletal muscle mass [48], therefore resistance/strength training (RST) can be considered in these patients.

Although concerns regarding the potential detrimental effect on left ventricular function and remodeling caused by increased afterload during resistance training have not been confirmed, current evidence remains controversial and, as a consequence, general recommendations on resistance training implementation as an exercise modality in HF patients cannot be upheld. Of note, aerobic exercise remains fundamental in patients with HF, whereas resistance training can reasonably complement, but not substitute [46].

The intensity of the expected cardiovascular stress during resistance training depends on the magnitude of the resistance, determined on the basis of 1 “repetition maximum” (1-RM), meaning the maximum weight an individual can lift once, properly and with full range of motion [49]. To ensure maximum safety, initiating an RST program should be adapted for each patient by an experienced physiotherapist, under medical supervision. Each patient should be individually introduced into the training program. The minimum recommendations for implementation of an RST consist of

an *instruction phase* to allow the patient to get accustomed to the modality of the exercise, intermuscular coordination and physical perception. These introductory exercises should be conducted slowly without or at a very low resistance (<30 % 1-RM), until the patient feels comfortable with the movements; the *strength/endurance phase*: RST can be started with a high number of repetitions (12–25) and at a low intensity (30–40 % 1-RM) corresponding rather to a combination of endurance and resistance due to a low hemodynamic load. When the patient gets accustomed with the exercise, he can progress to the next phase (strength phase). *Strength phase*: RST at higher intensity (40–60 % 1-RM) to increase muscle mass [50].

Resistance training of moderate-to-high intensity performed 2–3 days/week (over 3–6 months) improves muscle strength by 25–100 %. However, since the pressure response to resistance training is proportionate to the percentage of maximum voluntary contraction, as well as to the muscle mass involved, the resulting increase in muscle strength leads to a reduction in HR and a blood pressure (BP) response at any given load, because at this point loading represents a smaller percentage of maximum voluntary contraction [7].

Training programs include a set of 8–10 types of exercises that involve major muscle groups, performed 2–3 days per week. Ten to 15 repetitions at a relatively small resistance is recommended. Weight can be adjusted in accordance with patient wishes (a maximum of 15 on the Borg scale) and should always be less than 50 % of the maximum weight that determines repetition [7].

Inspiratory Muscles Training

Trials using respiratory muscle training in patients with HF suggest that it can improve exercise capacity and quality of life and, in particular, it contributes to additional improvement in inspiratory muscles performance. Adding specific inspiratory muscles training to the standard aerobic training program could prove beneficial. It was suggested to begin respiratory training at 30 % of the maximum inspiratory pressure (PI max) measured at functional capacity and adjusting intensity every 7–10 days up to a maximum of 60 %. Training sessions can last 20–30 min/day with a frequency of 3–5 sessions/week for at least 8 weeks [51]. Different protocols and respiratory muscle devices are utilized in various clinical variants, including isocapnic hyperpnea, spirometry, or resistive pressure. Exercising and strengthening the abdominal muscles is also recommended.

Additional Measures: Cardiovascular Risk Factors Modification

Regular physical training programs have demonstrated their efficacy in improving care, the number of readmissions, functional status and global mortality. Improving biological or lifestyle-related risk factors requires counseling or real time treatment

(depending on each case), continuation of care and patient access to treatment regardless of socio-economic status [52].

A superior adherence to lifestyle changes recommendations and to medical treatment is determined by the social support of medical personnel and physicians alike. A positive, friendly doctor-patient relationship is extremely useful in helping the patient maintain healthy habits and compliance. Changing negative into positive experiences can be achieved through establishing realistic objectives and behavior self-monitoring.

Diet Nutritional counseling is an integral part in the management of cardiovascular risk. All patients should receive specialized counseling in reviewing risk-reducing diet options. Caloric intake should be adjusted, while encouraging fruit, vegetables, whole bread and grains, fish, lean meat and defatted dairy products consumption. Substitution of saturated fats with mono- and polyunsaturated fats of vegetable origin or from fatty fish is essential to reduce total lipids to less than 30 % of dietary intake, out of which saturated fats should comprise less than a third of lipid intake. If blood pressure is high, salt intake should be restricted by avoiding adding salt when cooking or dining. In addition, fresh food consumption should also be recommended [52].

Body Weight *Body weight* is part of the cardiovascular risk, given that adipose tissue and, more specifically, abdominal visceral adipose tissue is a metabolically active endocrine tissue, able to synthetize and release in the circulation a great variety of peptides and non-peptides that could have a role in cardiovascular homeostasis. Excessive adipose tissue is associated with an increase in free fatty acids production, hyperinsulinemia, insulin resistance and dyslipidemia [53]. In obese patients (BMI >30 kg/m^2) weight loss should be recommended, while in overweight patients (BMI >25 kg/m^2 – <30 km/m^2) it needs to be taken into consideration. Total caloric intake reduction and regular exercising are essential to control body weight. Recent studies have shown that exercising can influence abdominal adipose tissue before weight loss [54].

The main target of weight management is reaching a BMI between 18.5 and 24.9 kg/m^2 [54].

Hypertension *Hypertension* is a cardiovascular risk factor for both males and females. Blood pressure (BP) values correlate inversely with cognition and hypertension is associated with a higher incidence in dementia [55].

Data from the Framingham study indicate that BP values ranging between 130–139/85–89 mmHg associate with more than a twofold increase in the relative risk of cardiovascular disease compared with values below 120/80 mmHg [56]. Therefore, management of BP is essential. In parallel, the doctor should prescribe a treatment regimen.

Diabetes Mellitus Trials conducted in patients with diabetes mellitus type 1 and type 2 have concordantly demonstrated that an optimal metabolic control averts microvascular complications, justifying the need for good blood sugar control and

specialized nutritional counseling, weight loss and increasing the level of physical activity. The utility of therapy education within cardiac rehabilitation programs transpires in better glycemic control [57].

Smoking Smoking has synergistic effects in cardiovascular pathology, particularly when other cardiovascular risk factors are also present. The benefits of smoking cessation have been extensively reported [58].

Smoking cessation should be encouraged, despite being a complex and difficult process due to strong psychological and physical dependence. Chewing gums and nicotine patches have been widely used. Antidepressant therapy demonstrated its efficacy in long term cessation. Bupropion and nortriptyline can prove useful in the process. Varenicline is a new pharmacological agent associated with a 23 % smoking cessation rate at 1 year compared to 15 % and 10.3 % cessation rate in the bupropion and placebo groups, respectively [58].

Lipids Relative risk reduction appears to be constant for all lipid levels, however the absolute risk reduction is low in people with low serum levels of lipids. There is little evidence to support reduction in total mortality.

Hypercholesterolemia has the highest percentage of risk. Yusuf et al. showed that each 1 mmol/l (38.7 mg/dL) decrease in LDL cholesterol results in a 21 % decrease in cardiovascular events [59].

EuroAspire studies have shown that this risk factor is not well controlled and there was little improvement in the percentage of patients who achieved target values for LDL cholesterol (33 %) [60].

Many aspects of cardiac rehabilitation will contribute to improvement of lipid profile. These include exercise, nutrition counseling and weight management.

No specific treatment targets have been defined for HDL and triglycerides, however, serum levels of HDL cholesterol of ~ 40 mg/dl in men, ~ 45 mg/dL in women and fasting triglyceride levels ~150 mg/dl are considered markers of increased cardiovascular risk [60].

Psychological and Social Factors Scientific evidence supports that psychological and social factors contribute independently to cardiovascular risk and prognosis worsening, even after achieving control of standard risk factors [61]. Social isolation, lack of social support, work and family stress, negative emotions, depression and hostility are factors that may act as barriers in treatment adherence and lifestyle changes [61]. Medical, psychological and social interventions adapted to the individual problems have been found to improve results.

Social and Professional Reinsertion in Patients with Heart Failure

In advanced stages of cardiovascular disease, *heart failure* represents an important cause of invalidity, and it contributes substantially to cost increase in the national health insurance system. Therefore, the beneficial effects of cardiac rehabilitation

are salutary, particularly when considering optimization of social and professional functionality. Ideally, social and professional reinsertion are the ultimate goal of cardiovascular rehabilitation [62].

Progresses in cardiovascular therapy (fibrinolysis, coronary angioplasty, coronary bypass, CRT, ICD etc.) enhance the possibility of restoring cardiovascular function for many patients in order to make possible return to work [63]. The supporting evidence for the beneficial effects of cardiac rehabilitation should be remarked not only in terms of mortality, but also in terms of improving health and return to work rates, the latter remaining still an important marker of the success of medical rehabilitation services in aiding the population to maintain economic independence [64].

It is estimated that approximately 90 million workers in the EU miss work due to cardiovascular disease [65].

Studies show that the rate of professional reinsertion after an acute cardiovascular event is relatively high, being estimated at 78–83 % [66]. However, a small set of trials has collected and reported these data by using only clinical variables, which can explain in part employment rate results. These trials have not collected information regarding non-clinical variables, therefore completion of these data seems compelling [67].

A study conducted on approximately 12,000 patients on their first admission for heart failure revealed that only a third have returned to work following discharge. In addition to the usual clinical parameters (hospitalization, death), HF determines an incapacity to maintain employment. This study enrolled patients aged 18–60. Of those alive 1 year after hospitalization, a significant 37 % has not returned to their workplace, further confirming HF as contributory to significantly reducing the capacity to lead a normal and self-sufficient existence. Younger patients (aged 18–49) had a return to work rate 3 times higher than their older counterparts (aged 51–60), chiefly due to less comorbidities and a greater determination to remain employed. Patients with higher education had a 2-times greater employment rate. Twenty-four percent more men than women returned to work, probably due to financial reasons. In addition, comorbidities and hospitalization longer than 7 days decreased return to work rates [68].

Moreover, other studies regarding return to work factors confirm the poor predictive value of the clinical variables (20 %), compared to demographic and socioeconomic variables (45 %) [60, 61]. Therefore, professional reinsertion represents a distinctive global approach, with complex factors that impact work capacity. The decision to green light return to work is difficult for the physician whose role in this particular setting is fundamental [69]. In general, guidelines do not provide relevant information in order to develop evaluation criteria for the degree of functional deficiency. On the contrary, their focus is on the decisions regarding diagnosis and treatment. No guideline addresses the patient with disability, thus remaining a major topic of discussion. There are, however, rare indications concerning employment restrictions or functional limitations related to reduction in functional capacity [70].

Psycho-social and professional factors have an important role for resuming activity. Research has found a demotivating individual profile for work return based on clinical

variables, individual and work characteristics: symptom persistence, approaching retirement age, limited education, unqualified work (regarded as non-profitable), inadequacy for requalification, fear of disease, or a defensive attitude of the employer among others. In addition, work is perceived as restrictive (heavy load, reduced power of decision), thus completing a negative professional profile [71].

The basic principle of evaluating work capacity consists of identifying and quantifying functional deficiency based on medical evidence of reduced organ functionality or anatomical region impairment. Quantifying functional deficit is based on the severity classification of the analyzed parameters. Work capacity is the result of a complementary evaluation system where functional deficiency is generated by functional loss which reflects upon the ability to perform daily activities and independence. There is a significant difference between invalidity and functional deficiency. These differences are essential to underscore that disease does not necessarily equal invalidity [63].

The invalidity period depends on cardiac function, the main cause for heart failure, treatment type, response to treatment, complications and comorbidities. A complex cardiac rehabilitation program can facilitate recovery and shorten or avert the invalidity period.

Work capacity is synonymous with the cardiovascular residual structural and functional status, assessed through traditional medical procedures [73]. Recovery of work capacity begins when a long-standing structural and functional deficit has developed and the procedure continues until reaching the maximal functional capacity required for performing a professional activity. This recovery period is maintained during the patient's lifetime to preserve his psychological and physical status.

To evaluate cardiovascular functional deficiency and, inherently, residual structural and functional status, the *global left ventricular systolic function* is not only essential, but the cornerstone of functional evaluation. Guidelines approved by the New York Heart Association (NYHA), with functional classification of symptom severity as a parameter for functional limitations in heart failure, and the Canadian Cardiovascular Society (CCS) classification of angina, based on physical limitations determined by precordial pain, correlate with the exertion level where symptoms develop, making both classifications an integral part to the model of evaluation of functional deficiency and activity limitations.

The weak correlation between functional capacity (peak VO_2) and LVEF is well known [74], however cardiac performance based on LVEF remains a strong objective and independent parameter, providing an argument to influence functional deficiency-related decisions in cases where clinical status seems contradictory to objective evidence.

LVEF is an important prognostic factor [75]. An EF of 40 % has been established as the cut-off value in order to discriminate between individuals with a high mortality risk and those with a low mortality risk [76]. An exponential rise in mortality has been observed for an EF <30 % [76]. When converting these prognostic data into functional severity indicators, it can be concluded that moderate systolic dysfunction (EF 44–40 %) marks a functional deficiency with invalidating impact.

In conclusion, heart failure patients with mild-to-moderate systolic dysfunction (LVEF 40–54 %) can return to their previous or another professional activity, if compatible with their current functional capacity.

The balance between functional capacity and professional activity is another important aspect to consider. Therefore, evaluating functional capacity is mandatory in all patients before returning to work.

Stress testing results can be exploited in order to advise patients concerning the possibilities available for a professional activity within complete safety limits [77].

Functional capacity is expressed as metabolic equivalents at rest (METs) and can be estimated by stress testing and converted to possible work activities by calculating energy expenditure. Only when the patient can achieve at least double the energy expenditure required of a given work activity, return to work is recommended [78]. In other words, both a healthy individual and a cardiovascular patient can work 6–8 h a day, with an oxygen consumption of approximately 35–40 % (max 50 %) of maximum aerobic capacity (peak VO_2) [79]. However, depending on work activity, certain adjustments to these general recommendations should be made in terms of peak VO_2: predominant isometric activity, repeated energy surges during light activity can superimpose baseline exertion, therefore compelling careful decision-making.

A series of tables showing energy expenditure of different common or professional activities help in translating the patient's performance during stress testing to professional activities, within reasonable safety limits (Table 28.1).

Professional activities can be continued and should be encouraged in patients with improved functional status (post-coronary bypass, PTCA or valve replacement). Therefore, a patient with chronic stable heart failure and an LVEF between 45–40 % and reasonable exercise capacity (7–8 METs) can perform light or sedentary professional activities (with a maximum energy expenditure of 4 METs) full-time (8 h). On the contrary, moderate-intensity professional activities imply reducing work time accordingly [80].

For patients with stable chronic heart failure (EF<40 %) light professional activities are recommended, usually with a reduced work time, depending on the profile of activity.

Work capacity reduced <7 METs could affect work performance, therefore vocational counseling is mandatory. Generally, light or sedentary activity (designating the majority of professions) is reasonable for chronic stable cardiovascular patients, provided that there are no concerns to believe that the cardiovascular affliction could put the employer, the public or the patient at risk.

Table 28.1 Activity grading according to METs and mean age (40–64 years) [68]

Activity	METs	Professional activities
Very light	<2.0	Office activities, driving, accountant, sketcher
Light	2.0–3.9	Car repair, light carpentry, transportation, chemical industry, food industry
Moderate	4.0–5.9	Heavy carpentry, air-powered tools, loader, unloader
Vigorous	6.0–8.4	Forestry, mining
Extremely vigorous	>8.5	Ditch-digging, heavy object pushing, road construction

A special mention is in order for those whose work is associated with workplaces that have critical security issues (bus drivers, pilots, train conductors, ship officers). Research shows that less than 0.1 % of all accidents can be attributed to health conditions and, of these, 10–25 % are related to a cardiovascular event [79]. The European Society of Cardiology published guidelines to address commercial vehicle driving in patients with cardiovascular disease as early as 1998 and updates have also been published in 2004 and 2007. The most recent guideline is provided by the CCS and does not contraindicate commercial vehicle driving in patients with heart failure classified as NYHA I-II (with satisfying exercise capacity, EF>35 % and no arrhythmias) [81].

Heart failure guidelines support encouragement of physical activity in patients with heart failure to prevent physical deconditioning and exercise intolerance, 'although many patients should not partake in heavy work or highly-demanding sports' [70]. Similarly, guidelines for stable chronic angina encourage normal physical activity, although special circumstances, such as employees engaging in activities of different intensity activities, require special counseling [67].

Based on these recommendations, previously working in a high-intensity activity profession mandates requalification in other professional domains to fit the cardiovascular status of the patient. Generally, professions related to the previous one seem appropriate as requalification requires prolonged effort and time [72]. For younger patients, vocational counseling is helpful in revealing skills and competence that can be translated in real life to a professional activity that is most appropriate according to their functional status, as well as in creating a bridge towards the work market.

In some countries, limiting access to patients with cardiovascular disease is a common practice. Such limitations disregard the recent medical progress in treating and managing cardiovascular disease. Employment decisions should not be based on generalization, nor stereotyping. Numerous situations have been reported where qualified workers, fully capable of efficiently and safely performing their tasks have been denied employment due to their cardiovascular diagnosis.

Unfortunately, as of yet, there are no collaboration protocols or guidelines established between the healthcare system and workforce recruitment agencies or employers, despite their potential to become useful and objective instruments in employment decisions. Those who depart from the guidelines should provide a concrete context to justify the exception, thus facilitating professional reinsertion of cardiac patients as potential or known prolific employees.

Future Directions

Strategies to improve the participation rate and to maximize the impact of rehabilitation in the future

Home-based cardiac rehabilitation programs can be a solid alternative to institutionalized cardiac rehabilitation and is recommended to improve participation rate. The Birmingham Rehabilitation Uptake Maximization study (BRUM), which included 525 participants post-myocardial infarction or coronary revascularization, compared home-based versus

center-based cardiac rehabilitation in four hospitals. Results showed that home-based cardiac rehabilitation has similar impact compared to in-hospital settings, in terms of risk factor control and walking distance improvement [82].

Other recent studies suggest that automated reference systems and patient education provided by physicians and other healthcare providers on the benefits of cardiac rehabilitation could be the most effective strategies to improve the participation rate to rehabilitation programs. Physician advice turned out to be one of the strongest predictors of participation [83]. Although cardiac rehabilitation programs are conducted mostly by cardiologists, the involvement of other primary health care providers is thought to improve access and adherence in the long term [84].

Emerging areas of research include exploring new methods of conducting cardiac rehabilitation programs to improve access and participation rates, as well as development of new exercise regimens that are more effective and versatile and incorporate new technologies to maximize its benefits.

Therefore, the widespread use of the resources and tools available in information and communications technology confers an innovative and potentially beneficial means for increasing adherence to physical activity in patients with HF. Moreover, it provides interesting prospects for conducting and expanding cardiac rehabilitation programs beyond supervised, group-structured programs, as well as contributing to increasing enrollment, reducing risk factors and improving the cost-benefit ratio. Specific modalities advancing within the information and communications technologies domain include Internet- and mobile-based communications, social media platforms and self-monitoring medical devices and can serve as a means to endorse increasing levels of physical activity and improve health status in patients with HF.

There is a robust body of evidence that supports the beneficial effects of high-intensity training (same results can be expected, despite performing for fewer days), which certainly improves the quality of life and functional capacity in healthy individuals. The physiological benefit of this type of exercise has also been increasingly discussed in patients with HF. Moreover, inspiratory muscle training is demonstrated to improve ventilation, the ventilation/perfusion ratio, functional performance and many pathophysiological manifestations of HF. Breathing exercises and respiratory muscle training in patients with HF can identify several key areas that need further investigation, including the role of expiratory and inspiratory muscle training during different phases of breathing or changes in inspiratory time, all of which have significant potential to improve the many pathophysiological manifestations of heart failure.

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Index

M. Dorobanţu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1