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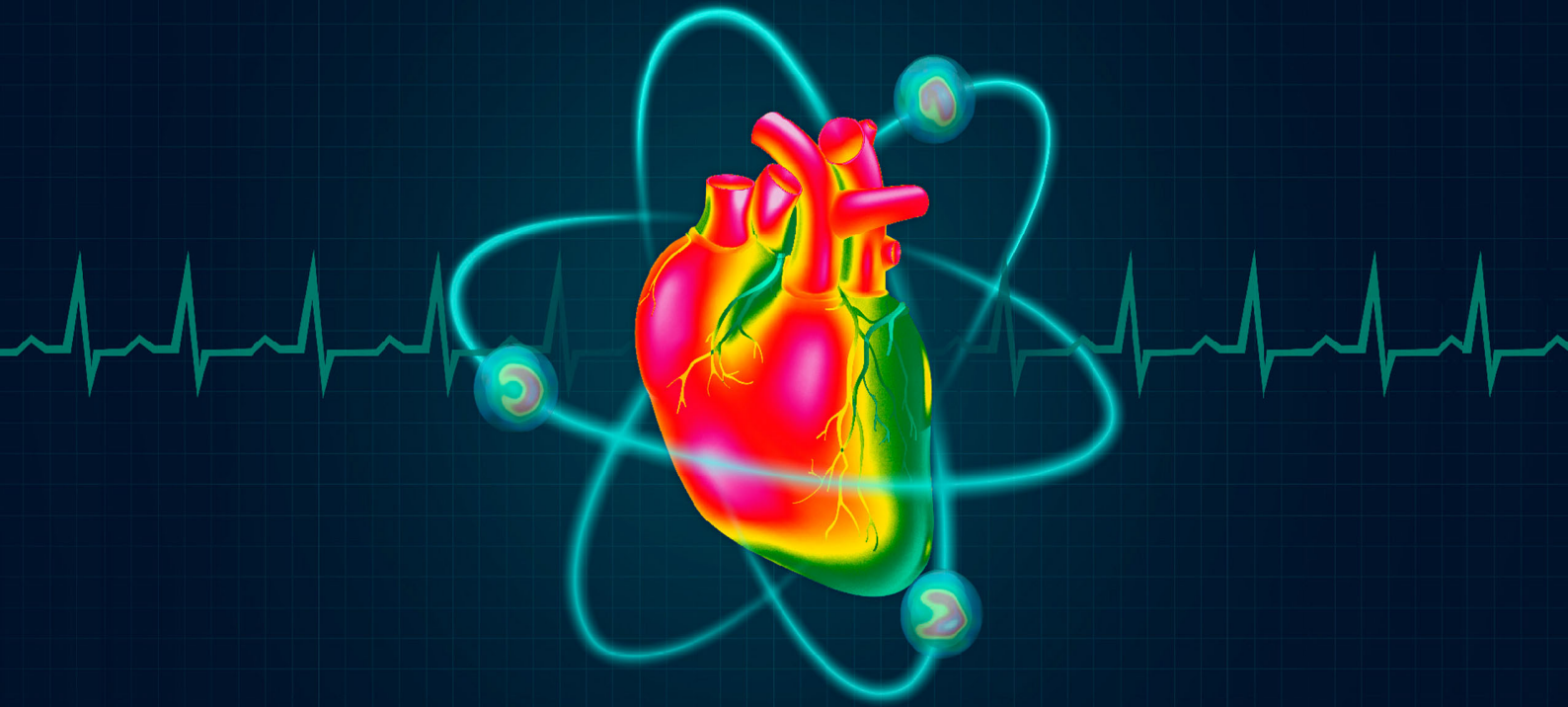
CLINICAL ISSUES

VOLUME 1



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Panagiotis Georgoulias

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(Volume 1)
Clinical Issues

Edited by

Panagiotis Georgoulias
Nuclear Medicine Department
School of Medicine, University of Thessaly
Larissa
Greece

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FOREWORD 1

When Dr. Georgoulias asked me to write this foreword, I was honored and thrilled to have the opportunity to introduce this outstanding work on the "Frontiers in Heart Failure – Molecular Imaging".

This book represents the collaborative effort of numerous talented physicians and scientists throughout Greece with expertise in heart failure to present this complex topic. This challenging task has been accomplished *via* a multidisciplinary approach in this well organized e-book that discusses all aspects of the disease. Heart failure is a very prevalent disease with high mortality and significant social and economic impact on societies. As such it is imperative to understand this silent epidemic, which affects all organs and systems of the body. We live in the era of personalized medicine where the potential exists to identify and in theory prevent factors that lead to heart failure as well as to slow the progression of disease.

The layout of this e-book follows a logical progression and thus gives the reader a comprehensive approach to the study of heart failure. The first several chapters discuss epidemiology, cardiac physiology and pathophysiology, genetics, clinical manifestations, laboratory variables and biochemical markers. The book goes on to address management of heart failure patients including the role of echocardiography, medical therapy, interventional and device therapy, as well as novel treatments for heart failure such as gene and cell therapy approaches. The second portion of the book is dedicated to imaging modalities for heart failure other than echocardiography. Computed tomography is first discussed as a fundamental method to delineate structural anatomy as well as to provide support for invasive techniques used in heart failure. Magnetic resonance imaging is then discussed as an imaging modality which can accurately establish the diagnosis of heart failure and which can also be used for quantification of ventricular function as well as tissue characterization. The bulk of the second portion of the book is a journey through the various imaging capabilities of Nuclear Medicine, which provide both functional and anatomic information. Myocardial Perfusion (SPECT) Imaging and Gated-SPECT are first highlighted, as they are particularly useful in the heart failure patient population, two thirds of which has ischemic heart disease as the underlying cause. The importance of identifying myocardium at risk, (ischemic yet viable), is emphasized in these chapters, as is the ability of these agents to assess myocardial viability and follow-up of left ventricular function after revascularization. Subsequent chapters discuss PET perfusion imaging, hybrid imaging, and assessment of viability with both SPECT and PET applications. More advanced topics such as cardiac neurotransmission SPECT and PET imaging, radiolabelled fatty acid metabolism imaging, and molecular imaging of: apoptosis, atheromatous plaques, and gene and stem cell therapies complete this

section of the book. The final portion of this book discusses important related topics including: artifacts and pitfalls in cardiac molecular imaging, radiation safety, and technical advances such as the rapidly evolving role of PET/MRI and as yet only experimental SPECT/MRI in heart failure management.

I would like to thank my colleague Efrosyni Sfakianaki MD, Assistant Professor in Radiology/NM at UM for her cooperation in reviewing this great e-book.

In conclusion, I am very excited about this e-book, not only because of its superbly organized, well- illustrated and presented content, but also because as an e-book it can be carried and propagated throughout the community much more easily than a hard copy book. The editor and chapter authors have succeeded admirably in the endeavor to produce what promises to be an outstanding resource for the examination and therapy of the patients with Heart Failure both now and in the future.

Dr. George N. Sfakianakis
Department of Radiology
University of Miami, Miller School of Medicine
Miami
FL
USA

FOREWORD 2

Heart failure represents a global healthcare challenge. The severity of the problem is well established in the industrialized countries, where heart failure incidence, prevalence, morbidity and mortality have affected a large population with significant medical and economic demands of the society. Ischemic cardiomyopathy constitutes the most common cause of heart failure in western societies, whereas other causes, such as valvular cardiomyopathy and Chagas disease, may play a more important role in the rest parts of the world. However, as the developing nations also became more urbanized, an increase of heart failure rate has been observed, particularly cases with ischemic aetiology.

We have witnessed major advances in our diagnostic and therapeutic options for heart failure during the last decades. In particular, molecular imaging methods have broadened our understanding of the failing heart at the molecular and cellular level. The continual upsurge in research is promising but this increase in the available literature makes it difficult to stay informed with selected topics in the field. Therefore, it is my pleasure to write a foreword for this e-Book, entitled "Frontiers in Heart Failure – Molecular Imaging", (Editor Professor P. Georgoulias, Bentham Science Publishers). Experts providing crucial and updated information concerning all aspects of heart failure management wrote the chapters in this excellent book.

The e-Book is divided into two sections. The first section includes an update on the pathophysiological and clinical characteristics of the heart failure syndrome, and the therapeutic strategies that can be implemented for these patients. It would be useful not only for cardiologists, but also for any health professionals interested in state-of-the-art heart failure management. Additionally, novel therapies are presented, such as gene and cell therapies. The role of molecular imaging for the evaluation and follow-up of heart failure patients is approached in the second section. It allows the reader to understand better the wide range of molecular imaging methods, including myocardial perfusion imaging, viability assessment, cardiac remodelling evaluation, cardiac neurotransmission imaging, atheromatous plaques imaging and free fatty acids studies. The most advanced imaging modalities in heart failure are also presented, such as single photon emission tomography, positron emission tomography, computed tomography, magnetic resonance imaging and hybrid imaging systems. Finally, important relevant technical factors and advances are comprehensively addressed in the last part of the e-Book.

Based on its strong clinical orientation, I believe that most clinicians will find “Frontiers in Heart Failure – Molecular Imaging” of immediate practical interest. I consider this e-Book an excellent contribution for anyone involved in health failure patients’ care or research.

Dr. Javed Butler
Heart Institute
Stony Brook University
New York
USA

PREFACE

During the last decades, heart failure has become a main reason for health care utilization by patients living in western countries. It represents one of the leading causes of morbidity and mortality due to cardiovascular disorders, particularly in the elderly. Undoubtedly, heart failure can be regarded as a contemporary epidemic since the prevalence of the syndrome has steadily risen. Despite its clinical importance, various aspects of the pathophysiology of the failing heart seem to be inadequately understood. A better understanding of this complex syndrome, at the molecular and cellular level, is expected to have significant consequences for the patients at the clinical setting. Therefore, more accurate investigation of the disorder and effective management of heart failure patients remain primary objectives in the field of cardiovascular research.

This e-Book aims to present cutting edge heart failure diagnostic methods and therapies related to the major fields of interest of the authors, along with findings obtained through their research work. After providing clinically oriented information in the first part, the second part of the e-Book focuses on molecular imaging techniques. The first chapter by G Giamouzis *et al.* includes current definitions, epidemiology, cost and health care policies in the field of heart failure management. In the second chapter, I Aidonidis *et al.* present fundamental cardiac cellular and subcellular physiology concepts that could permit a better assessment of myocardial pathophysiology. The third chapter by F Triposkiadis *et al.* is devoted to molecular and cellular alteration in heart failure, while recent advances regarding the genetic basis of the syndrome are reported by D Koumbi *et al.* in the next chapter. J Skoularigis *et al.* focus on clinical manifestations, patients' investigation, co-existing diseases and prognosis estimation. Laboratory variables and biomarkers represent useful tools for clinicians when treating patients with heart failure clinical findings. This chapter by CA Zivlas and DV Cokkinos reviews well established and novel laboratory tests that may support clinical decision making. By assessing cardiac structure and function, echocardiography offers diagnostic and prognostic information. E Tsougos summarizes the role of echocardiography based on current applications and future developments. Three chapters are devoted to heart failure therapies. S Katsanos and JT Parissis present up-to-date medical therapy of the syndrome, while P Antonitsis *et al.* review available interventional and device therapies. The novel gene and cellular therapeutic strategies are discussed by E Papanikolaou and NP Anagnou in the last chapter of the first section of the e-Book.

The second section of the e-Book starts with computed tomography (CT) and magnetic resonance imaging (MRI) in heart failure that are reviewed by IA Chryssogonidis *et al.* and MA Mademli and NL Kelekis in the first two chapters, respectively. Radiopharmaceuticals

and techniques used for myocardial perfusion single photon emission computed tomography (SPECT) imaging are presented in the next chapter by PA Georgoulias *et al*. Electrocardiographically gated SPECT (G-SPECT) combines assessment of myocardial perfusion and left ventricular function within a single study. Applications of G-SPECT for functional evaluation and remodelling investigation in the failing heart are discussed by S Tsiouris *et al*., Positron emission tomography (PET) perfusion imaging is reviewed by S Chatziioannou *et al*., based on its advantages, such as high diagnostic accuracy, short study time and lower radiation doses compared to SPECT. Hybrid imaging systems (SPECT/CT, PET/CT, PET/MRI) are reported in the chapter by DJ Apostolopoulos as the integration of structural and functional or metabolic information, achieved by multimodality imaging, offer valuable insights in heart failure syndrome. The presence of myocardial viability has been considered a significant determinant of patients' outcome. Two chapters are devoted to myocardial viability assessment; E Moralidis presents SPECT and PET techniques for these purposes, whereas VI Valotassiou and JV Malamitsi provide a comparison of radioisotopic and non-radioisotopic methods for viability identification. Furthermore, cardiac neurotransmission imaging in heart failure is reviewed by D Agostini *et al*., based on SPECT techniques, and SI Koukouraki according to PET imaging. Cardiac metabolism is essential for myocardial contractility and maintenance of cardiomyocyte integrity. HJ Verberne presents various SPECT and PET tracers for the assessment of myocardial free fatty acids imaging. Moreover, A Doumas and I Iakovou focus on current and future applications of molecular imaging in heart failure regarding cell apoptosis and atheromatous plaques formation. Molecular imaging of the novel gene and cell therapies is presented by A Katsikis and M Koutelou. In the last three chapters of the e-Book, potential artifacts and pitfalls are reported by I Tsougos and PA Georgoulias, radiation protection considerations are reviewed by C Kappas and K Theodorou, and various technical advances in the field of cardiac molecular imaging are provided by GK Loudos.

In conclusion, the purpose of this e-Book is to capture and explore improvements towards the diagnosis and therapy of heart failure by established and novel strategies and procedures, focusing on molecular imaging methods.

This e-Book represents significant work of chapters' authors who deserve all appreciation. I would like to highlight the major contribution of G Angelidis and I Tsougos. Further, I wish to acknowledge the contribution of E Kapitsaki (SPEG Consulting Co., Athens, Greece) for the designing of the cover page of this e-Book. Finally, I would like to thank the excellent team of Bentham Science Publishers and especially Faryal Sami for the cooperation.

Dr. Panagiotis A. Georgoulias
Nuclear Medicine Department
School of Medicine, University of Thessaly
Larissa, Greece

List of Contributors

Andreas Xanthopoulos	Department of Cardiology, University Hospital of Larissa, University of Thessaly, Larissa, Greece
Antonios Ziakas	1st Department of Cardiology, AHEPA University Hospital, Thessaloniki, Greece
Chrissi Hatzoglou	Department of Physiology, School of Medicine, Faculty of Health Sciences, University of Thessaly, Larissa, Greece
Christos A. Zivlas	Biomedical Research Foundation of the Academy of Athens, Athens, Greece
Chrysovalantou Nikolaidou	1st Department of Cardiology, AHEPA University Hospital, Thessaloniki, Greece
Constantina Sambani	Laboratory of Health Physics, Radiobiology & Cytogenetics, NCSR "Democritus", Athens, Greece.
Daphne Koumbi	Laboratory of Health Physics, Radiobiology & Cytogenetics, NCSR "Democritus", Athens, Greece. Department of Genetics & Biotechnology, Faculty of Biology, National & Kapodistrian University of Athens, Athens, Greece
Dennis V. Cokkinos	Biomedical Research Foundation of the Academy of Athens, Athens, Greece
Eleni Papanikolaou	Laboratory of Cell and Gene Therapy, Biomedical Research Foundation of the Academy of Athens, Athens, Greece. Laboratory of Biology, National & Kapodistrian University of Athens, Medical School, Athens, Greece
Elias Tsougkos	2nd Cardiology Clinic (Heart Failure and Preventive Cardiology Section), Henry Dunant Hospital Center, Athens, Greece
Filippos Triposkiadis	Department of Cardiology, University Hospital of Larissa, University of Thessaly, Larissa, Greece
George P. Patrinos	Department of Pharmacy, University of Patras, Patras, Greece
Gregory Giamouzis	Department of Cardiology, University Hospital of Larissa, University of Thessaly, Larissa, Greece
Isaac Aidonidis	Department of Physiology, School of Medicine, Faculty of Health Sciences, University of Thessaly, Larissa, Greece
John Skoularigis	Department of Cardiology, University Hospital of Larissa, University of Thessaly, Larissa, Greece
John T. Parissis	Heart Failure Unit, Attikon University Hospital, Athens, Greece

Konstantinos Gourgoulianis	Department of Physiology, School of Medicine, Faculty of Health Sciences, University of Thessaly, Larissa, Greece
Nicholas P. Anagnou	Laboratory of Cell and Gene Therapy, Biomedical Research Foundation of the Academy of Athens, Athens, Greece. Laboratory of Biology, National & Kapodistrian University of Athens, Medical School, Athens, Greece
Panagoula Kollia	Department of Genetics & Biotechnology, Faculty of Biology, National & Kapodistrian University of Athens, Athens, Greece
Paschalis-Adam Molyvdas	Department of Physiology, School of Medicine, Faculty of Health Sciences, University of Thessaly, Larissa, Greece
Polychronis Antonitsis	Cardiothoracic Department, AHEPA University Hospital, Thessaloniki, Greece
Rodopi Stamatiou	Department of Physiology, School of Medicine, Faculty of Health Sciences, University of Thessaly, Larissa, Greece
Sotirios Zarogiannis	Department of Physiology, School of Medicine, Faculty of Health Sciences, University of Thessaly, Larissa, Greece
Spyridon Katsanos	Heart Failure Unit, Attikon University Hospital, Athens, Greece

“Everything that is really great and inspiring is created by the individual who can labor in freedom”

Albert Einstein

“Out of My Later Years”, 1950

CHAPTER 1

Definition, Epidemiology, Economic Cost and Health Policies

Gregory Giamouzis*, **John Skoularigis** and **Filippos Triposkiadis**

Department of Cardiology, University Hospital of Larissa, University of Thessaly, Larissa, Greece

Abstract: Heart failure (HF) is a complex clinical syndrome that is a consequence of any functional or structural impairment of left ventricular filling or pumping of blood. It is considered as a crucial healthcare issue and has been called "the epidemic of the 21st century", namely because of its rising prevalence and the considerably high mortality, morbidity, and care expenditures it poses to the health care systems; HF prevalence is increasing with advancing age. 2-3% of the general population worldwide has HF, whereas among elderly individuals (≥80 years of age) about 12% of both genders have HF. Mortality is exceptionally high, since almost half of the patients will die 5 years after the establishment of diagnosis. The cost of HF care is high, mostly driven by the frequent hospitalizations for HF, and will remain an important concern for the healthcare systems. The estimated HF prevalence and cost of care will significantly increase in the near future, in part because of the longer survival of HF patients due to the continuous optimization of life-prolonging medical and interventional therapies, as well as the aging of the population in the developed countries, which eventually leads to a greater number of individuals at risk for incident HF. Therefore, strategies aiming to HF prevention and improvement of care efficiency are urgently needed. The purpose of this chapter is to provide an in-depth look at the current definitions, epidemiology, cost and health care policies regarding HF in the developed world.

Keywords: Decompensation, Economic cost, Epidemiology, Health care, Heart failure, Health policies, Hospitalization, Left ventricular dysfunction, Prevention, Structural heart disease, Telemonitoring.

* **Corresponding author Gregory Giamouzis:** Department of Cardiology, University Hospital of Larissa and University of Thessaly, Larissa, Greece; Tel: +30 2414 00 2721; Fax: +30 2410 67 0248; E-mail: grgiamouzis@med.uth.gr.

Panagiotis Georgoulias (Ed.)

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome that is a consequence of any functional or structural impairment of left ventricular filling or pumping of blood [1]. It results in the inability of the heart to deliver oxygen at a rate commensurate with the metabolic needs of the tissues, despite normal filling pressures or to do so the left ventricle needs to work at the cost of elevated filling pressures [2]. The principal manifestations of the syndrome are i) dyspnea at exertion or even at rest and fatigue, which impair exercise capacity, and ii) water and sodium retention that may lead to pulmonary and peripheral congestion/edema. A proportion of patients show primarily exercise intolerance with no clinical evidence of congestion; others exhibit mainly signs and symptoms of fluid retention. Since not all patients manifest clinically significant volume overload, the term "chronic heart failure" is prefered over the previously used "congestive heart failure". The diagnosis of HF can be challenging and is mainly a clinical diagnosis based on a careful history and physical examination; therefore, there is no single diagnostic procedure for a definite diagnosis. However, many of HF symptoms are of limited diagnostic value since they are non-discriminating, therefore demonstration of an underlying cardiac cause is fundamental to the diagnosis [3]. In many cases, the underlying cause is myocardial disease leading to impaired systolic ventricular function. In the rest, impairment of ventricular diastolic function or pathologies of the valves and the pericardium, or even heart rhythm and conduction abnormalities are the main cause of HF. Identification of the underlying heart disorder is crucial, as the specific pathophysiologic mechanism usually dectates the optimal therapeutic intervention to be made. Notably, HF should not be confused with either cardiomyopathy or left ventricular (LV) dysfunction; these latter terms describe underlying structural etiology for incident HF.

DEFINITIONS

HF may be related to a wide spectrum of LV disorders, ranging from normal LV size and preserved ejection fraction (EF) to severe dilatation and markedly reduced EF [4]. In the majority of the patients, the consequences of systolic and diastolic dysfunction coexist, irrespectively of EF. EF has traditionally been given an important role in phenotyping HF patients; most clinical trials enrolled patients

based on the EF, since such classification underscores differences in patient demographics, comorbidities, long-term prognosis, and responsiveness to therapeutic modalities. Nevertheless, one should take into account that EF measurements are significantly affected by the imaging technique used and the experience of the operator. Preferably, the terms "preserved" or "reduced EF" should be used over the terms "preserved" or "reduced systolic function", since systolic function disorders can be demonstrated among HF patients with preserved EF and vice versa. Below we present the terminology used by the European Society of Cardiology (ESC) in the 2012 HF Guidelines, based on the LVEF, the time-course and the symptomatic severity of the syndrome [2].

Terminology Related to Left Ventricular Ejection Fraction (LVEF)

Historically, the terminology that has been used to describe HF is based on LVEF values. EF mathematically represents the quotient of the stroke volume (end-diastolic volume minus the end-systolic volume) and the end-diastolic volume. In patients with systolic dysfunction, *i.e.* impaired contraction and therefore decreased active emptying of the LV, the stroke volume can be maintained by an increase in the end-diastolic volume (*i.e.* the LV dilates); consequently the heart ejects a smaller fraction of a larger volume. As the systolic dysfunction becomes more severe, the volumes of the left ventricle (end-diastolic and end-systolic) gradually increase and the EF decreases, a process known as "remodeling" of the left ventricle. Most of the major HF trials have enrolled patients with a reduced EF (HF-rEF), *i.e.* LVEF ≤35%, previously called "systolic HF", and it is only in these patients that effective therapies have been confirmed to date. Other, more recent, studies enrolled patients with HF and an EF >40-45% and no other causal cardiac abnormality (such as valvular or pericardial disease). Some of these patients did not have a normal EF (generally considered to be >50%) but also did not show a major reduction in systolic function either. Because of this, the term HF with 'preserved' EF (HF-pEF) was introduced to describe these patients. Patients with an EF in the range 40-50% therefore represent a 'grey area' and most probably suffer primarily from mild systolic dysfunction. The diagnosis of HF-pEF is more challenging than the diagnosis of HF-rEF because it is largely one of exclusion, *i.e.* other non-cardiac underlying causes of the patient's symptoms (such as anemia or chronic lung disease) must first be discounted [5].

CHAPTER 2

Basics of Cardiac Physiology

Isaac Aidonidis*, Rodopi Stamatiou, Sotirios Zarogiannis, Chrissi Hatzoglou, Konstantinos Gourgoulianis and **Paschalis-Adam Molyvdas**

Department of Physiology, School of Medicine, Faculty of Health Sciences, University of Thessaly, Larissa, Greece

Abstract: Despite painstaking investigations on the pathogenetic mechanisms of heart failure, there still remains a long distance to completely understand the complexity of the events dominating its progression. In this direction, many efforts have been made by recruiting both basic physiology and imaging techniques in order to overcome gaps that are present in diagnostic and therapeutical interventions in heart failure. Intact heart muscle physiology and circulation are the cornerstone for a comprehensive insight into the mechanistic understanding of the relationship between contractility, coronary blood flow, and myocardial perfusion. The latter seems to be a major cause of cardiac muscle damage leading to progression into systolic heart failure. Therefore, it is a matter of urgency to re-evaluate and extend the spectrum of imaging techniques for achieving a better assessment of myocardial perfusion based on fundamental concepts of cardiac cellular and subcellular physiology.

Keywords: Actin, Calcium kinetics, Cardiac physiology, Diastolic dysfunction, Endothelin, Excitation-contraction coupling, Myocardial contractility, Myocardial perfusion, Myosin, Phospholamban, Relaxation, Ryanodine receptor, Tropomyosin, Troponin.

INTRODUCTION

This chapter emphasizes the physiologic mechanisms governing cardiac muscle systole and diastole in order to facilitate understanding of possible dysfunctions

* **Corresponding author Isaac Aidonidis:** Department of Physiology (Cardiovascular Research Section), School of Medicine, Faculty of Health Sciences, University of Thessaly, Larissa, Greece; Tel: +30 2410 68 5560; Fax: +30 2410 68 5546; E-mail: iaido@med.uth.gr.

Panagiotis Georgoulias (Ed.)

that may eventually intermingle in pump incompetence of failing heart. More specifically, the role of intracellular calcium (Ca^{+2}) kinetics for an adequately ejected blood volume and an isovolumic relaxation phase will be presented in detail.

Molecular processes taking place in contractility of physiologic cardiac myocytes that could be affected in the setting of heart failure would be the major objective of this chapter. The topic upon cardiac contractility and coronary flow physiology will synoptically focus on the mechanisms addressing regulation of myocardial perfusion.

CARDIAC MECHANIC FUNCTION

Excitation - Contraction Coupling

Major players in excitation-contraction coupling (ECC) are free Ca^{+2} concentration in the myoplasm, and integrity of the components of the cross-bridge complex (contractile apparatus). This system incorporates the contractile proteins (actin and myosin) and the regulatory proteins (troponin and tropomyosin). Contraction is possible to occur only when adenosine triphosphate (ATP) and Ca^{+2} are present. Availability of adequately high cytosolic Ca^{+2} concentrations is gained by Ca^{+2} entering the cell *via* the voltage-gated L-type Ca channels after depolarization of the cell membrane, which activates in cardiac muscle the mechanism of Ca-induced Ca^{+2} release from the sarcoplasmic reticulum (SR) [1].

Normally, the actin and myosin filaments do not interact (non-contracted state). This happens only when Ca^{+2} binds to the regulatory domain of troponin C, an action that abrogates inhibition of actin-myosin interaction through troponin I. Muscle shortening (systole) occurs by interaction of myosin heads with binding sites on the actin filament, resulting to increased overlapping of actin and myosin, an effect that brings the Z lines together during contraction.

When the intracellular Ca^{+2} concentration is reduced during electrical repolarization, predominantly *via* the reverse-mode activation of Na/Ca exchanger (NCX) and by re-entering of Ca^{+2} into the SR *via* the SR Ca-ATPase (SERCA), diastole starts. This process is significantly slower than the contraction event. By

interventions aiming at enhancing cardiac muscle contractility of a failing myocardium, the mechanisms governing deranged myofilament Ca^{+2} sensitivity and altered Ca^{+2} fluxes still remain investigational.

Removal of cytosolic Ca^{+2} is necessary to allow relaxation and diastole of the heart. SERCA seems to be responsible for removing 70% of the activator Ca^{+2} from the cytosol, followed by activation of the forward-operated NCX that removes almost the rest of Ca^{+2} content. After a contraction phase, slowed or inhibited Ca^{+2} extrusion from the cytoplasm (*e.g.*, due to failed sarcolemmal Ca-ATPase or reverse-mode NCX activation by high [Na]i) may impede relaxation and increase appearance of Ca-triggered after depolarizations and cardiac arrhythmias. Moreover, sustained increase of intercellular Ca^{+2} during diastole may augment cardiac oxygen demand and compress small intramural coronary vessels, particularly in subendocardium, thus reducing coronary blood flow [2].

Pathophysiologic Alterations in Heart Failure

Defective ECC could be responsible for many contractility abnormalities encountered in congestive heart failure. It has been suggested that the mechanism of Ca-induced Ca release (ECC gain) is impaired in the failing heart, possibly due to a widening of the space between the T tubular membrane and the SR [3]. It must be pointed out that in order to have a normal ECC, several signalling pathways have to function properly. The checkpoints of these pathways enable therapeutic interventions in both arrhythmia management and hemodynamic improvement of the failing heart.

Certain types of cardiac G-protein-coupled receptors (GPCRs), including the beta-adrenergic and the angiotensin II type 1 receptors, are abundantly expressed in myocyte membranes and represent possible targets of drug action, directly modulating cardiac contractility and function [4, 5]. Lymperopoulos *et al.* highlighted in a review article the molecular pathways governing the pathophysiology of cardiac inotropic function in heart failure [6]. They focused on multiple genetic variations in several genes responsible for encoding abnormal intracellular proteins that could derange these molecular pathways in the failing heart and finally the translation of specific stimuli, such as hormones or drugs into

CHAPTER 3

Aetiology and Pathophysiology: Cellular and Molecular Alterations of Heart Failure

Filippos Triposkiadis[*], **Gregory Giamouzis** and **John Skoularigis**

Department of Cardiology, University Hospital of Larissa, Larissa, Greece

Abstract: Heart failure is a worldwide health challenge representing the most common admission diagnosis in patients aged ≥65 years. It is associated with worse prognosis even compared to that of most malignancies, despite therapeutic improvements. Research efforts are underway to combat this complex disease by increasing our understanding of the underlying molecular mechanisms associated with the structural and functional abnormalities. Here we review the molecular changes associated with the fundamental derangements observed in heart failure such as the depressed myocardial contractility and relaxation, increased cardiac fibrosis, increased cardiomyocyte stiffness and profound cytoskeletal changes.

Keywords: Calcium kinetics, Cardiomyocyte physiology, Contraction, Coupling mechanisms, Diastolic function, Excitation, Heart failure, Myocardial contractility, Myocardial perfusion, Myofibroblasts, Phospholamban, Relaxation.

INTRODUCTION

In developed countries, heart failure (HF) prevalence is 1–2% in adults and rises to ≥10% among individuals aged ≥70 years [1]. Although about 50% of HF patients show a preserved left ventricular (LV) ejection fraction (HF-pEF), and the remainder display reduced ejection fraction (HF-rEF), it has not been delineated yet whether HF-pEF and HF-rEF are distinct or overlapping phenotypes within the HF spectrum [2 - 4]. Increased LV mass is a common characteristic of most forms of HF. However, the patterns of LV remodeling in

[*] **Corresponding author Filippos Triposkiadis:** Department of Cardiology, University Hospital of Larissa, Larissa, Greece; Tel: +30 2413 50 2821; Fax: +30 2410 67 0248; E-mail: ftriposk@med.uth.gr.

Panagiotis Georgoulias (Ed.)

HF-pEF and HF-rEF differ, with LV chamber dilation being a defining characteristic of HF-rEF, and increased wall thickness with normal or near normal size of ventricular chamber, increased ratio of wall thickness to chamber dimension, and increased ratio of ventricular mass to chamber volume being reported in most but not all studies in HF-pEF [3, 5, 6].

Exercise intolerance, impaired LV filling dynamics, disordered relaxation and neurohumoral activation are observed not only in HF-rEF but also in HF-pEF patients [7]. Moreover, although the normal LV ejection fraction indicates that the hemodynamic compression pump performance is adequately compensated in HF-pEF, strain imaging detects impaired myocardial systolic function contributing to the pathophysiology of the syndrome [8]. Regardless of the LV ejection fraction, the severity of HF, patients' prognosis and the grade of impaired exercise tolerance are strictly linked to the degree of diastolic filling impairments [9]. Finally, chronic catecholamine excess has a fundamental role in HF pathophysiology [10]. Sympathetic nervous system upregulation is organ specific and directly proportional to disease severity. Patients with mild to moderate HF exhibit preferential stimulation of the sympathetic nervous system in the cardiac tissue, whereas the upregulation of sympathetic neurotransmission in the kidney and other organs becomes apparent only in severe HF. Other neurohormonal factors in HF pathophysiology include the renin-angiotensin-aldosterone system, natriuretic peptides, and vasopressin [10].

CARDIOMYOCYTE CONTRACTION AND RELAXATION

Histopathological studies have shown that the cardiomyocyte is narrow and elongated in HF-rEF, with reduced myofibrillar density, whereas the myocyte diameter and resting tension are both increased in HF-pEF, particularly among diabetics [11 - 13]. Abnormalities in calcium-handling proteins and disordered metabolic pathways are present.

Cardiomyocyte function is based on the coordinated calcium currents both intracellularly and out of the cell, and the adequate provision of ATP to energy-utilizing enzymes (Fig. **1**). Normally, depolarization of the plasma membrane and the transverse tubules stimulates the entry of small amounts of calcium into the cardiomyocyte, *via* L-type ion-specific channels located in the sarcoplasmic

reticulum (SR) membrane of the cell [14]. Calcium influx leads to the opening of the adjacent calcium release channels, termed type 2 ryanodine receptors (RyR2), which are large tetrameric polypeptide complexes. The activation of L-type calcium channels and RyR2 is regulated by the sympathetic nervous system through the β1-adrenoreceptors on cardiomyocytes [10]. The release of much greater amounts of calcium from the SR *via* the RyR2 causes a significant rise of calcium into the cytoplasm. The binding of calcium on troponin C is a crucial step for the activation of the cross bridges between actin and myosin filaments in the sarcomeres, resulting in cardiac contraction [15]. Catecholamine - induced RyR2 hyper-activation is linked to ventricular arrhythmias in HF patients due to disordered cardiomyocyte calcium handling.

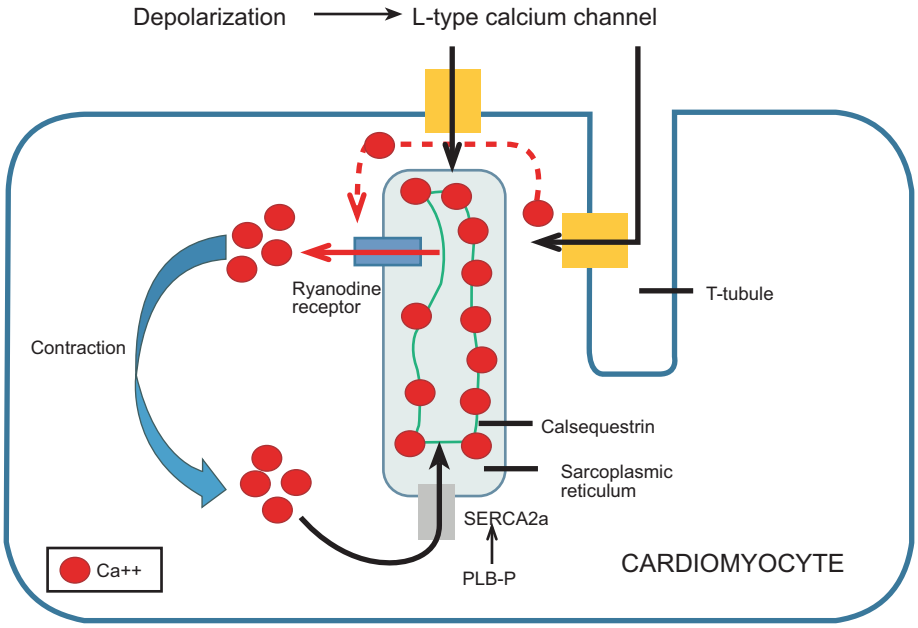

Fig. (1). After depolarization, calcium enters the cardiomyocyte *via* L-type calcium channels and activates the ryanodine receptors on the SR, leading to release of calcium stored within the SR by calsequestrin and increasing intracellular calcium availability, which initiates contraction. Subsequently, calcium is pumped back into the SR by SERCA2a, the calcium uptake pump which is ATP-dependent. An enhanced rate of calcium uptake into the SR increases the myocyte relaxation rate. PLB phosphorylation reverses the SERCA2a pump inhibition, enhancing calcium uptake either in response to increased cytosolic calcium or to β-adrenergic agonists or both.

ATP: adenosine triphosphate; P: phosphorylated; PLB: phospholamban; SERCA2a: sarcoplasmic-endoplasmic reticulum ATPase 2a; SR: sarcoplasmic reticulum.

CHAPTER 4

Gene Polymorphisms, Mutations and Epigenetics in Heart Failure

Daphne Koumbi[1,2], Constantina Sambani[1], George P. Patrinos[3] and **Panagoula Kollia[2,*]**

[1] *Laboratory of Health Physics, Radiobiology & Cytogenetics, NCSR "Democritus", Athens, Greece*

[2] *Department of Genetics & Biotechnology, Faculty of Biology, National & Kapodistrian University of Athens, Athens, Greece*

[3] *Department of Pharmacy, University of Patras, Patras,Greece*

Abstract: Heart Failure (HF) is a complex clinical syndrome characterized by compromised cardiac output that leads to inadequate blood supply failing to meet the requirements of the metabolizing tissues of the body. HF is a silent epidemic that affects ~2% of the general population in the western world and its prevalence is steadily increasing. Although survival has improved, high morbidity and mortality render HF the most devastating cardiovascular disorder with considerable financial burden on public health care. The phenotypic variability of HF syndrome reflects the complexity of the underlying genetic background of the disease, as well as the inter-individual susceptibility to external triggers. Although acquired clinical conditions account for the majority of HF development, a proportion of HF cases are due to inherited pathological states comprising myocardial disorders, mitochondrial diseases, metabolic disorders and congenital heart defect syndromes. Among those, inherited forms of cardiomyopathies constitute "naturally-occurring" disease models that provide the opportunity for an in depth investigation of the genotype–phenotype relationships. Advances in technology permitting high-throughput whole genome genotyping and sequencing, have provided invaluable insights into the genetic architecture, disease evolution and therapeutic response. However, despite the enormous wealth of genetic information derived from those studies and their contribution towards the identification

* **Corresponding author Panagoula Kollia:** Department of Genetics & Biotechnology, Faculty of Biology, National & Kapodistrian University of Athens, Athens, Greece; Tel: +30 210 727 4041; Fax: +30 210 727 4318; E-mail:pankollia@biol.uoa.gr

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of disease-specific genetic variants in complex diseases such as HF, a considerable amount of genetic information related to heritability is missing. In this chapter, we will review knowledge regarding the underlying complex genetic architecture of both acquired and inherited forms of HF, the role of epigenetics as a significant modifier mechanism in disease susceptibility and phenotypic heterogeneity, as well as advances in the field of pharmacogenetics of HF.

Keywords: Cardiomyopathies, Chromatin remodelling, Congenital heart defects, DNA methylation, Epigenetics, Genetics, Genetic testing, Heart failure, Histone, MicroRNAs, Pharmacogenetics, Single nucleotide polymorphisms.

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome characterized by compromised cardiac output that leads to inadequate blood supply, failing to meet the requirements of the metabolizing tissues of the body. HF affects ~2% of the general population in the western world and its prevalence is increasing both in the developed and developing countries, mainly due to population aging, advances in clinical management of coronary artery disease (CAD) and growing incidence of clinical conditions that constitute important risk factors for HF (*e.g.* diabetes, hypertension). Although survival has improved, high morbidity is still a considerable issue and mortality rates remain approximately 50% within 5 years of diagnosis, thereby rendering HF the most devastating cardiovascular disorder with considerable financial burden on public health care. The clinical syndrome of HF may result from disorders mainly of the myocardium, and comorbid clinical conditions [CAD, hypertension, diabetes mellitus type 2 (T2DM)] are also underlying causes of this pathological state [1 - 5]. Although the majority of HF incidence is due to acquired forms of disorders, emerging data from the Framingham heart study project, shed light onto the genetic components of sporadic forms of HF in regard to the relative risks for offsprings of parents with HF (1.69 if one parent has HF and 1.92 if both parents are affected) [6]. Acquired forms of HF are characterized by a complex genetic architecture, interplaying between environmental and genetic factors, and numerous studies highlight the contribution of the genetic components to HF susceptibility, disease evolution and therapeutic outcome. In addition to sporadic/acquired forms of HF, a small but substantial proportion of HF cases are due to inherited clinical conditions

comprising myocardial disorders, mitochondrial diseases, metabolic disorders and congenital heart defect syndromes. Mendelian-inherited myocardial disorders are due to myocardium impairment and comprise the following cardiomyopathies: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular dysplasia/ cardiomyopathy (ARVD/ARVC) and left ventricular non-compaction (LVNC) [2, 5]. Inherited cardiomyopathies constitute "naturally-occurring" HF disease models and in this direction, more profound understanding of their genetic architecture may aid toward an in depth understanding of the cross-talk between inborn genetic composition and epigenetic modifiers. In recent years, with the application of high-throughput technologies, Genome Association-based Meta-analyses studies have enabled for the whole-genome screening of a large number of individuals and in this direction, substantial advances in the discovery of loci contributing to HF development have been achieved [7, 8]. Still, only a small fraction of the genetic information explaining the heritability of HF is known. In the future, larger-scale studies using higher-density reference panels will provide new biological insights into the complex nature of HF, with the ultimate goal to improve our understanding of the disease susceptibility and progression, as well as to identify novel targets for the treatment and prevention of this clinical condition.

GENETICS OF HEART FAILURE (HF) IN ACQUIRED DISORDERS

Genetic Defects and Inborn Genetic Variants in the Ca^{+2} Signaling Pathway - General Aspects

Cardiomyocytes express all three β-adrenergic receptor subtypes β1, β2 and β3, with β1 being the most prominent one. The latter mediates positive chronotropic, inotropic and lusitropic effects, thereby participating in the regulation of heart rate, muscular contraction and diastolic relaxation. β2 receptor is also involved in the enhancement of cardiac frequency and contractility, with a role in smooth muscle relaxation [9 - 12]. Following β-receptor coupling to stimulative regulative G-protein (Gs), increase in cAMP levels and ensuing activation of the protein kinase A (PKA) take place. The latter phosphorylates a number of proteins fundamental for cardiac function: L-type calcium channels (LTCC),

CHAPTER 5

Clinical Manifestations, Co-existing Diseases, Patients' Investigation and Prognostication

John Skoularigis*, Andreas Xanthopoulos, Gregory Giamouzis and **Filippos Triposkiadis**

Department of Cardiology, University Hospital of Larissa, University of Thessaly, Larissa, Greece

Abstract: Heart failure is an important cause of morbidity and mortality worldwide and despite recent advances in therapeutic management, hospitalization rates remain high. The complex interactions of various physiologic, psychological, social, and health care delivery issues make heart failure a challenging chronic disease to manage. A better understanding of the underlying pathophysiological mechanisms, as well as novel diagnostic and therapeutic approaches, may result in cost-effective strategies achieving more drastic control of the epidemic. Prompt diagnosis and optimal treatment of heart failure can affect long-term outcome. A tool with diagnostic, prognostic, and treatment-guiding properties in this respect would be valuable. Recent evidence in the field of molecular biology and heart failure pathophysiology has led to the identification of novel biomarkers that may have significant advantages. Furthermore, heart failure is associated with several cardiac and non-cardiac comorbidities that play an integral role in its development, progression, and response to treatment. The comorbidity burden is highly associated with hospitalization rate in patients with heart failure and preserved left ventricular ejection fraction, as well as in those with heart failure and reduced ejection fraction. In the current review we address these issues and try to analyze this patient population focusing on the need for re-hospitalization and the poor prognosis.

Keywords: Bendopnea, Comorbidities, Dyspnea, Ejection fraction, Epidemiology, Fatigue, Heart failure, Peripheral edema, Prognosis, Re-hospitalization, Symptoms.

* **Corresponding author John Skoularigis:** Department of Cardiology, University Hospital of Larissa, Larissa, Greece; Tel: +30 2413 50 2977; Fax: +30 2413 50 1812; E-mail: iskoular@med.uth.gr, iskoular@gmail.com.

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INTRODUCTION

A widely used definition of heart failure (HF) states that "HF is a pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues" [1]. Moreover, the ESC guidelines define HF clinically, as a syndrome in which patients have typical symptoms (*e.g.* breathlessness) and signs (*e.g.* increased jugular venous pressure) resulting from cardiac structural or functional abnormalities [2]. The prevalence of HF is estimated at 5.7 million people in the USA and it is expected to increase by 46% from 2012 to 2030, resulting in more than 8 million people with HF aged 18 or above [3, 4]. With respect to incidence, 870.000 new HF cases are emerging annually and the lifetime risk of developing HF, for both men and women at the age of 40, is 1 in 5 [3]. The reasons for this pandemic are multiple and include the aging of the population, the rising incidence of arterial hypertension (HT), diabetes mellitus (DM) and obesity, the expanding performance of primary percutaneous coronary intervention which improves survival after ST elevation myocardial infarction and the primary and secondary prophylaxis of sudden cardiac death with the use of implantable cardioverter defibrillators (ICDs). New therapies in HF are effective and improve outcomes based on a patient's thorough clinical assessment. Therefore, the physician should take a complete medical history and proceed to a focused physical examination in patients complaining for symptoms compatible with HF. This information guides the further investigation (invasive or non-invasive) and assists to risk stratification of the HF patients.

DIAGNOSTIC INVESTIGATION

Medical History

The diagnosis of HF [either with reduced ejection fraction (rEF) or with preserved EF (pEF)] is often challenging (Tables **1**, **2**). HF patients present with a variety of symptoms (Table **3**), although none of them is specific for this syndrome. For example, a patient complaining of acute dyspnea may have (apart from congestive HF) pneumonia, chronic obstructive pulmonary disease (COPD) exacerbation, pneumothorax or even pulmonary embolism. Thus, the initial diagnostic

investigation, that involves the medical history, is of great importance. It is essential the physician to detect the patient's stage in the natural history of HF syndrome [5].

Table 1. Diagnosis of heart failure (European Society of Cardiology Guidelines).

Heart failure with reduced ejection fraction	Satisfaction of three conditions is required: • Symptoms typical of heart failure • Signs typical of heart failure • Reduced left ventricular ejection fraction
Heart failure with preserved ejection fraction	Satisfaction of four conditions is required: • Symptoms typical of heart failure • Signs typical of heart failure • Normal or only midely reduced left ventricular ejection fraction and left ventricle not dilated • Relevant structural heart disease (left ventricular hypertrophy / right atrial enlargement) and/or diastolic dysfunction

Table 2. Diagnosis of heart failure (Framingham Criteria).

Major criteria	• Paroxysmal nocturnal dyspnea • Weight loss of 4.5 kg in 5 days in response to treatment • Neck vein distention • Rales • Acute pulmonary edema • Hepatojugular reflux • S_3 gallop • Central venous pressure >16 cmH_2O • Circulation time of 25 seconds • Radiographic cardiomegaly • Pulmonary edema, visceral congestion, or cardiomegaly at autopsy
Minor criteria	• Nocturnal cough • Dyspnea on ordinary exertion • A decrease in vital capacity by one third of the maximal value recorded • Pleural effusion • Tachycardia (rate of 120 bpm) • Bilateral ankle edema **Note:** The Framingham criteria for the diagnosis of heart failure require the concurrent presence of either 2 major criteria or 1 major and 2 minor criteria.

The timely identification and management of HF risk factors, such as HT, coronary artery disease (CAD), exposure to cardiotoxins, and positive family history for DM or cardiomyopathy in asymptomatic patients, may prevent HF

CHAPTER 6

Laboratory Variables and Biochemical Markers

Christos A. Zivlas[*] and **Dennis V. Cokkinos**

Biomedical Research Foundation of the Academy of Athens, Athens, Greece

Abstract: Heart failure is a syndrome affecting not only the heart, but in fact all the organs and systems of the body. Therefore, common serum laboratory variables, such as creatinine, play an important role in diagnosis and follow-up of specific organ dysfunction in heart failure. Actually, treatment is tailored according to these variables. More recently, natriuretic peptides were suggested as a valuable tool for the diagnosis of acute and chronic heart failure, substituting echocardiography at the emergency department. Furthermore, these peptides are used for the prognosis of heart failure patients. Many newer biochemical markers related to a variety of pathophysiological processes, such as inflammation, oxidative stress, remodeling of the extracellular matrix and neurohormones, have been investigated in the past few years. Some of them have shown promising characteristics, not only as diagnostic tools, but also as potential treatment targets. Finally, manipulation of genes *via* micro-RNAs has emerged as a vast new era in the understanding and treatment of heart failure. In this chapter, the majority of laboratory variables and biochemical markers used in heart failure will be discussed. Moreover, information will be given for the clinical benefits of an integrated approach in the management of heart failure patients. Latest advances regarding novel biomarkers will be also presented.

Keywords: Biomarker, Cystatin-C, Galectin-3, Heart failure, Interleukin-1β, Micro-RNAs, Natriuretic peptide, NGAL, Osteopontin, Prolactin, ST2.

INTRODUCTION

Laboratory variables and biomarkers are widely used in heart failure (HF) patients, for diagnostic and treatment purposes. In this chapter biological substan-

[*] **Corresponding author Christos A. Zivlas:** Biomedical Research Foundation of the Academy of Athens, Athens, Greece; Tel: +44 777 419 9134; Fax: +30 210 659 7545; E-mail: christosazivlas@hotmail.com.

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ces, enzymes, hormones and other markers detected in the blood will be discussed, reflecting the pathophysiological alterations that occur in cardiac myocytes, cardiac interstitium and many other organs. All these changes result from increased tissue/organ water and decreased tissue/organ perfusion [1]. Six categories of biomarkers (plus one category of novel biomarkers) in HF have been generally proposed. Each category is related to a distinct pathophysiological process (Table **1**). Certainly, there are no boundaries in the living organism and different pathophysiological pathways have been recently elucidated to interact with each other, such as the ST2 – interleukin-33 (IL-33) system responsible for inflammation, as well as fibrosis.

Table 1. Categories of biomarkers in heart failure [1].

Biomarkers in alphabetical order	Categories based on pathophysiological process*						
	INF	**OXS**	**EMR**	**NEH**	**MIA**	**MYS**	**NBM**
Adiponectin							x
Aldosterone				x			
Angiotensin II				x			
Antidiuretic hormone				x			
Biopyrins (urinary)		x					
Brain natriuretic peptide						x	
C-reactive protein	x						
Cardiac-specific troponin I					x		
Cardiac-specific troponin T					x		
Creatine kinase MB fraction					x		
Cystatin C			x				
Endothelin				x			
Fas (APO-1)	x						
Galectin 3			x				
Growth differentiation factor 15							x
Heart-type fatty-acid protein					x		
Interleukin 1	x						
Interleukin 6	x						
Interleukin 18	x						
Isoprostanes (plasma, urinary)		x					

(Table 1) contd.....

Biomarkers in alphabetical order	Categories based on pathophysiological process*						
	INF	**OXS**	**EMR**	**NEH**	**MIA**	**MYS**	**NBM**
Malondialdehyde (plasma)		x					
Matrix metalloproteinases			x				
Micro-RNAs							x
Midregional fragment of proadrenomedullin						x	
Myeloperoxidase		x					
Myosin light-chain kinase I					x		
N-terminal pro-brain natriuretic peptide						x	
Norepinephrine				x			
Osteoprotegerin	x						
Osteopontin			x				
Oxidized low-density lipoproteins		x					
Procollagen type I			x				
Procollagen type III			x				
Prolactin				x			
Renin				x			
sFas					x		
Suppression of Tumorgenicity 2 (ST2)						x	
Tissue inhibitors of metalloproteinases			x				
Tumor necrosis factor a	x						

***** INF: inflammation; OXS: oxidative stress; EMR: extracellular-matrix remodeling; NEH: neurohormones; MIA: myocyte injury/apoptosis; MYS: myocyte stress; NBM: new biomarkers.

Independently of the pathway, the main characteristics of useful biomarkers include reasonable cost with short turn-around times, provision of information not already available through a careful clinical assessment, and significant aid in decision making [2]. According to the National Institutes of Health making group, a biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [3]. Multi-marker approaches for better risk stratification of HF patients are more commonly used recently, as the use of a single biomarker provides less information [4]. Finally, many biomarkers are potential therapeutic targets, thus their study may lead to

CHAPTER 7

Echocardiography in the Management of Patients with Heart Failure

Elias Tsougkos*

2nd Cardiology Clinic (Heart Failure and Preventive Cardiology Section) Henry Dunant Hospital Center Athens Greece

Abstract: Echocardiography is a valuable diagnostic tool for the management of heart failure (HF), by demonstrating structural and functional abnormalities in individuals characterized by increased risk of developing HF, patients with clinical features indicating HF, or cases of symptomatic HF. Echocardiography evaluates cardiac structural and functional parameters, having an important role in investigating the aetiology of heart conditions and providing prognostic information. During past years, two-dimensional echocardiography has been a valuable technique because of its ability to provide reliable diagnostic and prognostic information in HF patients. On the other hand, Doppler ultrasound, as a non-invasive tool, contributes to the identification of systolic and diastolic dysfunction. In clinical trials, the predictive value of ejection fraction has been consistently demonstrated; lower ejection fraction has been related to higher risk of cardiac death. Although a normal left ventricular function is observed in 40–50% of HF patients based on the results of recent clinical trials, the development of a global parameter, reflecting the remodelling process and functional abnormalities, is required. In this regard, recently developed three-dimensional volumetric measures of left ventricular anatomy and function seem very promising; however, more trials should be performed for further validation. Echocardiographic evaluation is considered as an essential part of HF management, despite the fact that no single examination meets all imaging requirements for HF investigation. Other modalities can provide additional evidence regarding specific questions, such as tissue characterization.

* **Corresponding author Elias Tsougkos:** 2nd Cardiology Clinic (Heart Failure and Preventive Cardiology Section) Henry Dunant Hospital Center Athens Greece; Tel: +30 217 722 1009; Fax: +30 210 697 2276; E-mail: Tsougkos@yahoo.com.

Panagiotis Georgoulias (Ed.)

Keywords: 2D echocardiography, 3D echocardiography, Cardiomyopathy, Diastolic function, Heart failure, Prognosis, Strain, Strain rate, Systolic function, Tissue Doppler imaging, Ventricle dysfunction.

INTRODUCTION

Heart failure (HF) is defined as "a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of ventricles to fill with or eject blood" [1]. In particular, it is a constellation of clinical signs and symptoms that are associated with impaired cardiac output in systolic HF (*e.g.*, fatigue, cardiac cachexia, hypotension), or the consequences of circulatory congestion in diastolic HF (*e.g.*, dyspnoea, hepatomegaly, ascites, dependent edema) [1].

Echocardiography represents the single most valuable examination in the diagnostic investigation and management of HF, given that morphological abnormalities, systolic dysfunction, diastolic dysfunction, or a combination of these aberrations need to be demonstrated in cases showing resting or/and exertional HF symptoms, for the establishment of a definitive diagnosis. Generally, echocardiography can contribute to the investigation of three principal clinical characteristics (Table **1**):

a. HF aetiology investigation.
b. Haemodynamic profile assessment.
c. Estimation of the short–medium-term risk in HF patients.

Table 1. Roles of echocardiography in heart failure management.

• Establishment of a definite diagnosis
• High-risk features identification
• Prognostic investigation
• Guiding therapeutic decisions

The role of echocardiography is valuable in clinical HF staging, differentiating reversible *versus* non-reversible causes of left ventricular (LV) dysfunction. In approximately two-third of HF cases, coronary artery disease (CAD) is considered as the underlying cause of the syndrome. Notably, systolic dysfunction is related

to the presence of viable, or irreversibly damaged, myocardium [2]. Also, echocardiography can identify high-risk features, predict prognosis in HF patients and finally guide therapeutic interventions [3].

The assessment of LV function may be qualitative (normal function, mild, moderate, or severely impaired function) or quantitative.

BASIC PRINCIPLES OF LEFT VENTRICULAR IMAGING

Initial attempts evaluating LV function involved only linear measurements (*e.g.* LV internal dimension in diastolic and systolic phase). These measurements permit the assessment of a number of parameters, such as fractional shortening and velocity of circumferential shortening [4]. However, area measurements and their derived volume calculations became available only after the introduction of two-dimensional echocardiography.

Systolic LV dysfunction is linked to spherical LV dilation, reduced wall thickness, ejection fraction (EF) less than 45%, but most of them appear to have diastolic dysfunction too (Table **2**). They often have right ventricular dysfunction, segmental wall motion abnormalities, and marked valvular disease [5].

Table 2. Basic echocardiographic findings in HF patients.

• LV spherical dilation • Normal or reduced wall thickness • Poor wall thickening • Dyssynchrony movement	• Abnormal systolic parameters • Four chamber enlargement • LVEDV >112%, EF <45%

EF: ejection fraction; LV: left ventricular; LVED: LV end-diastolic volume.

Dimensions and Thickness

LV dimensions and thickness are measured in the parasternal long-axis (PLAX), or parasternal short-axis (PSAX) view, using two-dimensional (2D) or M-mode:

a. M-mode measurements should be made from leading edge to leading edge.
b. 2D echocardiographic measurements should be made from trailing edge to leading edge.
c. M-mode echocardiographic measurements are always slightly greater than 2D

CHAPTER 8

Medical Therapy of Heart Failure

Spyridon Katsanos and **John T. Parissis***

Heart Failure Unit, Attikon University Hospital, Athens, Greece

Abstract: Diuretics are first line drugs to improve symptoms of heart failure patients; however they do not increase their long term survival. Administration of medications blocking the neurohormonal activation, such as angiotensin converting enzyme(ACE) inhibitors (alternatively, angiotensin II receptor blockers in patients with intolerance to ACE inhibitors), mineralocorticoid receptor antagonists and beta blockers, lead to long term improvement of both symptoms and prognosis of chronic heart failure patients with reduced ejection fraction (EF<40%). Digoxin and ivabradine are also therapeutic options for heart failure patients in specific clinical scenarios. LCZ 696 is the new promising medication that improves more effectively cardiovascular outcomes in chronic heart failure cases in comparison to ACE inhibitors. In contrast, there are no available life prolonging medications for patients with preserved ejection fraction (EF>50%), and treatment remains empirical targeting only to symptomatic improvement. Treatment of comorbidities, including renal dysfunction, anemia and depression, may improve the well-being and quality of life in chronic heart failure patients, although evidence-based data are still limited.

Keywords: Angiotensin converting enzyme inhibitors, Angiotensin II receptor blockers, Beta blockers, Digoxin, Diuretics, Heart failure, Hydralazine, Isosorbide dinitrate, Ivabradine, Mineralocorticoid receptor antagonists.

INTRODUCTION

Heart failure (HF) syndrome affects almost 10% of the population > 60 years with expected mortality of 50% within 5 years of diagnosis [1]. Survival of HF has dramatically improved in the last decays; however, the prevalence of the synd-

* **Corresponding author John T Parissis:** Heart Failure Unit, Attikon University Hospital, Athens, Greece; Tel: +30 210 583 2355; Fax: +30 210 53 26520; E-mail: jparissis@yahoo.com.

Panagiotis Georgoulias (Ed.)

rome is paradoxically growing. Until the late 70s the therapeutic armamentarium of HF consisted of only two drugs, diuretics and digoxin, and focused on symptomatic patients' relief. Currently, the key element of the medical management of HF syndrome is the blockage of the neurohormonal stimulation that aims to prevent the vicious circle of the stimulation of renin-angiotensin-aldosterone axis and restrain the deleterious effects of catecholamines over-secretion. Accordingly, 3 new classes of drugs were introduced [angiotensin converting enzyme (ACE) inhibitor/angiotensin II receptor blockers (ARBs), mineralocorticoid receptor (MR) antagonists and beta blockers] which have improved the quality of life and life expectancy of these patients [2, 3]. Diuretics are still first-line drugs that relieve pulmonary congestion by reducing plasma volume and venous return (Fig. **1**). As such, they provide fast but temporary symptom relief; however, they have not shown to improve long term survival. Digoxin may still be used with caution in limited subgroups of HF patients. The advantages of medical therapies recommended for the management of chronic HF patients, as well as the pivotal trials that have supported the evidence for their clinical use, are summarized in this chapter. Additionally, therapeutic challenges and adjustments in different clinical scenarios and specific subgroups will be described.

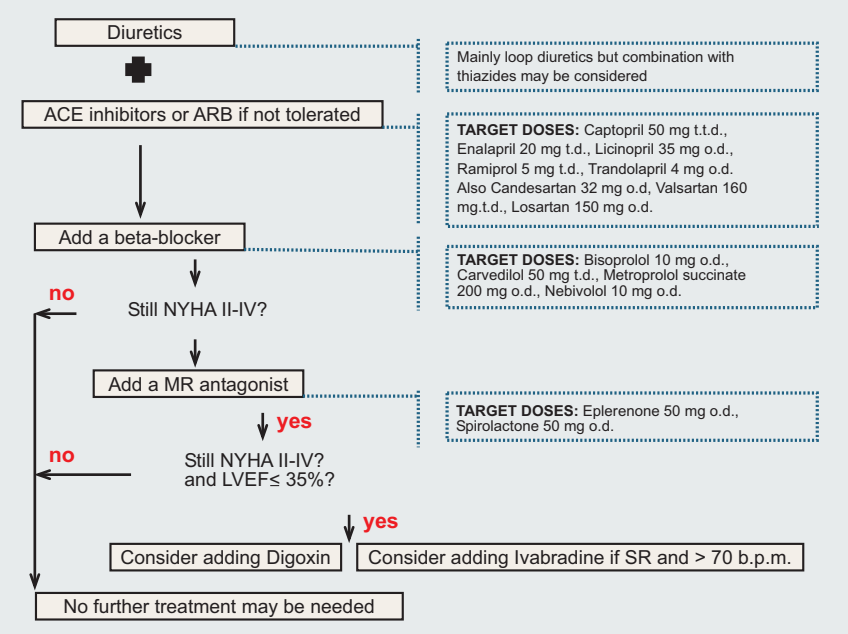

Fig. (1). Practical recommendations for the medical treatment of patients with chronic systolic heart failure. ACE: angiotensin converting enzyme; ARB: angiotensin II receptor blocker; b.p.m.: beats per minute; LVEF: left ventricular ejection fraction; MR; mineralocorticoid receptor; NYHA: New York Heart Association; o.d.: once daily; SR: sinus rhythm; t.d.: twice daily; t.t.d.: three times daily.

DIURETICS

Secreted from the proximal tubule, loop diuretics inhibit re-absorption of sodium and chloride ions at the thick ascending loop of Henle in the kidney. Their use is recommended in all HF patients with signs of fluid retention (Fig. **1**). Loop diuretics provide fast relief of edema, congestion and dyspnea and their dose may be adjusted to the clinical features of the patient. Complications of their excessive use include renal dysfunction, hypotension, dehydration, and serum electrolyte imbalances. It has been observed that higher doses of diuretics are linked to an increase in morality of HF patients, possibly related to HF syndrome deterioration. In the Diuretic Optimization Strategies Evaluation (DOSE) trial, enrolling patients with decompensated HF, bolus (every 12 hours) administration of furosemide as compared to continuous infusion did not affect clinical symptoms or creatinine level [4]. Similarly, high-dose (2.5 times the previous oral dose) *vs.* low-dose (patient's previous oral dose) strategy had only a weak effect on symptom reduction; however, at the expense of more frequent renal deterioration (23% in the high-dose compared to 14% in the low-dose group) [4]. Resistance to diuretics is prevalent in up to 35% of chronic HF patients and a few strategies may be recommended to overcome this problem: a) continuous intravenous (iv) infusion, b) alternative administration of bumetanide or torasemide instead of furosemide, c) combination of loop and thiazide diuretics (*e.g.* metolazone) and peripheral ultrafiltration.

ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS

Chronic overstimulation of the renin-angiotensin-aldosterone axis in HF syndrome leads to oxidative stress, inflammation, endothelial dysfunction, vascular smooth muscle proliferation, apoptosis and collagen formation. Inhibition of ACE results in decreased angiotensin II formation and inhibition of bradykinin breakdown. The hypothesis that ACE inhibitor administration could be beneficial for HF patients was first tested in the late 80s in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). Interestingly, enalapril (an ACE inhibitor) reduced mortality by 27% compared to placebo in severely symptomatic HF patients [5]. These findings were confirmed in the subsequent SOLVD trial in which enalapril reduced mortality of symptomatic HF patients

CHAPTER 9

Interventional Therapy and Device Therapy

Polychronis Antonitsis[1,*], Chrysovalantou Nikolaidou[2] and **Antonios Ziakas[2]**

[1] *Cardiothoracic Department, AHEPA University Hospital, Thessaloniki, Greece*

[2] *1st Department of Cardiology, AHEPA University Hospital, Thessaloniki, Greece*

Abstract: Despite therapeutic advances in the medical treatment of HF patients, the prognosis remains poor. Coronary revascularization in patients with ischaemic cardiomyopathy is associated with amelioration of symptoms and survival benefit. Percutaneous coronary intervention with stenting is associated with excellent outcome, high procedural success rate, low event rates, and can be safely performed in patients with ischaemic cardiomyopathy. Patients with complex coronary artery disease require surgical revascularization (Coronary Artery Bypass Grafting - CABG). Cardiac resynchronization therapy (CRT) aims to re-establishing synchronous contraction between the left ventricular free wall and the interventricular septum, resulting in an increase in stroke volume. In clinical terms, this is translated in functional class improvement. This generally involves biventricular pacing (pacing of the left and right ventricle through separate leads). Surgical strategy for the management of patients with end-stage ischaemic heart disease includes "conventional" techniques (surgical revascularization, the most common surgical procedure, surgical ventricular restoration in patient with a dyskinetic part in the left ventricle and mitral valve surgery for mitral regurgitation). Mechanical circulatory support aims to restore blood flow and pressure, and thus end-organ function, in patients with profound cardiogenic shock or in end-stage patients (stage D) with advanced NYHA III-IV symptoms as a bridge to transplantation or as lifelong support (destination therapy). Heart transplantation is associated with excellent long-term results in terms of symptomatic relief and prognostic benefit under strict criteria involving the recipient and the donor. In the face of evolving technology, lifetime mechanical support provides a realistic alternative to heart transplantation.

Keywords: Cardiac resynchronization therapy, Coronary artery bypass grafting,

* **Corresponding author Polychronis Antonitsis:** Cardiothoracic Department, AHEPA University Hospital, Thessaloniki, Greece; Tel: +30 2310 99 4871; Fax: +30 2310 99 4814; E-mail: antonits@auth.gr.

Panagiotis Georgoulias (Ed.)

Coronary heart disease, Extracorporeal life support, Heart transplantation, Implantable cardioverter defibrillator, Ischeamic heart failure, Left ventricular assist device, Mechanical circulatory support, Percutaneous coronary intervention, Surgical ventricular restoration.

INTRODUCTION

Coronary artery disease (CAD) constitutes a major cause of mortality, morbidity and disability worldwide and imposes a significant financial burden on global healthcare systems. The number of patients afflicted worldwide makes CAD a global epidemic. In 2008, epidemiological data from the United States showed that heart disease was the predominant cause of death for those aged 65 years and older, and second leading cause for those aged 45 - 64 years with an estimated total prevalence of 16,300,000 people [1]. In Europe CAD is responsible for almost 1.8 million deaths annually (20% of all deaths) [2]. Although the abovementioned mortality rates have shown striking improvement during the last decades in developed countries, the prevalence of the multifaceted symptoms and the various clinical presentations of CAD remains high due to the improved survival of patients after acute myocardial infarction, and the ageing world population [3].

Currently, CAD represents the most common underlying cause of heart failure (HF) in developed countries, and is referred to as ischaemic cardiomyopathy (ICM). In the United States the estimated prevalence of HF for the year 2008 was 5,700,000 people. CAD accounts for almost half to two thirds of all cases of HF worldwide [4 - 6]. The prognosis of ischaemic HF is poor. The annual mortality is 10 to 15 times higher than age-matched controls for patients with systolic heart failure [HF with reduced ejection fraction (EF)], and 5 to 8 times higher for patients with diastolic HF (HF with preserved EF) [7].

The term ICM is used to describe severe myocardial dysfunction caused by CAD, with clinical manifestations and symptoms that resemble those of primary dilated cardiomyopathy. ICM is characterized by a combination of myocardial dysfunction and hibernation, diffuse fibrosis, or multiple infarctions. In the early stages of chronic CAD, angina may be the main clinical feature. When HF

becomes more prominent, dyspnea predominates. Other patients with silent ischaemia finally develop ICM, with no history of angina or myocardial infarction [8].

PATHOPHYSIOLOGY OF ISCHAEMIC MYOCARDIAL DYSFUNCTION

CAD can lead to impaired ventricular function and HF through different mechanisms (Fig. **1**). After an acute ischaemic event, such as a myocardial infarction, there is a loss of functioning myocytes, which leads to myocardial fibrosis and dilatation of the left ventricle (LV). The ensuing neurohormonal activation and LV remodeling result in progressive deterioration of the remaining viable myocardium. This LV remodeling may occur even after the achieved patency of the infarct-related artery with revascularization. Acute ischaemia also causes impaired regional LV function, presenting with hypokinesia or dyskinesia, and impaired LV relaxation, resulting in elevated filling pressures [9].

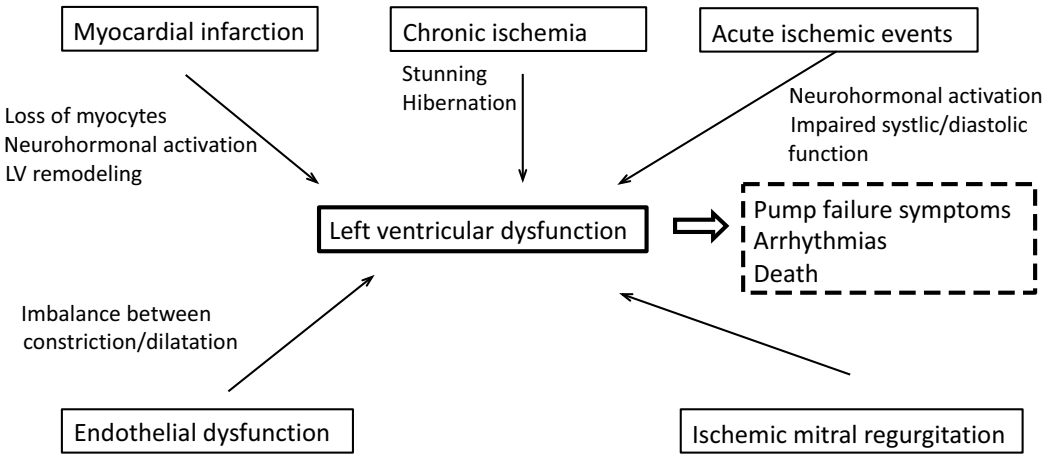

Fig. (1). Mechanisms of ischaemic heart failure and its consequences [9].

Chronic ischaemia results in hibernation and/or stunning of the myocardium, with further decline in LV function. Stunned myocardium refers to dysfunction in viable myocardium associated with transient ischaemia, such as demand-induced ischaemia, with normal resting blood flow. Thus, there is a dissociation of the usual close relationship between subendocardial flow and function. Repeated reversible ischaemia results in persistent dysfunction or chronic “repetitive”

CHAPTER 10

Novel Therapies for Heart Failure: The Gene and Cell Methods

Eleni Papanikolaou and **Nicholas P. Anagnou***

Laboratory of Cell and Gene Therapy, Biomedical Research Foundation of the Academy of Athens, Athens, Greece

Laboratory of Biology, National & Kapodistrian University of Athens, Medical School, Athens, Greece

Abstract: Heart disease still remains one of the leading causes of mortality in the developed world. Therefore, finding the right cure for cardiovascular disease remains a current umnet medical need. However, the recent advances in understanding the molecular basis of myocardial dysfunction, the characterization of novel properties of cardiac progenitors, the identification of the plasticity of several subpopulations of cardiac cells and the development of more efficient gene transfer technologies, has made heart failure another excellent candidate for cell and gene-based therapies.

Keywords: Acute myocardial infarction, β-adrenergic system, Calcium cycling proteins, Cardiac stem cells, Gene therapy, Heart failure, Hematopoietic stem cells, Insertional mutagenesis, Lentiviral vector, Retroviral integration.

INTRODUCTION

By definition, gene therapy is a strategy aiming to manipulate an individual's abnormal genes expression or to correct mutated genes by employing administration of a specific DNA or RNA sequence. These therapeutic sequences, termed transgenes, are delivered to the patient's cells enclosed inside specific vectors. In most types of viral vectors, the transgene is integrated into the host

* **Corresponding author Nicholas P Anagnou:** Laboratory of Cell and Gene Therapy, Biomedical Research Foundation of the Academy of Athens, Athens, Greece; Tel: +30 210 746 2356; Fax: +30 210 746 2412; E-mail: anagnou@med.uoa.gr

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genome and is expected to be expressed throughout the entire life of the patient, thus leading to the successful treatment of the given disease [1]. It should be emphasized, however, that gene transfer in general, is not applicable to diseases with complex phenotypes linked to networks of affected genes. Thus, excluding cancer, gene therapy is mostly suited to treat monogenic disorders, such as certain hereditary diseases caused by specific mutations and is especially applicable for treatment of certain blood diseases such as hemoglobinopathies or immunodeficiencies [2].

The definition of cell therapy though, differs in the sense that cell therapy refers to the administration of modified over unmodified cell populations to the patient, or the induction of maturation of a specific cell population [1].

Therefore, while in cell therapy the aim is to restore or regenerate the damaged tissue, in gene therapy the aim is to correct the damaged cells through genetic manipulations. These two notions are complementary, *i.e.* it is conceivable to characterize gene therapy as cell therapy of genetically corrected cells.

Although in the original concept gene therapy was specifically designed for treatment of monogenic diseases, the latest advances towards the understanding of the molecular basis of myocardial dysfunction, the characterization of novel properties of cardiac progenitors, the identification of the plasticity of several subpopulations of cardiac cells and the development of more efficient gene transfer strategies, has made heart failure another excellent candidate for cell and gene-based therapies.

GENE THERAPY

Gene therapy is considered successful when there is adequate correction of the phenotype of the disease. This implies that the therapeutic vector has to be efficient in terms of a) gene delivery, b) tissue specificity, c) stability and d) safety. Furthermore, the selection of the appropriate cell type for correction is of critical importance, and depends on the type of organ(s) and/or tissues in which the abnormal phenotype is manifested.

As a general principle, the cells under manipulation are the stem cells since they are the only cell type that confers life-long correction. However, when the disease phenotype affects a solid organ, then the challenging issue is to target each

individual population of stem cells within the specified organ. Therefore, there are three main types of gene therapy/gene delivery approaches:

a. *In situ* gene therapy, which employs direct administration of the vector carrying the therapeutic genetic material to the affected tissue, such as by an injection into an organ or a tumor nodule [1]. This type of therapy is suitable for gene transfer to the heart.
b. *Ex vivo* gene therapy, which employs isolation of stem cells from the affected individual, correction of these cells at the laboratory by co-cultivation with the therapeutic vector and infusion of the corrected cell material back to the patient from whom they were originally derived [1]. In this sense, this type of gene therapy can be considered as autologous transplantation of genetically corrected cells and assumes that the cells can be easily removed from the patients. Ex-vivo gene therapy applies for diseases of the blood such as hemoglobinopathies and immunodeficiencies.
c. *In vivo* gene therapy which employs direct administration of the therapeutic vector to a live animal. The vector can be administered either by an intravenous injection or by other physical means such as hypodermic injection, aerosol, or employing other routes [1].

Gene Therapy Vectors

The most important part in a gene therapy setting is the construction of the appropriate vehicles to deliver the therapeutic gene to the patient or to the selected cell population. Specifically for the heart, the strategy must be designed considering both the tissue-specific and spatial patterns of the cardiovascular pathophysiological process and taking into account whether the aim is to treat heart failure which is a broader process *versus* a focal damage such as nodal dysfunction. Since the cardiac stem cells cannot be removed in order to be processed, it is mandatory that the optimal vector format must first demonstrate broad transduction efficiency to the majority of cardiomyocytes to ensure significant impact on ventricular function and second be able to effectively deliver and drive sustained transgene expression to guarantee long term therapy. For safety reasons, the designed vector should also pose the least possible cytotoxic effects.

SUBJECT INDEX

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Panagiotis Georgoulias

Panagiotis Georgoulias is an Assoc. Professor and Head of the Nuclear Medicine Laboratory at the Faculty of Medicine, School of Health Sciences, University of Thessaly, Greece. He graduated from the School of Medicine, National & Kapodistrian University of Athens, Greece, in 1991. In 2004, he became the director of the Department of Nuclear Medicine, University Hospital of Larissa, Greece. Previously, he worked as the director of the Nuclear Medicine Department in a private diagnostic centre in Athens (1998-2004). Between 1996 and 1998, he served as a nuclear medicine consultant at the Department of Nuclear Medicine, Hellenic Army Share Fund Hospital (NIMTS), where he had also completed his residency training in nuclear medicine. His post-graduation experience includes specialization in PET/PET-CT techniques at the PET-CT Department, University of Berlin (Charite Virchow Clinicum), Germany.

His teaching activities include undergraduate and postgraduate nuclear medicine teaching, lectures for medical personnel and technologists of the University Hospital of Larissa, and post-graduate studies supervision. Assoc. Professor Panagiotis Georgoulias is also a visiting lecturer at the postgraduate programme of Medical Physics and Biomedical Engineering of the University of Patras, Greece. To date, he has published 106 papers in International (peer reviewed) Journals, 6 papers in Greek/peripheral journals, 4 books and 10 book chapters. His research activities include nuclear cardiology and molecular biology, with a special focus on the genetic mechanisms involved in myocardial ischemia. Additional research topics include clinical evaluation of novel molecular targets, radionuclide therapeutic applications, brain single photon emission computed tomography and radioimmunoassays. The Nuclear Medicine Department of the University of Thessaly is constantly taking part in various national and international research projects.

Assoc. Professor Panagiotis Georgoulias is the vice president (2016-present) and elected member of the Board of Directors (2004-present) of the Hellenic Society of Nuclear Medicine and Molecular Imaging (HSNM&MI). Further, he is a member of the Cardiovascular Working Group of the HSNM&MI and a substitute member of the Athens and Patras Examination Committee of nuclear medicine specialty. Between 2002 and 2004, he was elected as the National Delegate of HSNM&MI in the European Association of Nuclear Medicine.