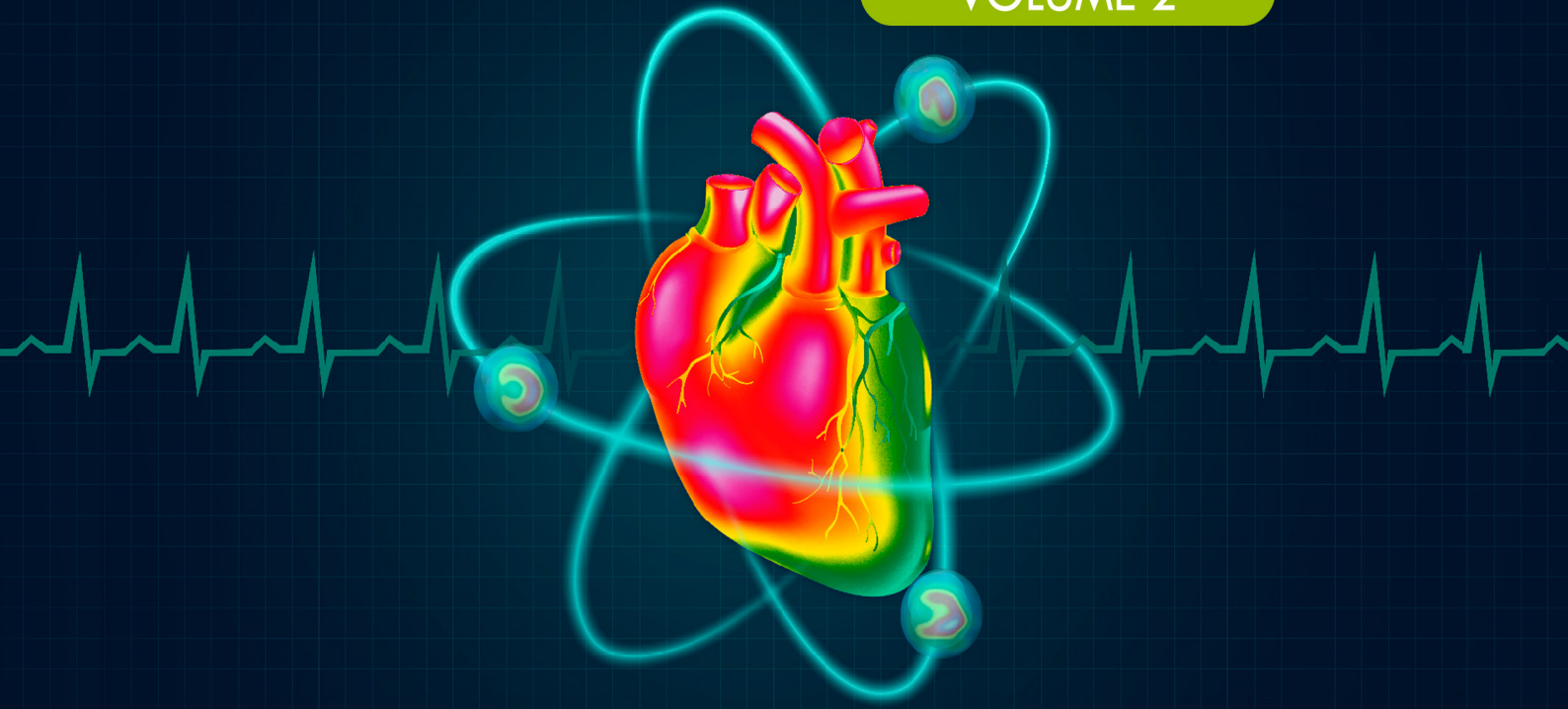
eISBN: 978-1-68108-377-3
ISBN: 978-1-68108-378-0

eISSN: 2468-8053
ISSN: 2468-8045

FRONTIERS IN HEART FAILURE

MOLECULAR IMAGING AND RELATED TOPICS

VOLUME 2



Editor:
Panagiotis Georgoulias

Bentham Books

Frontiers in Heart Failure
(Volume 2)

Molecular Imaging and Related Topics

Edited by

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

Series Title: Frontiers in Heart Failure

Volume Title : *Molecular Imaging and Related Topics*

Volume # 2

Editor/Author: Panagiotis Georgoulias

ISSN (Online): 2468-8053

ISSN: (Print): 2468-8045

ISBN (Online): 978-1-68108-377-3

ISBN (Print): 978-1-68108-378-0

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CONTENTS

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 C.A. Zivlas and D.V. 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 J.T. 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 N.P. 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 I.A. Chryssogonidis *et al.* and M.A. Mademli and N.L. 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 P.A. 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 D.J. 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 V.I. Valotassiou and J.V. 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 S.I. Koukouraki according to PET imaging. Cardiac metabolism is essential for myocardial contractility and maintenance of cardiomyocyte integrity. H.J. 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 P.A. 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 G.K. 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

Alain Manrique	Nuclear Medicine Department, CHU Côte de Nacre, Caen, France. EA 4650, Normandie Université, Caen, France
Alexandros Georgakopoulos	Nuclear Medicine Division, PET/CT Section, Clinical and Translational Research, Biomedical Research Foundation, Academy of Athens, Athens, Greece
Andreas Fotopoulos	Department of Nuclear Medicine, University Hospital of Ioannina, Ioannina, Greece
Argyrios Doumas	2nd Department of Nuclear Medicine, "AHEPA" University Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece
Athanasios Katsikis	Department of Nuclear Medicine, Onassis Cardiac Surgery Centre, Athens, Greece
Athanasios Papadopoulos	Department of Nuclear Medicine, University Hospital of Ioannina, Ioannina, Greece
Athanasios S. Zisimopoulos	Department of Nuclear Medicine, University Hospital of Alexandroupolis, Democritus University of Thrace, Alexandroupolis, Greece
Christos A. Papadopoulos	Department of Radiology, "AHEPA" General University Hospital, Thessaloniki, Greece
Constantin Kappas	Department of Medical Physics, University of Thessaly, Medical School, Larissa, Greece
Damien Legallois	EA 4650, Normandie Université, Caen, France. Cardiology Department, CHU Côte de Nacre, Caen, France
Denis Agostini	Nuclear Medicine Department, CHU Côte de Nacre, Caen, France. EA 4650, Normandie Université, Caen, France
Dimitrios J. Apostolopoulos	Department of Nuclear Medicine, University Hospital of Patras, University of Patras, Medical School, Patras, Greece
Efstratios Moralidis	Department of Nuclear Medicine, Papageorgiou Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece
George C. Angelidis	Department of Nuclear Medicine, University Hospital of Larissa, University of Thessaly, Larissa, Greece
George K. Loudos	Department of Biomedical Engineering, Technological Educational Institute of Athens, Athens, Greece
Hein J. Verberne	Department of Nuclear Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Ioannis A. Chryssogonidis	Department of Radiology, "AHEPA" General University Hospital, Thessaloniki, Greece
Ioannis C. Tsougos	Department of Nuclear Medicine, University Hospital of Larissa, University of Thessaly, Larissa, Greece Department of Medical Physics, University of Thessaly, Larissa, Greece
Ioannis Iakovou	3rd Department of Nuclear Medicine, "Papageorgiou" Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece
Iokasti E. Gkogkou	Department of Radiology, "AHEPA" General University Hospital, Thessaloniki, Greece
Julia V. Malamitsi	Department of Medical Physics, Medical School, National & Kapodistrian University of Athens, Athens, Greece
Kiki Theodorou	Department of Medical Physics, University of Thessaly, Medical School, Larissa, Greece
Maria A. Mademli	2nd Department of Radiology, "Attikon" General University Hospital, National & Kapodistrian University of Athens, Athens, Greece
Maria Koutelou	Department of Nuclear Medicine, Onassis Cardiac Surgery Centre, Athens, Greece
Nikolaos L. Kelekis	2nd Department of Radiology, "Attikon" General University Hospital, National & Kapodistrian University of Athens, Athens, Greece
Nikoletta Pianou	Nuclear Medicine Division, PET/CT Section, Clinical and Translational Research, Biomedical Research Foundation, Academy of Athens, Athens, Greece
Panagiotis A. Georgoulias	Department of Nuclear Medicine, University Hospital of Larissa, University of Thessaly, Larissa, Greece
Sofia Chatziioannou	Nuclear Medicine Division, PET/CT Section, Clinical and Translational Research, Biomedical Research Foundation, Academy of Athens, Athens, Greece. 2nd Department of Radiology, Medical School, National & Kapodistrian University of Athens, General University Hospital "ATTIKON", Athens, Greece
Sophia I. Koukouraki	Department of Nuclear Medicine, Medical School, University of Crete, Iraklion, Greece
Spyridon Tsiouris	Department of Nuclear Medicine, University Hospital of Ioannina, Ioannina, Greece
Varvara I. Valotassiou	Department of Nuclear Medicine, University Hospital of Larissa, Larissa, 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

Computed Tomography in Heart Failure

Ioannis A. Chryssogonidis*, Iokasti E. Gkogkou and **Christos A. Papadopoulos**

Department of Radiology, "AHEPA" General University Hospital, Thessaloniki, Greece

Abstract: Multidetector computed tomography is an imaging modality which constantly gains ground in the field of cardiovascular imaging. Accurate imaging of coronary arteries, cardiac structure and function, pulmonary and cardiac venous anatomy can be explored with this non-invasive, easily reproducible technique, providing valuable information in the diagnosis and management of patients with heart failure. Computed tomography can support invasive techniques used in patients with heart failure, as in cardiac resynchronization and ablation for atrial fibrillation, with all necessary anatomic data, increasing the safety and efficacy of the procedures. In addition, patients after heart transplantation can be evaluated with multidetector computed tomography, avoiding more invasive procedures.

Keywords: Cadiomyopathy, Calcium score, Cardiac ablation, Cardiac dyssynchrony, Cardiac resynchronization, Coronary computed tomography angiography, Ejection fraction, Heart failure, Heart transplantation, Multidetector computed tomography, Myocardial perfusion.

INTRODUCTION

Heart failure is a worldwide life threatening disease with increasing prevalence. It is characterized by frequent and recurrent hospitalizations, and the mortality and morbidity of the disease are associated with the diagnosis. Thus, the necessity of a fast, non-invasive test which provides useful information about the diagnosis and could guide the therapy is mandatory. Ideally, the diagnostic tool would provide

* **Corresponding author Ioannis A. Chryssogonidis:** Department of Radiology, "AHEPA" General University Hospital, Thessaloniki, Greece; Tel: +30 6945 68 0225; Fax: +30 2313 30 3096; E-mail: chryssog@med.auth.gr.

Panagiotis A. Georgoulias (Ed.)

information about the structure and function of the heart with accuracy, at low cost, without complications and independently of implanted devices from previous interventions.

Technological developments have turned computed tomography (CT) into a good candidate for this demand. State-of-the-art CT scanners have improved to provide images of the whole heart in almost a single beat. Nowadays, temporal resolution is higher providing images at 75 ms with dual source CT scanners, while 320-row CT scanners can provide detector coverage of 160 mm.

This evolving technology has emerged into the field of cardiology, quickly expanding into the imaging of the coronary vessels and the ventricles functional imaging. CT technique is performed for guidance of intervention and surveillance of heart failure patients. In the next pages we present the potentialities and uses of multi-slice CT in the imaging of heart failure.

CORONARY ARTERIES

Coronary arteries imaging has been the major purpose of the heart CT scanning. The aim of coronary computed tomography angiography (CCTA) is to provide accurate information about arteries anatomy and stenoses. (Fig. **1a** and **b**, Fig. **2**).

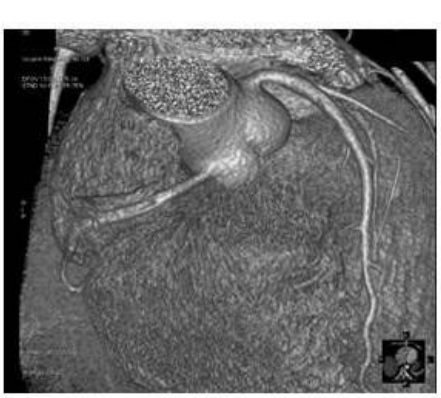

Fig. **1a**

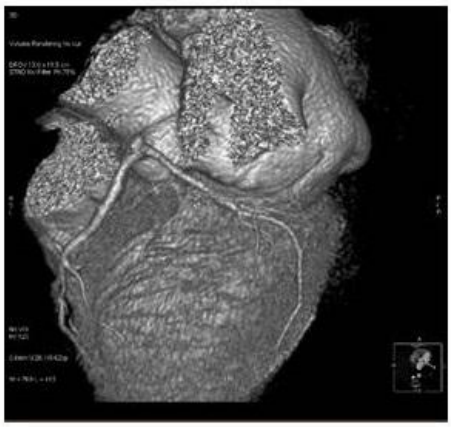

Fig. **1b**

Fig. (1). 3D volume rendering depicting the origin (**1a**) and course (**1b**) of the coronary arteries.

Nowadays, CCTA is playing a major role in the evaluation of coronary artery disease (CAD) and management of heart disease. Technical advances of modern CT scanners with increasingly detector rows and dual source scanners, provide high quality images in shorter times with good temporal and spatial resolution in any desired plane. Constant movement of the area of interest can produce various artifacts, as well as heavy calcified vessels can lead to an overestimation of the stenosis (Fig. **3**).

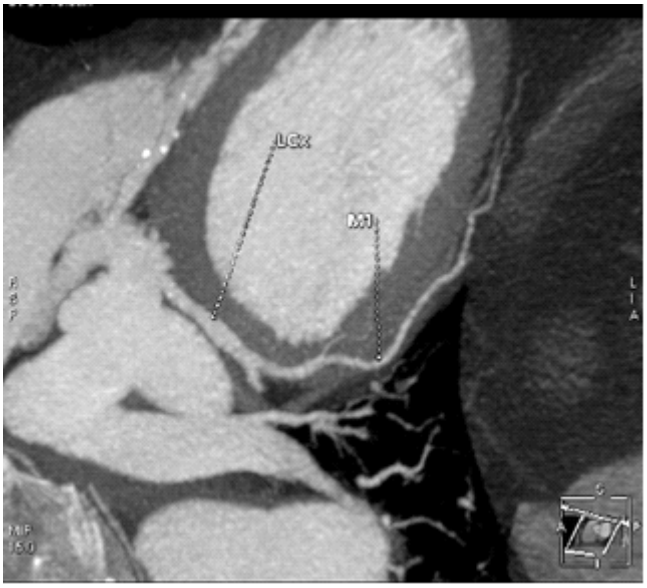

Fig. (2). Normal appearance of the coronary arteries.

Multi-detector coronary CTA (CCTA) can depict the anatomy of the coronary arteries, including small branches, with high negative predictive value for CAD. Analysis of the obtained images should be made in order to select the optimal sequence of cardiac cycle phase in which fewer artifacts interfere with the coronary arteries, and contrast agent fills the vessels lumen. Artery lesions should be classified and reported as for the: a. artery involved; Left Anterior Descending (LAD), Left Circumflex (LCx), Right Coronary Artery (RCA) (Fig. **4**), b. location of the lesions along the artery segments (ostial, proximal, mid, distal), c. location according to the vessel lumen (concentric, eccentric), and d. degree of stenosis in percentage. Further analysis may include plaque characterization according to its components (adipose, calcified, or mixed).

CHAPTER 2

Magnetic Resonance Imaging in Heart Failure

Maria A. Mademli and **Nikolaos L. Kelekis***

2nd Department of Radiology, "Attikon" General University Hospital, National & Kapodistrian University of Athens, Athens, Greece

Abstract: Heart failure (HF) may be the endpoint of various cardiac diseases. This emphasizes the need for a diagnostic method that can accurately establish the diagnosis of HF and define the underlying mechanisms of the condition. This is necessary for the selection of the appropriate therapeutic method (medication, revascularization or resynchronization therapy) in order to achieve the optimal response. Cardiac magnetic resonance imaging (MRI) is an emerging imaging method that can be used for quantification of ventricular function, as a baseline and also for follow-up of HF patients after treatment. It has great contribution in differentiation of the cardiac diseases (*e.g.* ischemic and non-ischemic cardiomyopathies, cardiomyopathies with myocardial hypertrophy, *etc.*) by providing tissue characterization. This chapter describes the technique of cardiac MRI examination and focuses on typical imaging characteristics that aid in the differentiation among cardiac conditions that may result in HF, according to their frequency and their importance in treatment selection. The parameters measured by cardiac MRI that play a role in the prognosis of the disease and therapeutic decision, are also discussed. Finally we present the role of cardiac MRI in cardiac resynchronization therapy and its predictive role in the therapeutic outcome.

Keywords: Cardiac magnetic resonance imaging, Cardiac resynchronization therapy, Cardiomyopathy, Congenital heart disease, Etiology, Heart failure, Ischemic heart disease, Late gadolinium enhancement, Pericardial disease, Prognosis, Valvular heart disease.

* **Corresponding author Nikolaos L. Kelekis:** 2nd Department of Radiology, "Attikon" General University Hospital, National & Kapodistrian University of Athens, Athens, Greece; Tel: +30 210 583 1816; Fax: +30 210 532 6418; E-mail: kelnik@med.uoa.gr.

Panagiotis A. Georgoulias (Ed.)

INTRODUCTION

Heart failure (HF) is a common debilitating and potentially lethal cardiac condition with increasing prevalence. The diagnosis of HF is based on patient's history, clinical examination, electrocardiography (ECG), blood tests and imaging examinations. HF may be the result of various cardiomyopathies (CMPs), ischemic and non-ischemic. The identification of the underlying causative cardiac condition plays a crucial role in the management of HF patients by modifying the treatment options, which include medical therapy, revascularization or device implantation for resynchronization with biventricular pacemakers, implantable cardioverter defibrillators (ICDs) and ventricular assist devices. These considerations designate the need for a non-invasive and reproducible imaging method for accurate assessment of cardiac function and measurement of other indices, establishing the diagnosis and following the patients' response to therapy. Echocardiography is the first line modality for patients suspected of having HF and when the syndrome is diagnosed, further evaluation is needed to explore the etiology [1].

Cardiac Magnetic Resonance Imaging (MRI) plays an important role in this field by facilitating the assessment of left and right ventricular systolic and diastolic function, cardiac structure in detail, myocardial pathology by tissue characterization, perfusion imaging and viability information, aiding to the diagnosis of HF etiology. It is also a modality that provides the determination of several parameters useful for the prognosis and prediction of response to therapy [2].

CARDIAC MAGNETIC RESONANCE IMAGING (MRI) EXAMINATION

The use of MRI in examinations of the heart is quite demanding due to the complex movement of the organ in three dimensions, which is addressed by the use of fast and ultra-fast sequences with ECG-triggering or gating. Various techniques are used to provide different information regarding cardiac structure, function, flow information, perfusion and viability of the myocardium, as well as more complex methods and analyses used to image intraventricular dyssynchrony [1].

Cine Imaging

For the generation of cine images, the preferred technique is ECG-gated steady-state free precession (SSFP). The whole heart is covered in the short axis (SA) view, in 12-16 slices of 6-8mm thickness, acquiring data during the whole cardiac cycle, during multiple 7-15sec breath holds [3]. The resulting images illustrate the blood pool with high signal intensity and the myocardium with intermediate signal intensity, providing high contrast between them (high spatial, temporal resolution). The resulting ability to accurately delineate the endocardial and epicardial contour facilitates the use of these images for measuring the volume of the ventricles, throughout the cardiac cycle, the myocardial mass and finally the estimation of ventricular functional biomarkers, such as ejection fraction (EF), cardiac output, myocardial wall thickness/thickening and motion. The functional results obtained are highly accurate and reproducible, so the method can be considered as the reference standard for quantification of left ventricular (LV) and right ventricular (RV) volume and function, regardless of the field strength of the scanner used (usually 1,5T) [4 - 7]. This is a very important feature considering LV dilatation and remodeling that may be encountered in HF patients and their possible change during the course of the syndrome or after treatment. SSFP sequences can be acquired in different imaging planes [SA, 4 chambers (4CH) or horizontal long axis, vertical long axis (VLA), *etc.*] and the resulting images can be reproduced as a video illustrating the cardiac movement. The visual assessment of cine images gives additional information of the cardiac anatomy, morphology, global and regional contractility. Cine images could be performed under mild stress low-dose of dobutamine (LDD-MRI) which is helpful in demonstrating the contractile reserve [1, 8].

Myocardial Tissue Characterization

Fast spin-echo T1-weighted sequences with adjustment to null the signal from the blood (‘black blood’ images) provide excellent depiction of the morphology and detailed anatomy of the heart and great vessels, as well as tissue information of the myocardium and pericardium [9].

T2-weighted sequences are very useful in cardiac MRI because of their property

CHAPTER 3

Myocardial Perfusion (SPECT) Imaging: Radiotracers and Techniques

Panagiotis A. Georgoulias[1,*], George C. Angelidis[1], Athanasios S. Zisimopoulos[2] and **Ioannis C. Tsougos[1,3]**

[1] *Department of Nuclear Medicine, University Hospital of Larissa, University of Thessaly, Larissa, Greece*

[2] *Department of Nuclear Medicine, University Hospital of Alexandroupolis, Democritus University of Thrace, Alexandroupolis, Greece*

[3] *Department of Medical Physics, University of Thessaly, Larissa, Greece*

Abstract: Heart failure remains a highly prevalent disease with significant morbidity and mortality. Millions of patients are affected worldwide and their treatment is associated with a significant cost for the healthcare systems, especially in developed countries. In approximately two-third of the cases, ischemic heart disease is the cause of the syndrome. Therefore, myocardial perfusion single photon emission computed tomography (SPECT) imaging is a key element in the diagnostic investigation, prognostication, and management of patients with heart failure. Perfusion images are obtained according to various well-established protocols, after the administration of either thallium-201 or technetium-99m labelled radiotracers in combination with several stress techniques. In the future, technological innovations and improvements of reconstruction methods are expected to strengthen the role of myocardial perfusion SPECT imaging as a useful tool for the investigation of heart failure and patient's management.

Keywords: Adenosine, Dipyridamole, Dobutamine, Exercise testing, Heart failure, Myocardial ischemia, Myocardial perfusion, Technetium-99m sestamibi, Technetium-99m tetrofosmin, Thallium-201, Regadenoson.

[*] **Corresponding author Panagiotis A. Georgoulias:** Department of Nuclear Medicine, University Hospital of Larissa, University of Thessaly, Larissa, Greece; Tel: +30 2413 50 2918; Fax: +30 2413 50 1863;
E-mail: pgeorgoul@med.uth.gr.

Panagiotis A. Georgoulias (Ed.)

INTRODUCTION

Heart failure (HF) is a common syndrome that results from cardiac structural abnormalities and functional disturbances. In the United States, the prevalence of HF had been increased dramatically from the 1970s to 1990s [1]. Its prevalence continued upward trend during the last years, varying between 1-2% in the adult population [2, 3]. According to a study published in 2010, the number of HF patients in the United States was over 5.8 million, while more than 550,000 new cases were diagnosed every year [4]. The syndrome mainly affects the elderly. The life-time risk of developing HF is 20% for people aged over 40 years [5, 6]. Both the prevalence and the incidence of the syndrome increase with advancing age and the average age at first diagnosis is 76 years [7]. This is even more important because of the population aging, particularly in the western world. For example, in the United Kingdom, the population aged 75 years and over is projected to significantly increase in the next 10 years, possibly altering health care needs for HF [8].

HF is linked to significant morbidity and mortality despite recent advances in patients' management [9]. It is the primary or secondary diagnosis in more than 2.4 million patients hospitalized in the United States, while it has become the most common reason for hospital admission in Germany since 2006 [4, 10, 11]. In many cases, the syndrome co-exists with other diseases, such as hypertension, diabetes mellitus, chronic kidney disease, smoking-related lung disorders, depression or cognitive impairment [12 - 24]. Annually, approximately 300,000 deaths in the United States are directly attributed to the syndrome [4]. In general, similar epidemiological results have been reported for many developed nations, with few exceptions. Interestingly, prevalence of HF remained essentially constant from 2006 to 2010 in Sweden, while incidence and mortality decreased [25].

Clinical and laboratory investigation provide diagnostic information for the assessment of the failing heart. The diagnosis of the syndrome is based on clinical characteristics and objective evidence of cardiac structural and functional abnormalities [26]. In particular, structural abnormalities are efficiently demonstrated through echocardiography. Radionuclide techniques provide

accurate and non-invasive means of evaluating cardiac function. Cardiac molecular imaging studies are usually indicated for patients with suspected coronary artery disease (CAD); nuclear cardiology techniques are often employed for myocardial perfusion evaluation in these patients. This chapter will review the role of myocardial perfusion single photon emission computed tomography (SPECT) in the diagnosis and management of HF, focusing on the radiopharmaceuticals administered and techniques that are implemented for the performance of the studies.

PATHOPHYSIOLOGY OF HEART FAILURE (HF): MOLECULAR IMAGING

HF could be considered as a pathophysiologic condition rather than a certain disease. CAD represents the leading cause of HF in developed countries and ischemic cardiomyopathy (ICM) is the most significant predisposing factor [27, 28]. Other etiologies include hypertension, valvular disease, and viral, alcoholic, or idiopathic cardiomyopathies. Further, HF may be developed due to extrinsic causes despite normal ventricular function (secondary HF), such as inadequate oxygen delivery (*e.g.* anemia), severe capillary vasodilatation (*e.g.* toxic shock) and inadequate venous return (*e.g.* tricuspid stenosis).

CAD accounts for 60-70% of HF cases in the United States, while ischemia was reported as the primary cause of hospitalization in 15% of HF patients [27, 29]. Given the fact that the prevalence of CAD is growing, myocardial infarction (MI) has an important role in the pathophysiology of HF [30]. Notably, MI increases the life-time risk of the syndrome in both males and females; it is estimated that HF is observed in more than one-third of patients 7 to 8 years post-MI [5, 31]. In addition, acute MI is a major cause of acute HF. In developing countries, as these societies go through epidemiological transition and undergo socio-economic development, HF pathophysiology becomes increasingly similar to that of the developed countries [30]. Previously, HF was mainly linked to valvular cardiomyopathy, Chagas' disease, or endomyocardial fibrosis [32 - 34]. Nowadays, ICM seems to represent a major factor for HF development in most parts of the world.

CHAPTER 4

Radionuclide Assessment of Cardiac Function and Modeling: The Clinical Application of Gated-SPECT

Spyridon Tsiouris, Athanasios Papadopoulos and **Andreas Fotopoulos***

Department of Nuclear Medicine, University Hospital of Ioannina, Ioannina, Greece

Abstract: Nuclear myocardial perfusion imaging (MPI) by single-photon emission computed tomography (SPECT) is a non-invasive method of evaluating left ventricular (LV) perfusion and viability that is widely used in clinical practice. Electrocardiographically (ECG)-gated SPECT (G-SPECT) is a state-of-the-art technique combining the evaluation of myocardial perfusion and LV function within a single study. It is among the most commonly performed cardiologic diagnostic procedures in nuclear medicine departments. Advances in γ-camera instrumentation and the software used for data acquisition, image processing and quantification have rendered this technique user-friendly, practical and highly reproducible in everyday practice. In patients with coronary artery disease, the introduction of ECG-gating enhances the diagnostic and prognostic capability of MPI, provides incremental functional information over the perfusion data alone and also bears potential for assessing myocardial viability and following-up LV function after revascularization. This chapter discusses the general principles of G-SPECT image acquisition, analysis and quantification, followed by a discussion on the additive diagnostic and prognostic value that is associated with the functional parameters obtained by G-SPECT.

Keywords: Cardiomyopathy, Coronary artery disease, Electrocardiographic gating, Gated-SPECT, Image quantification, Left ventricular function, Myocardial infarction, Myocardial perfusion imaging, Radiotracers, Single-photon emission computed tomography.

* **Corresponding author Andreas Fotopoulos:** Department of Nuclear Medicine, University Hospital of Ioannina, Ioannina, Greece; Tel: +30 2651 09 9377; Fax: +30 2651 04 6617; E-mail: afotopou@cc.uoi.gr.

Panagiotis A. Georgoulias (Ed.)

INTRODUCTION

The impact of myocardial perfusion imaging (MPI) by single-photon emission computed tomography (SPECT) in the clinical setting of coronary artery disease (CAD) has been indisputably established for decades. Since the late 1980s the modality has been enhanced by the introduction of electrocardiographically (ECG)-gated acquisition. ECG gating of a standard myocardial perfusion SPECT allowed the qualitative and quantitative simultaneous assessment of the left ventricular (LV) perfusion and function in a single-injection, single-acquisition study [1]. The functional status of a hypoperfused or even a normally perfused LV wall has significant clinical relevance. The addition of functional information obtained through gated acquisition has been demonstrated to be of high clinical value in several studies, since LV function and volumes are principal predictors of long-term outcome in critical CAD or after acute myocardial infarction (AMI) and their assessment plays a key role for patient prognostication [2].

Various protocols have been developed for imaging modalities studying LV function. Echocardiography is the most commonly used technique, since it is widely available, cost-effective and imparts no ionizing radiation. It has moderate spatial resolution and is easily performed, but it comes with inherent subjectivity issues in image analysis that make it highly operator-dependent, while there are also acoustic window limitations rendering the technique unsuitable for certain patients. Function of the LV –a three-dimensional (3D) structure– is measured by extrapolating calculations using two-dimensional (2D) techniques, which leads to suboptimal accuracy and reproducibility for quantitative measurements. Cardiac computed tomography (CT) utilizing contrast media measures LV function in a high quality 3D imaging approach, displaying high spatial resolution and short acquisition time (below 10 sec), but it delivers a considerable amount of radiation dose to the patient. Contrast-enhanced cardiac magnetic resonance imaging (MRI), on the other hand, provides sufficient spatial resolution with the advantage of no radiation burden, but still is not a first-choice examination due to its high cost, subprime availability and unsuitability for patients with pacemakers or implantable cardioverter defibrillators.

First-pass radionuclide angiography (FPRNA) and equilibrium gated radionuclide

ventriculography (EGRNV) –also known as multigated acquisition (MUGA) scan– with the use of single-photon emitting radiotracers opened the field of myocardial function imaging to nuclear medicine. FPRNA is preferred for assessing peak-exercise ventricular function and measuring right ventricular (RV) ejection fraction (EF), whilst EGRNV/MUGA is an equilibrium ECG-gated technique considered as the most accurate for estimating LV systolic function and EF. The incorporation of ECG-gating technology into MPI SPECT gave the opportunity of a reliable simultaneous assessment of LV perfusion and function within the same study.

Several factors contributed to the growing popularity that gated SPECT (G-SPECT) has gained since its introduction. This has been principally based on the development of new radiopharmaceuticals, as well as on improvements in imaging hardware, computer processing and software technology. The introduction of sestamibi and tetrofosmin, two technetium-99m (^{99m}Tc)-labeled perfusion radiotracers with favorable biokinetics and dosimetric characteristics, allowing higher administered activities and enhanced count rate statistics, has been a mainstay for G-SPECT. These tracers permitted the reliable evaluation of myocardial wall motion and thickening, LV volumetry and LVEF calculation by flexible ECG-gated acquisition protocols. Instrumentation advances in the form of multidetector γ-cameras, matched with the enhanced computational power of modern imaging systems, shortened substantially the acquisition and processing time. All these improvements have been accompanied by software developments incorporating automated image processing and quantification algorithms, to reproducibly calculate functional LV parameters with minimal operator interaction [3]. This accounted for a simple, practical and user-friendly imaging technique in everyday practice, thus facilitating its widespread use [4 - 8]. All these innovations established the role of G-SPECT as a leading method of choice for the non-invasive evaluation of myocardial blood flow and cardiac function in a variety of clinical settings related to CAD and its measurements have been extensively validated against LV function assessments, by many other standard cardiac imaging modalities [9 - 15].

CHAPTER 5

Evaluation of Heart Failure Patients Using PET Perfusion Imaging: Radiotracers and Techniques

Sofia Chatziioannou[1,2,*], Nikoletta Pianou[1] and **Alexandros Georgakopoulos[1]**

[1] *Nuclear Medicine Division, PET/CT Section, Clinical and Translational Research, Biomedical Research Foundation, Academy of Athens, Athens, Greece*

[2] *Second Department of Radiology, Medical School, National & Kapodistrian University of Athens, General University Hospital "ATTIKON", Athens, Greece*

Abstract: Positron emission tomography has become an increasingly alternative method for clinical application in patients with coronary artery disease. Although, various myocardial perfusion PET tracers are available, the most commonly used in clinical setting are Rubidium-82 (^{82}Rb) and nitrogen-13-ammonia (^{13}N-ammonia). ^{82}Rb is a cation and an analog of potassium with kinetic properties similar to those of Thallium-201. It combines the advantages of a short 75 seconds physical half-life and its independency of an onsite cyclotron through the availability of a relative small onsite Strontium-82 / ^{82}Rb generator. Although it is not the ideal tracer for absolute quantification (first–pass extraction of 65%), it has been used extensively for this purpose showing valuable data in the clinical setting. ^{13}N-ammonia is a cyclotron product with physical half-life of 9.96 minutes. Due to the combination of the high first-pass myocardial extraction fraction (80%) and the relatively long physical half-life of the radiotracer, high-contrast resolution myocardial perfusion images can be obtained. Oxygen -15-water (^{15}O-water) is used in research studies, mainly for precise measuring of myocardial blood flow. ^{18}F-Fluripiridaz is a new promising tracer with excellent biological and imaging characteristics, including longer half-life, availability in unit doses from regional cyclotrons, low positron range, and high myocardial extraction. It is now in advanced clinical evaluation with encouraging results. Due to the short half-life of the radiotracers a PET rest-stress study is obtained in a shorter time than a single photon emission computed tomography study, while PET myocardial

* **Corresponding author Sofia Chatziioannou:** Second Department of Radiology, Medical School, National & Kapodistrian University of Athens, Athens, Greece; Tel: +30 210 583 1782; Fax: +30 210 583 1778; E-mail: sofiac@bcm.edu.

Panagiotis A. Georgoulias (Ed.)

perfusion imaging provides higher diagnostic accuracy, using lower radiation doses compared to single photon emission tomography.

Keywords: ^{13}N-ammonia, ^{15}O-water, ^{18}F-FBnTP, ^{18}F-Fluripiridaz, ^{18}F-Fluorodihydrorotenone, ^{18}F-FTPP, Coronary artery disease, Myocardial blood flow, Myocardial perfusion imaging, Positron emission tomography, Rubidium-82.

INTRODUCTION

Coronary artery disease (CAD) is a major cause of death and disability. Myocardial perfusion imaging (MPI) is a valuable tool for identification and stratification of patients who need medical management or interventional therapy with coronary angiography and possible revascularization. The most commonly used imaging method for this purpose is single photon emission computed tomography (SPECT) [1].

Despite the success of cardiac SPECT imaging, positron emission tomography (PET) has become an increasingly alternative method for clinical application in these patients. This is primarily attributed to two reasons: firstly due to its ability to evaluate myocardial perfusion and blood flow (MBF) and secondly for the evaluation of myocardial metabolism and viability in patients with ischemic left ventricular (LV) dysfunction [2]. Additionally, PET has better spatial and contrast resolution with more accurate attenuation and scatter correction. All new PET systems enable a simultaneous computed tomography (CT), making both structural imaging and CT-based attenuation correction possible.

Although various myocardial perfusion PET tracers are available, the most commonly used in clinical setting are rubidium-82 (^{82}Rb) and nitrogen-1--ammonia (^{13}N-ammonia). Also, oxygen-15-water (^{15}O-water) is used in research studies, mainly for precise measuring of MBF. Finally, the last few years, new ^{18}F-labelled myocardial perfusion tracers have been developed with great promise.

RADIOTRACERS

Rubidium-82 (^{82}Rb)

^{82}Rb is a cation and an analog of potassium with kinetic properties similar to those of thallium-201 (^{201}Tl). The tracer is taken up by the myocardium through active transport by the Na^+-K^+ adenosine triphosphatase pump. ^{82}Rb uptake is mainly depended on MBF, although its extraction can be affected by severe acidosis, hypoxia and ischemia. Thus, ^{82}Rb myocardial uptake is a function of both MBF and of myocardial viability [2 - 4]. It has received U.S Food and Drug Administration (FDA) approval and in recent years it is the most widely used radionuclide for evaluation of myocardial perfusion with PET in the USA.

^{82}Rb combines the advantages of a short 78 seconds physical half-life (Table **1**) and its independency of an onsite cyclotron through the availability of a relative small onsite strontium-82 (^{82}Sr) / ^{82}Rb generator [5]. Recently, a new ^{82}Rb generator delivery system has been developed. It consists of a ^{82}Sr/^{82}Rb generator and an elution system, that may offer improvement in safety (Jubilant Draximage). It is available in Canada and under review by the US FDA [6]. ^{82}Sr has a physical half-life of 26 days. Consequently, the ^{82}Sr/ ^{82}Rb generator needs to be replaced every 4-6 weeks. The generator is fully replenished every 10 minutes. More than 90% of maximal available activity can be obtained within 5 minutes after the last elution, allowing fast sequential perfusion imaging and high patient throughput. Despite the very high cost per patient at a low volume of studies, the cost over six studies per day is competitive to SPECT tracers [7].

^{82}Rb after intravenous administration rapidly crosses the capillary membrane. The maximum kinetic energy of positrons emitted during ^{82}Rb decay is significantly higher than that of ^{18}F or ^{13}N. Image resolution and quality are slightly compromised because of this high energy of positrons and the lower count rates due to the short half-life [8]. It has a first–pass extraction of 65%, which is similar to ^{201}Tl and slightly less than ^{13}N-ammonia and decreases in a non-linear manner, with increasing blood flow [3, 9]. Although due to low extraction fraction it is not the ideal tracer for absolute quantification, it has been used extensively for this purpose showing valuable results in the clinical setting [10, 11].

CHAPTER 6

Hybrid Imaging (SPECT/ CT, PET/CT, PET/MR)

Dimitrios J. Apostolopoulos*

Department of Nuclear Medicine, University Hospital of Patras, University of Patras, Medical School, Patras, Greece

Abstract: Multi-modality imaging achieves the integration of structural and functional or metabolical information in a single examination. Apart from patient convenience and improved workflow, this "one-stop shop" approach is featured by enhanced diagnostic accuracy compared to either modality alone or side-by-side image interpretation. These advantages also apply on cardiovascular and molecular-targeted imaging where hybrid systems facilitate the detection of molecular signals and their accurate localization by fusion with anatomical structures. The role of SPECT/CT, PET/CT and PET/MR in studying patients with heart failure is reviewed in this chapter. Before mentioning the potential clinical utility, various issues concerning the principles of hybrid imaging, commercially available devices, image interpretation, possible technical errors and diagnostic pitfalls are addressed. Due to its wider availability, lower cost and the author's experience, the value of cardiac hybrid SPECT/CT is emphasized.

Keywords: Attenuation correction, Computed tomography, Coronary artery disease, Heart failure, Hybrid imaging, Magnetic resonance, Multi-modality imaging, Myocardial viability, Positron emission tomography, Single photon emission computed tomography.

INTRODUCTION

Multi-modality or hybrid imaging has emerged during the previous decade as a powerful method for combining structural with functional information in a single examination. Its use has gained widespread clinical acceptance for various appli-

* **Corresponding author Dimitrios J. Apostolopoulos:** Department of Nuclear Medicine, University Hospital of Patras, University of Patras, Medical School, Patras, Greece; Tel: +30 6972 12 2372; Fax: +30 2610 99 4470; E-mail: dimap@med.upatras.gr.

Panagiotis A. Georgoulias (Ed.)

cations, including cardiac imaging [1 - 8]. Particularly in molecular-targeted imaging, novel hybrid systems facilitate the detection of molecular signals and their accurate localization by fusion with anatomical structures [9 - 11].

The outburst of positron emission tomography (PET) in oncology experienced in the past years has actually kept pace with the advent of hybrid PET/multi-detector computed tomography (MDCT) devices which have largely replaced the older stand-alone PET systems. Significant progress in the hardware and software of PET and MDCT has taken place, which resulted in the increase of system speed, efficiency, spatial resolution and patient throughput, while radiation exposure of patients and laboratory personnel has been reduced [12]. These innovations have also impacted on the expansion of PET/CT cardiac applications. Depending on the MDCT capabilities, hybrid PET/CT can be used today for acquisition of attenuation-free myocardial perfusion images, accurate estimation of myocardial blood flow and myocardial flow reserve, calculation of the coronary artery calcium score (CACS) and CT coronary angiography (CTCA) [7]. However, PET technology and radiotracers for cardiac applications remain expensive and, consequently, the clinical penetration of cardiac PET/CT remains limited at present.

The first dual-modality systems combining single photon emission computed tomography (SPECT) with CT appeared in the clinical arena almost simultaneously with PET/CT scanners. Although the spread of SPECT/CT lingered behind PET/CT, probably because of less oncological applications of SPECT compared with PET, SPECT/CT is much cheaper and the interest in its use is rapidly increasing. As regards to cardiac imaging, the first hybrid devices were coupled to low-resolution CT scanners mounted on the same gantry with the gamma-camera heads and aimed only at attenuation correction (AC) of SPECT images. Later on, MDCT machines capable of accomplishing CACS calculation and performing CTCA have joined scintillation cameras, being arranged in a separate gantry. The advent of high-efficiency cardiac gamma-cameras, either by the use of semiconductor detectors or by novel collimator designs, has broadened the horizons of SPECT myocardial perfusion imaging (MPI). Some of these novel cameras are integrated with CT devices [12 - 14].

Recently, dual-modality PET/magnetic resonance (MR) has become a clinical reality. Currently, available PET/MR systems perform PET and MR imaging either simultaneously or sequentially [15]. Although their number is limited in few medical centers to date, their use will probably increase in the future owing to the great potential of this hybrid technique. The clinical value of PET/MR is still being investigated, but cardiac imaging seems to be one of the most attractive applications [16]. With technological advances running fast, other multi-modality devices such as SPECT/MR, PET/CT/MR, MR/CT, Nuclear/Optical and MR/optical are anticipated in the future [9, 17]. Adequate training in both radiology and nuclear medicine is a prerequisite for high-quality hybrid image interpretation. Small hybrid designs for imaging animals have contributed a lot to medical research, particularly in the field of molecular imaging [10, 11].

Nuclear techniques (SPECT and PET) provide valuable information regarding left and right ventricular function, myocardial perfusion, metabolism and sympathetic innervation in patients with heart failure [5 - 7, 9]. The role of imaging modalities in the evaluation of heart failure is discussed in other chapters of this e-book. This chapter focuses on the potentially added value of dual-modality imaging over stand-alone systems. Before mentioning potential clinical utility, various issues concerning the principles of hybrid imaging, commercially available devices, image interpretation, possible technical errors and diagnostic pitfalls are addressed. Due to its wider availability, lower cost and the author's experience, the value of cardiac hybrid SPECT/CT is emphasized in this chapter.

CARDIAC IMAGING WITH SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT)/COMPUTED TOMOGRAPHY (CT)

The clinical utility of SPECT MPI for the evaluation of coronary artery disease (CAD) has been supported by a large body of evidence and the method is considered well-established [18]. MPI is more accurate than exercise treadmill test in demonstrating myocardial ischaemia and it is the most powerful technique for predicting adverse coronary events. Recent studies indicate this also applies to heart failure. In a large prospective study involving patients with renal dysfunction, Nakata *et al.* reported that stress induced perfusion abnormalities and elevated end-systolic volume index independently predicted refractory heart

CHAPTER 7

Assessment of Myocardial Viability Using SPECT and PET Techniques

Efstratios Moralidis*

Department of Nuclear Medicine, Papageorgiou Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece

Abstract: Heart failure is a significant health problem and coronary artery disease is by far the leading cause. Despite advances in medical and device therapy the prognosis of patients with ischemic cardiomyopathy remains unfavorable, but revascularization may further improve the outcome in terms of contractile function, symptomatic relief, exercise capacity and mortality. Over the years, the presence of myocardial viability has been considered a significant determinant of the benefit from revascularization and a variety of noninvasive techniques have been developed to assess viable and nonviable myocardium in patients with ischemic systolic dysfunction. Viability imaging with ^{201}Tl and ^{99m}Tc-agents SPECT can evaluate perfusion, cell membrane and mitochondria structural and functional integrity, whereas ^{18}F-FDG PET is used for the assessment of glucose metabolism in myocytes. Dobutamine stress echocardiography provides information on the contractile reserve and cardiac magnetic resonance imaging can delineate the transmural extent of scar. In general nuclear imaging techniques have a higher sensitivity for the detection of myocardial viability, whereas techniques evaluating contractile reserve display a lower sensitivity but a higher specificity. This review focuses primarily on the radionuclide modalities for the assessment of myocardial viability and discusses the clinical value of viability imaging, including earlier retrospective work and the more recent prospective data.

Keywords: Coronary artery disease, Heart failure, Left ventricular remodeling, Myocardial metabolism, Myocardial perfusion, Myocardial viability,

* **Corresponding author Efstratios Moralidis:** Department of Nuclear Medicine, Papageorgiou Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece; Tel: +30 2310 99 4688; Fax: +30 2310 991466; E-mail: emoral@med.auth.gr.

Panagiotis A. Georgoulias (Ed.)

Positron emission tomography, Prognosis, Revascularization, Single-photon emission tomography.

INTRODUCTION

Approximately 1–2% of the adult population in the industrialized countries has heart failure, with the prevalence amounting to ≥10% among persons ≥70 years old [1, 2]. Population longevity, advances in the treatment of acute coronary syndromes and improved survival of heart failure patients all fuel the heart failure epidemic. This disorder is the single most frequent cause of hospitalization among persons ≥65 years old with excessive costs and thereby constituting a significant public health problem [3, 4]. Most patients with heart failure symptoms have a low left ventricular ejection fraction (LVEF). Coronary artery disease (CAD) is the cause of the systolic dysfunction in almost two-thirds of cases and despite therapeutic improvements the 5-year mortality rate remains high, approaching 50% [2, 5 - 8].

More than 35 years ago, clinicians and cardiac surgeons realized improvements in both regional and global LV function in patients with chronic ischemic heart disease having undergone coronary artery bypass grafting (CABG) surgery [9 - 12]. Approximately 40% of patients with preoperative LV dysfunction manifested appreciable improvement in LV function after CABG, with normalization of LVEF in approximately one fourth of cases [10, 13]. Since 1982, when Rahimtoola described the recovery of LV contractile dysfunction after revascularization in patients with CAD, the concept of hibernating myocardium has been popularized and the interest in myocardial viability has progressed from determining its pathophysiology to developing techniques for its assessment and finally its application in the clinical setting [9, 14, 15].

Progress in pharmacologic therapy, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers and aldosterone antagonists, has contributed considerably to the improved outcome of patients with systolic heart failure [16 - 20]. Device therapy with biventricular pacing and implantable cardioverter defibrillators (ICDs) may further prolong survival in selected patients and heart transplantation is the last resort due to limited

availability of donor hearts [8, 21]. Coronary revascularization is an alternative effective therapy, but decisions to proceed with this type of therapy in patients with moderate to severe LV dysfunction often are difficult, because of comorbidities and the procedure-associated risk. The perioperative mortality rate of surgical revascularization in patients with severe LV dysfunction may be as high as 10% [10]. Therefore, it is useful to identify patients most likely to obtain benefit from invasive procedures.

A variety of techniques have been developed and tested for the prediction of reversibility of contractile impairment [9]. This review principally addresses nuclear techniques for the assessment of myocardial viability. For reasons of completeness, however, other non-invasive modalities are presented briefly and to the extent that comprehensive comparisons can be made.

DEFINITION OF MYOCARDIAL VIABILITY

In the context of myocardial viability several terms have been used in literature inconsistently to describe various states of the myocardium, such as stunning, hibernation, infarction (partial or full-thickness) and scar. The term “viable” describes myocardium containing alive myocardial cells and may be normal, stunned or hibernating, while transmural scar with no remaining myocytes represents typical nonviable myocardium [22, 23]. It is also conceivable that myocardium subtended by diseased coronary arteries may exhibit a continuum of states which may coexist in the same patient or even in the same myocardial territory [22].

For the purposes of this review, myocardial viability describes jeopardized dysfunctional myocardium with no or limited subendocardial scarring and with the potential of temporal improvement in contractile function, irrespectively of the underlying etiology or the specific therapeutic intervention employed [24 - 26]. In a broader sense this term may also imply a potentially favorable clinical outcome attained from timely interventions in dysfunctional myocardium which may or may not be related to contractile recovery at rest.

CHAPTER 8

Radioisotopic *vs* Non-Radioisotopic Methods for Myocardial Viability Identification

Varvara I. Valotassiou[1,*] and **Julia V. Malamitsi**[2]

[1] *Department of Nuclear Medicine, University Hospital of Larissa, Larissa, Greece*

[2] *Department of Medical Physics, Medical School, National & Kapodistrian University of Athens, Athens, Greece*

Abstract: Left ventricular (LV) systolic dysfunction associated with coronary artery disease (CAD) comprises a major diagnostic and therapeutic dilemma. Hibernating myocardium refers to a chronic dysfunctional condition, as a result of repeated episodes of ischemia, of a still viable myocardium. In viable dysfunctional myocardium, the integrity of myocyte membrane and contractile fibers are preserved. Revascularization may promote LV function in cases of residual myocardial viability in dysfunctional segments of the heart. The identification of viability is pivotal for patients' management, and viability testing is a valuable tool to guide therapeutic options in these patients. Various non-invasive viability assessment procedure can be used in the clinical practice and novel applications are emerging which are likely to provide higher diagnostic accuracy in the future. Nuclear myocardial perfusion imaging with single photon emission computed tomography (SPECT) has been used for several decades and is a well-established method for viability evaluation, while positron emission tomography (PET) has been considered the "gold standard" for this scope. Other non-radioisotopic cardiac imaging modalities have been also developed, such as cardiac magnetic resonance (CMR) and echocardiography with high image quality and no radiation exposure, and lastly cardiac computed tomography (CCT). In the last years, great advances have been made in image processing software, as well as in hybrid imaging for the simultaneous analysis of functional and anatomical datasets based on different modalities.

[*] **Corresponding author Varvara I. Valotassiou:** Department of Nuclear Medicine, University Hospital of Larissa, Larissa, Greece; Tel: +30 6976 79 1889; Fax: +30 2413 50 1863; E-mail: valotasiou@med.uth.gr.

Panagiotis A. Georgoulias (Ed.)

Keywords: Cardiac computed tomography, Cardiac magnetic resonance, Echocardiography, Left ventricular dysfunction, Myocardial infarction, Myocardial viability, PET radiotracers, Positron emission tomography, Single photon emission tomography, Technetium-99m, Thallium-201.

INTRODUCTION

In coronary artery disease (CAD), left ventricular (LV) systolic dysfunction may be attributed either to myocardial infarction (MI) resulting in irreversible myocardial damage and replacement fibrosis, or to chronic impairment of myocardial function despite the fact that the myocardium is viable, as indicated by the preservation of myocyte membrane and contractile fibers integrity [1]. The latter is known as hibernating myocardium and was first described by Rahimtoola in the ‘80s [2]. Myocardial hibernation is considered as the consequence of repeated ischemic events and represents an adaptive status of muscle contraction down-regulation linked to chronic coronary blood flow impairment [2, 3]. This condition is potentially reversible following revascularization or other treatment strategies, leading to improvement in patient outcomes [4, 5]. Histopathologic studies have revealed that hibernating myocardium is characterized by gradual loss of myocyte bundles, expanding collagen deposition and disordered muscle fascicular architecture, fibrosis, elevated glycogen storage, mitochondrial abnormalities, decline in connexin 43, vacuolization and a reversion to fetal myoglobin [3]. Stunning myocardium refers to transient contractile dysfunction following episodes of ischemia [6]. Repetitive, or chronic, stunning results in the development of hibernating myocardium. The term myocardial viability is referred to viable but ischemically compromised dysfunctional myocardium with potentially reversible LV dyssynergy using appropriate treatment, in patients with chronic CAD [1]. The detection of myocardial hibernation associated with CAD and chronic LV impairment using various myocardium viability methods can help in patient selection regarding the performance of coronary revascularization procedures.

Myocardial viability assessment has been explored mainly using either nuclear cardiac imaging techniques, such as single photon emission computed tomography (SPECT) and positron emission tomography (PET), or

echocardiography and cardiac magnetic resonance (CMR). Currently, cardiac computed tomography (CCT) has emerged in this context.

RADIOISOTOPIC METHODS

Single Photon Emission Computed Tomography (SPECT) Imaging

Thallium-201 (^{201}Tl)

The retention of thallium-201 (^{201}Tl) in myocardium is an active process and depends mainly on the function of the Na^+/K^+ pump located on the myocyte membrane, thus reflecting cell viability, cell membrane activity and blood flow [7]. Several ^{201}Tl imaging procedures have been widely used for the viability assessment of dysfunctional myocardium, *e.g.* stress-redistribution imaging, late thallium-redistribution imaging, re-injection technique and rest-redistribution imaging.

Initial experience with ^{201}Tl showed that tracer redistribution in a dysfunctional region with a defect on stress imaging predicts improvement after revascularization [8]. However, additional studies found that stress – 4-hour redistribution imaging cannot always differentiate hibernating myocardium from infarction as the cause of LV dysfunction, since a proportion of irreversible defects showed improvement after revascularization, corresponding obviously to hibernating myocardium [9, 10]. After enrollment of 52 patients with single-vessel left anterior descending (LAD) CAD, Liu *et al.* found that 75% of myocardial regions with persistent defects prior to coronary angioplasty were normal post-angioplasty [9]. These defects may correspond to hypoperfused regions of viable myocardium, and the depiction of such blood supply abnormalities should not considered as a reason for not performing a revascularization procedure [9]. Therefore, the standard stress-redistribution protocol may underestimate viability in an irreversible defect.

Modification of the standard protocol with the acquisition of late (18 to 72 hours) redistribution images has been found to be useful in viable myocardium identification in cases of irreversible defects at 3 to 4 hours. Kiat *et al.* studied 21 patients before and after revascularization interventions and demonstrated a post-

CHAPTER 9

Clinical Value of Cardiac Neurotransmission SPECT Imaging in Heart Failure Patients

Denis Agostini[1,2,*], Damien Legallois[2,3] and **Alain Manrique[1,2]**

[1] *Nuclear Medicine Department, CHU Côte de Nacre, Caen, France*

[2] *EA 4650, Normandie Université, Caen, France*

[3] *Cardiology Department, CHU Côte de Nacre, Caen, France*

Abstract: In patients with ischemic or non-ischemic cardiomyopathy and left ventricular ejection fraction <35%, ^{123}I-metaiodobenzylguanidine (MIBG) imaging can contribute to risk stratification, identifying those patients who are at high risk of sudden cardiac death. This chapter reviews in the first part: recent publications concerning the interest of ^{123}I-MIBG scintigraphy to stratify patients suffering from heart failure and / or ventricular tachyarrhythmia. Then, in a second part, we selected among different therapeutic devices (implantable cardioverter-defibrillator – cardiac resynchronization therapy) some publications about the effects of left ventricular assistance device on the neuronal function of the heart in patients with severe cardiac impairment. Finally, the interpretation of different parameters, such as Heart-Mediastinum Ratio (HMR) or myocardial SPECT scores as regional LV dysinnervation using ^{123}I-MIBG scintigraphy, need some recommendations from the European and Japanese Cardio-Vascular committees.

Keywords: Cardiac autonomous nervous system, Dilated cardiomyopathy, Heart failure, Heart – mediastinum rate, Ischemic cardiomyopathy, Left ventricular assistance device, MIBG, Scintigraphy, Ventricular tachyarrhythmia, Washout ratio.

[*] **Corresponding author Denis Agostini:** Head of Nuclear Medicine Department, CHU Côte de Nacre, University Hospital, Caen, France; Tel: +33 2310 63 246; Fax: +33 2310 64 927; E-mail: agostini-de@chu-caen.fr.

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INTRODUCTION

Heart failure (HF) has become a worldwide health challenge, leading to substantial disability and mortality rates, and a rise in healthcare expenditures. ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy is considered as the only imaging study approved by several regulatory agencies that can evaluate the adrenergic function of the heart. ^{123}I-MIBG scintigraphy is an important imaging modality for investigating sympathetic disorders in different cardiomyopathies. ^{123}I-MIBG planar imaging and single photon emission computed tomography (SPECT) can provide valuable evidence for the management of HF patients. Cardiac ^{123}I-MIBG uptake can vary in appearance on ^{123}I-MIBG scintigraphy because of different technical, physiological and pathological conditions that should be properly identified.

RISK STRATIFICATION OF PATIENTS WITH HEART FAILURE (HF)

To date, there is no considerable improvement in long-term prognosis of HF patients, with a 5-year mortality rate of 59% for males and 45% for females. Moreover, reliable determination of prognosis is possible only in HF patient populations and not for individual patients. Notably, significant improvements in survival cannot be achieved without proper risk stratification of the patients. The most important parameters that influence survival in HF patients are:

1. Decreasing left ventricular ejection fraction (LVEF).
2. Deterioration in New York Heart Association (NYHA) functional class.
3. Severity of hyponatremia.
4. Decreasing peak exercise oxygen uptake ($V0_2$).
5. Low haematocrit levels.
6. Resting tachycardia
7. Renal impairment.
8. Patient intolerance to conventional therapy.
9. Refractory volume overload.

Disordered adrenergic innervation in the heart, as evaluated by ^{123}I-MIBG imaging, is significantly linked to mortality in HF patients, independently of the

underlying cause. Merlet *et al.* enrolled ninety patients with either ischemic (n = 24) or idiopathic (n = 66) cardiomyopathy in order to investigate the prognostic value of ^{123}I-MIBG scintigraphy in comparison to that of other non-invasive cardiac imaging parameters [1]. Twenty-two patients died during a follow-up period of 1-27 months, whereas heart transplantation was performed in 10 patients. The researchers collected data regarding the following clinical and imaging variables: cardiac ^{123}I-MIBG uptake, radionuclide LVEF, X-ray cardiothoracic ratio and echographic end-diastolic diameter; among them, the late heart – mediastinum ratio (HMR) was reported to be the best predictor of event-free survival. Afterwards, 112 HF patients with dilated cardiomyopathy (DCM) were assessed (NYHA classes II-IV, LVEF <40%, LV end-diastolic diameter 70 ± 8 mm, and pulmonary capillary wedge pressure 19 ± 8 mm Hg) [2]. Seven types of data were collected [cardiac ^{123}I-MIBG uptake, circulating nor-epinephrine (NE) levels, LVEF, peak $V0_2$, X-ray cardiothoracic ratio, M-mode echographic end-diastolic diameter and right-sided heart catheterization parameters]. However, only the late HMR and LVEF were associated independently with mortality (mean follow-up 27 ± 20 months). Moreover, ^{123}I-MIBG uptake and circulating NE concentrations were the only variables that independently predicted life duration. A late HMR value of 1.2 was used in both studies for the identification of reduced ^{123}I-MIBG uptake. The use of a low HMR value (1.2) was due to the absence or the non-recommendation of certain HF therapeutic options, such as beta-blockers, angiotensin receptor blockers or aldosterone antagonists, during the period of the studies (1988-1990).

After enrolling 93 HF patients with LV dysfunction, Cohen-Solal *et al.* found that late HMR was decreased and linked to other prognostic factors, like LVEF, cardiac index, pulmonary wedge pressure and peak V02 [3]. Furthermore, over a follow-up period of 10±8 months, late HMR values (lower than or equal to 1.2) and peak V02 were predictive of mortality or cardiac transplantation. On the other hand, early HMR and wash-out rate (WR) were not. Nakata *et al.* investigated 414 patients (42% suffering from symptomatic HF) with the performance of ^{123}I-MIBG scintigraphy [4]. Thirty-seven cardiac deaths were reported over a mean follow-up period of 22±7 months. Late HMR was found to be the most significant predictor of cardiac mortality among the parameters under investigation. Late

CHAPTER 10

Applications of PET Cardiac Neurotransmission Imaging in Heart Failure

Sophia I. Koukouraki*

Department of Nuclear Medicine, Medical School, University of Crete, Iraklion, Greece

Abstract: Congestive heart failure is a very serious disease that affects many people. Increased sympathetic tone, noradrenaline release, decreased neuronal noradrenaline transporter function and noradrenaline concentration are present in the failing heart. An impairment of sympathetic and parasympathetic function increases the risk of mortality in patients with heart disease. Non invasive imaging modalities are used to evaluate heart failure patients like echocardiography, magnetic resonance imaging and radioisotopique techniques. Single photon emission computed tomography (SPECT) and positron emission tomography (PET) are now used for the assessment of the cardiac sympathetic and parasympathetic function. SPECT imaging with 123I metaiodobenzylguanidine is a very useful modality for patients with abnormal cardiac sympathetic function but its role in the quantitative assessment of myocardial autonomic nervous system is limited due to the relative low spatial resolution. PET, the new functional imaging modality, offers more detailed information about the biology of the heart failure helping to the accurate detection, and monitoring of dedicated therapeutic procedures. Another advantage of PET is that multiple tracers may be used providing deeper insights into nerve biology, such as tracers of sympathetic neuronal integrity [^{11}C-hydroxyephedrine (^{11}C-HED), ^{11}C-epinephrine (^{11}C-EPI), ^{11}C-phenyl--phrine (^{11}C-PHE) *etc.*], tracers of adrenergic receptors (^{11}C-CGP12177, ^{11}C-CGP 12388, ^{11}C-GB 67), and tracers of parasympathetic integrity (vesamicol derivatives *etc.*). PET can assess the sympathetic innervation and activation of the heart. Therefore, clinical applications in heart failure patients include risk stratification, assessment of ventricular arrhythmias and of risk of sudden cardiac death, identification of patients who should undergo implantation of defibrillators and therapy assessment.

* **Corresponding author Sophia I. Koukouraki:** Department of Nuclear Medicine, Medical School, University of Crete, Iraklion, Crete; Tel: +30 2810 39 2567; Fax: +30 2810 39 2563; E-mail: skoukou@med.uoc.gr.

Panagiotis A. Georgoulias (Ed.)

Keywords: ^{11}C-CGP12177, ^{11}C-CGP12388, ^{11}C-epinephrine, ^{11}C-GB 67, ^{11}C-hydroxyephedrine, ^{11}C-phenylephrine, Heart failure, Implantable cardioverter defibrillator, Neurotransmission imaging, Positron emission tomography, Sudden cardiac death, Vesamicol derivatives.

INTRODUCTION

Congestive heart failure (CHF) is increasing worldwide, with a prevalence of 1-2% of general population [1]. The clinical syndrome of heart failure (HF) is a serious condition with high rates of morbidity and mortality, resulting from an impaired cardiac pump capacity and of a reduced ability to meet the peripheral tissues metabolic demands [1].

Neurohormonal system and myocardial blood flow play an important role in HF patients. Neurohormonal mechanisms are activated in order to keep the heart rate, the blood pressure and the tissue perfusion in normal rates. Increased sympathetic tone, noradrenaline release, and decreased neuronal noradrenaline (NA) transporter (NAT) function and NA concentration are observed in the failing heart [2, 3]. The sympathetic nervous system is activated in HF patients and cardiac innervation regulates the cardiac output in both conditions at rest and at increased metabolic demand. A pathologically impaired sympathetic and parasympathetic function increases the risk of mortality in patients with heart disease [4].

The function of the sympathetic nervous system (SNS) is based on the synthesis, the uptake, and the release of norepinephrine (neurotransmitter) from the presynaptic cleft. Two important mechanisms control the amount of NE within the presynaptic cleft: a) the uptake-1 mechanism (neuronal, by the norepinephrine transporter) and b) the uptake-2 mechanism (non-neuronal by the sodium dependent non- neuronal transport mechanism) [5 - 7].

Various non invasive imaging modalities are used including echocardiography (ECHO), magnetic resonance imaging (MRI), and radioisotopique modalities that are considered the methods of choice for the evaluation of cardiac autonomic function. They represent the only available diagnostic techniques with acceptable sensitivity in the evaluation of the myocardial blood flow and the sympathetic innervation. SPECT imaging with the use of ^{123}I-metaiodobenzylguanidine

(MIBG) was first reported in the 1980s [8, 9].

NEURONAL IMAGING WITH POSITRON EMISSION TOMOGRAPHY (PET) IN HEART FAILURE (HF)

Neuronal imaging is increasingly used in clinical cardiology. Clinically useful imaging methods should provide accurate measurements with as low as reasonable cost. Among currently available non-invasive imaging modalities for the evaluation of the HF severity, molecular imaging has an important role offering information about the biology in cellular and subcellular level. These techniques are based on the evaluation of pre and postsynaptic targets by the uptake of the radiolabeled neurotransmitters. Several clinical trials investigate the radioisotopique imaging of the sympathetic nerve activity, whereas investigation of the parasympathetic nervous system has been performed only in animals. Currently, the only two imaging modalities that are available for *in vivo* evaluation of cardiac sympathetic innervations utilizing dedicated imaging protocols are SPECT and PET [10]. Both methods allow non-invasive evaluation of regional and global disorders in cardiac sympathetic innervation and activation. SPECT techniques with ^{123}I-MIBG SPECT imaging give information about the uptake, reuptake, storage and release of norepinephrine at presynaptic nerve terminals. However, technical problems reduce the role of myocardial ^{123}I-MIBG imaging due to the limited spatial resolution [9 - 14].

PET imaging provides further information about the biological processes of the failing heart, as well as for monitoring the available therapeutic procedures. PET imaging is superior to SPECT imaging with ^{123}I-MIBG in quality and in the ability to detect regional abnormalities. PET is a highly dedicated scintigraphic imaging modality for the evaluation of the cardiac sympathetic nervous system, with higher spatial (4 - 7 mm) and temporal resolution *vs*. SPECT imaging. It allows the development of dynamic images (tracer kinetics assessment), provides quantitative information for presynaptic neuronal function, and quantifies the absolute amount of the radiotracer within the myocardium [9]. Another advantage of PET is that multiple tracers can be used providing deeper insights into nerve biology. There are several imaging protocols according the radiotracer used and the available equipment. According to standardized axes, volumetric datasets are

CHAPTER 11

Imaging of Radiolabelled Fatty Acid Metabolism

Hein J. Verberne*

Department of Nuclear Medicine, Academic Medical Center, University of Amsterdam, The Netherlands

Abstract: Myocardial metabolism is essential for cardiac contraction and maintenance of cell integrity. Under aerobic, fasting conditions, the primary myocardial substrates are fatty acids. Imaging of myocardial metabolic processes *in vivo* yields valuable insights into myocardial pathophysiological mechanisms. Thereby, it offers a better understanding of various cardiac diseases and may contribute to the evaluation of therapeutic effectiveness of various interventions. Consequently, there is a great interest regarding the development of reliable non-invasive techniques for the imaging of myocardial substrate metabolism. This chapter focuses on several single photon emission computed tomography (SPECT) and positron emission tomography (PET) tracers for the assessment of myocardial fatty acid metabolism. In addition, the impact of different clinical conditions on fatty acid metabolism is discussed, and how these changes in metabolism can be assessed with the radiolabelled tracers.

Keywords: Acetate, Beta-oxidation, Fatty acids, Metabolism, Myocardial ischemia, Myocardium, Palmitate, Positron emission tomography, Radiolabelled tracers, Single photon emission computed tomography.

INTRODUCTION

This chapter focusses on the physiology of the myocardial fatty acid (FA) metabolism and the impact of different clinical conditions on the myocardial FA metabolism. The role of radiolabelled fatty acids and scintigraphic techniques for the imaging of myocardial FA metabolism are also discussed. This chapter is lar-

* **Corresponding author Hein J. Verberne:** Department of Nuclear Medicine, Academic Medical Center, University of Amsterdam, The Netherlands; Tel: + 31 2056 69 111; Fax: +31 2056 69 092; E-mail: h.j.verberne@amc.uva.nl.

Panagiotis A. Georgoulias (Ed.)

gely based on the excellent reviews by Peterson and Gropler, Stanley *et al.*, van der Vusse *et al.* and Giedd and Bergmann [1 - 4].

MYOCARDIAL METABOLISM

Myocardial metabolism is essential for cardiac contraction and maintenance of cell integrity. Myocardial metabolism is primarily aerobic and has a high metabolic rate for which the heart uses a variety of substrates. Under aerobic (*i.e.* non-ischemic), fasting conditions, the primary myocardial substrates are FA, whereas in non-fasting conditions, glucose is the other major substrate. Under these non-ischemic conditions lactate, ketone bodies, and amino acids are less significant energy sources. Nearly all (over 95%) of the myocardial adenosine triphosphate (ATP) derives from oxidative phosphorylation of FA, under non-ischemic conditions. Glycolysis and guanosine triphosphate contribute to the production of the remaining ATP [5]. However, the metabolic substrate in the myocardium can change from FA to other sources. This phenomenon is also referred to as "plasticity in substrate use" [6]. A change in metabolism can be an early marker, and often the first, in cardiac disease, even before changes in function occur or electrocardiograph changes appear. For example, during ischemia, oxidation of FA is reduced or even completely stopped and ATP is derived from anaerobic glycolysis.

Generally, the arterial available substrate (*i.e.* plasma FA levels), albumin-to-FA ratio, FA chain length, hormone concentrations and inotropic state regulate myocardial metabolism in combination with other well-established factors, such as coronary blood flow, oxygen availability and the nutritional status [7, 8]. Notably, the regulatory mechanisms of glucose and FA metabolism do not take place independently in the myocardium. Randle *et al.* and, subsequently, other research teams have described the "cross-talk" between the use of glucose and FA in myocardial metabolism [9, 10].

Free Fatty Acid (FFA) Metabolism

Myocardial FA metabolism is quite complex (Fig. **1**). In myocardial cells, FAs uptake occurs through passive diffusion or protein-mediated transport across the plasma membrane. These transport mechanisms involve a FA translocase or

plasma membrane FA–binding protein [3, 4]. Once FAs have been entered into myocytes, they are first activated by acyl-CoA synthetase to fatty acyl coenzyme A (acyl-CoA). This esterification process is ATP consuming. Under normoxic conditions, about 70-90% of the activated FAs are shortly oxidized in mitochondria. The remaining activated FAs (10-30%) may be either accumulated as intra-cardiac triglycerides or be transformed in the heart to structural lipids. The acyl CoA molecules are transferred from the cytosol into the mitochondrial matrix by the carnitine-dependent transport system. First, in the compartment between the inner and outer mitochondrial membranes, the long-chain acylcarnitine production is catalysed by carnitine palmitoyl transferase I (CPT-I). Then, this long-chain acylcarnitine is transported across the inner mitochondrial membrane by carnitine acyltranslocase. Finally, long-chain acyl CoA is regenerated in the mitochondrial matrix by CPT-II. The rate of FA mitochondrial uptake is controlled by CPT-I, which represents the key enzyme in the regulation of FA mitochondrial transport. After FAs uptake in the mitochondria, a reduced form of nicotinamide adenine dinucleotide (NADH) and a reduced form of flavin adenine dinucleotide [$FADH_2$] are generated through FAs beta-oxidation. Four reactions are involved in the beta-oxidation process (with certain enzymes for each step), finally resulting in the synthesis of acetyl CoA which enters the citric acid cycle.

Under conditions of normal myocardial perfusion, the acetyl-CoA is generated through beta-oxidation of FAs (60 - 90%), and to a lesser extent *via* the oxidation of pyruvate (10 - 40%). Pyruvate comes from glycolysis and lactate oxidation, in approximately equal amounts [11 - 15].

FAs in the bloodstream are derived from lipolysis and the breakdown of triglycerides. Lipolysis is activated by catecholamines and suppressed by insulin [16, 17]. Plasma FAs levels increase under fasting conditions, when insulin concentration is low and catecholamine concentration is increased, promoting FA myocardial uptake. When insulin concentration is elevated, for example post-prandial, adipocyte FAs release is decreased, in combination with higher myocardial glucose utilization [18]. In arterial blood, the most abundant FFA is the 16-carbon FA palmitate, which corresponds to 25-30% of plasma FAs.

CHAPTER 12

Molecular Imaging of Apoptosis and Atheromatous Plaques: Current and Future Applications in Heart Failure

Argyrios Doumas[1,*] and **Ioannis Iakovou**[2]

[1] *2nd Department of Nuclear Medicine, "AHEPA" University Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece*

[2] *3rd Department of Nuclear Medicine, "Papageorgiou" Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece*

Abstract: Nowadays, chronic heart failure patients are assessed by various modalities in order to investigate the extent of jeopardized myocardium. This is extremely important for cardiac remodeling prevention. Radionuclide studies have been extensively used for more than 30 years in the evaluation of these patients. In chronic heart failure, the extent, severity and localization of myocardial damage, as well as the underlying pathology, affect clinical decision-making, including the selection of the optimal therapeutic intervention. A significant portion of heart failure cases is associated with atherosclerotic cardiovascular disease. Plaque rupture represents the main pathophysiological mechanism in these patients, leading to myocardial necrosis and apoptosis. Even though myocardial necrosis and apoptosis almost always co-exist, necrosis is considered as a non-reversible state, whereas apoptosis can be reversed and the affected myocardium may be salvaged. Notably, nuclear medicine techniques can detect and quantitate the amount of myocardial mass that has entered the apoptotic process. On the other hand, while classic imaging modalities have failed to identify the prone to rupture plaques, breakthroughs in molecular imaging may achieve early identification of vulnerable plaques and, therefore, recognition of patients at risk. This chapter focuses on the pathophysiology of apoptosis and plaque rupture, as well as on the available imaging techniques for these phenomena.

[*] **Corresponding author Argyrios Doumas:** Department of Nuclear Medicine, "AHEPA" University Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece; Tel: +30 6944 38 1364; Fax: +30 2310 26 9813; E-mail: dumas@hyper.gr.

Panagiotis A. Georgoulias (Ed.)

Keywords: Anexin-V, Anti-apoptotic therapy, Apoptosis imaging, Atherogenesis, Endothelial dysfunction, Matrix remodeling, Myocardial apoptosis, Neovascularization, Thrombosis, Vulnerable plaque.

INTRODUCTION

The term “apoptosis” comes from a Greek word that means falling down because of a predetermined death, like the leaves from trees. The term was first introduced by Kerr *et al.* to describe a cell stage beyond necrosis [1]. Necrosis is a well-recognized phenomenon, characterized by irreversible loss of cell membrane integrity, consequent cell swelling and rupture, release of intracellular content, and finally inflammation of the surrounding tissues. On the other hand, apoptosis is characterized by maintenance of the cellular membrane integrity, absence of inflammation, cytoplasm and chromatin condensation and finally cellular fragmentation and phagocytosis of the apoptotic cell. All the apoptotic procedures are energy depended.

Apoptosis is taken place as a physiologic process during the embryonic development for the formation of the digits, and during the entire life for the eradication of aged or diseased cells. On the other hand, both hyper-or hypo-activity of apoptosis can lead to various pathologies, such as carcinogenesis (as a result of hypo-function), or heart failure (HF) and scaring because of a hyper-reacting apoptotic process and extensive myocardial loss.

MECHANISMS OF APOPTOSIS

Apoptosis is driven by two mechanisms: a) the extrinsic pathway that utilizes cell surface receptors, and b) the intrinsic pathway, which involves mitochondria and other intra-cellular components (Fig. **1**).

The extrinsic mechanism is triggered by the binding of cytokines (FAS-ligand, TNF-alpha factor, *etc.*) to specific cellular surface receptors. This binding initiates the activation of specific polypeptides which are called caspases (mainly caspase-8). The initial activation is followed by several steps, during which additional caspases are triggered. Among them, caspase-3 represents the main enzyme of the

apoptotic procedure. Caspases (cysteine-aspartic proteases, or cysteine-dependent aspartate-directed proteases) were discovered in the mid-1990s as a family of cysteine proteases that play essential roles in programmed cell death (apoptosis), necrosis, and inflammation [2]. They have been termed "executioner" proteins for their roles in the cell. As of November 2009, twelve caspases had been identified in humans [3].

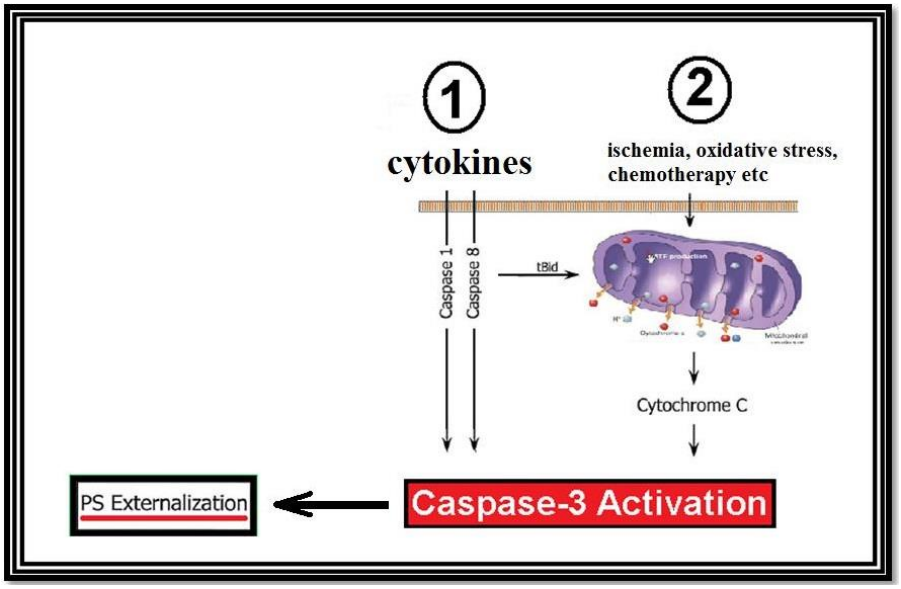

Fig. (1). The two different mechanisms of apoptosis: extrinsic pathway (**1**) and intrinsic pathway (**2**), both leading to caspase-3 activation.
PS: phosphadyl-serin.

The intrinsic mechanism (mitochondrial pathway) is triggered by a wide range of extra- and intra-cellular stimuli, such as impaired blood supply and ischemia, reperfusion injury, oxidative stress, chemotherapeutic factors, or other less understood stimuli (*e.g.* mechanisms involved in the graft rejection process). These factors affect the mitochondria, causing the intracellular release of several peptides, including cytochrome-c and caspase-9.

From this point onward, extrinsic and intrinsic pathways have a common route, leading to caspase-3 activation and phosphadyl-serin (PS) externalization on the cell surface membrane.

CHAPTER 13

Molecular Imaging Techniques of Gene and Cell Heart Failure Therapies: State of the Art and Future Perspectives

Athanasios Katsikis and **Maria Koutelou***

Department of Nuclear Medicine, Onassis Cardiac Surgery Centre, Athens, Greece

Abstract: Cardiovascular molecular imaging demonstrates an enormous potential to promote the understanding of pathophysiology, risk stratification, therapy monitoring and treatment of heart failure. Applications of molecular imaging in the field of stem cell and gene therapy constitute the only way to investigate their mechanisms of action and adequately evaluate the equivocal clinical results, obtained from human trials at the initial steps of transforming these experimental strategies into therapeutic options, with clear benefits for the patients. In this chapter, the principles and methods of molecular imaging will be presented, focusing on its current status regarding clinical applications in the field of heart failure research, and stem cell and gene therapies, in particular. Finally, we will attempt to present the potential of these promising imaging techniques, which advance in parallel with the transition of stem cell and gene therapy from the research laboratory to the clinical setting of heart failure management.

Keywords: Cell therapy, Gene therapy, Heart failure, Imaging, Molecular, Optical imaging, Positron emission tomography, Single photon emission computed tomography, Tracking, Ultrasound imaging.

INTRODUCTION

Molecular imaging can be defined as the non-invasive, real-time imaging of biochemical processes at both cellular and subcellular level in living cells, tissues

* **Corresponding author Maria Koutelou:** Department of Nuclear Medicine, Onassis Cardiac Surgery Centre, Athens, Greece; Tel: +30 210 949 3000; Fax: +30 210 949 3000; E-mail: marinucl@hotmail.com.

Panagiotis A. Georgoulias (Ed.)

and/or intact subjects [1 - 3]. In detail, it involves the use of conventional or specialized imaging modalities to visualize appropriately labelled imaging targets specific for various tissue characteristics and biochemical events, in a receiver-receptor form of coupling.

In contrast to traditional imaging methods for investigating diseases, which depict anatomical and physiological changes, molecular imaging aims toward visualization of specific molecular targets and pathways that precede or underlie changes in morphology, physiology, and function [1, 3]. A characteristic paradigm of this crucial difference is atherosclerotic cardiovascular disease in which patients with absent or non-significant plaque formation in a coronary artery, as detected by angiography or functional testing, experience a thromboembolic event related to the lesion located at this "diagnosed as non-significantly stenosed" vessel.

Molecular imaging of living subjects has emerged from nuclear medicine methodology, more specifically techniques implemented in the research of malignant diseases during the last decades. The development of highly sensitive radionuclide imaging modalities, like single photon emission computed tomography (SPECT) and positron emission tomography (PET), combined with the synthesis of novel molecular imaging probes specific for various different biochemical targets, led to a new era of diagnostic imaging [1 - 4]. Although nuclear medicine remains at the forefront of molecular imaging, new technologies have also emerged during the last few decades based on the general framework of injecting molecular compounds into living subjects to target specific biochemical processes. Techniques using optical and magnetic resonance signalling, ultrasound (US), Raman spectroscopy (RS), photo-acoustics and computed tomography (CT) are considered as the most important among methods that are not included in nuclear medicine applications. Hence, nowadays a wide array of imaging modalities for molecular imaging exist, some of which however are used only in the animal research field and also in clinical trials [1 - 4].

MOLECULAR IMAGING IN HEART FAILURE (HF)

Cardiovascular molecular imaging, although currently in its clinical infancy, is a

rapidly emerging discipline which holds the promise to provide insights on the mechanisms of various cardiovascular diseases at the molecular level, enable earlier detection and more accurate monitoring of these conditions, improve therapy monitoring, promote drug discovery and development and assess the efficacy of treatments such as stem cell transplantation and gene therapy. Many contemporary reviews on the current status of cardiovascular imaging in general, have been published [1 - 7].

Regarding myocardial dysfunction, although the classic assessment of HF patients is performed by echocardiography, molecular imaging has provided tools to visualize many molecular processes involved in HF, including cellular injury, neurohormonal receptor function and metabolism [8 - 10]. Imaging of cardiomyocyte apoptosis at a preclinical level using annexin-labelled fluorescent iron oxide (IO) - nanoparticles and magnetic resonance imaging (MRI), and the use of ^{123}I-metaiodobenzylguanidine (MIBG) for the risk stratification of HF patients, represent characteristic examples in this field [11 - 14].

The most promising applications of molecular imaging in HF however are linked to stem cell and gene therapies. HF is a major public health issue with a prevalence of over 23 millions worldwide, substantial morbidity and a 5-year mortality that rivals those of many cancers [15]. Moreover, the cost for the health care system has been estimated at 39 billion dollars annually only in the USA [15]. Regardless of the specific aetiology, the failing myocardium is composed of malfunctioning, permanently lost and normal cardiomyocytes in combination with varying degrees of fibrous tissue replacement. Since the heart lacks any significant regenerative capacity, the survival of patients who develop advanced HF not amenable to satisfactory management with the currently available medical or interventional therapies hinges on heart transplantation.

The goal of cardiac cell-based therapy is to repopulate areas of damaged myocardium with cells capable of engraftment and trilineage differentiation into cardiomyocytes, vascular smooth muscle cells and endothelial cells [16]. Stem and progenitor cells have the ability of self-regeneration and the potential for multi-lineage differentiation. Locally targeted implantation of skeletal myoblasts, bone marrow-derived stem cells, mesenchymal stem cells, circulating progenitor

CHAPTER 14

Artifacts and Pitfalls in Cardiac Molecular Imaging

Ioannis C. Tsougos[1,*] and **A. Panagiotis Georgoulias**[2]

[1] *Department of Medical Physics, University of Thessaly, Larissa, Greece*

[2] *Department of Nuclear Medicine, University Hospital of Larisa, University of Thessaly, Larissa, Greece*

Abstract: Single Photon Emission Computed Tomography (SPECT) has the unique ability to evaluate myocardial perfusion, at the cellular level, under peak stress conditions. In that sense, by evaluating viability, SPECT myocardial perfusion imaging (MPI) can establish prognosis and assess the effectiveness of therapy, thus becoming a valuable modality in diagnosing and managing cardiac patients. Nevertheless, SPECT MPI can be exposed to various pitfalls and artifacts that may affect negatively the reliability of the technique, arising from a number of sources at any stage of this complex imaging process that includes patient-related, software- and equipment-related and user-related factors. By understanding and recognizing the sources of these pitfalls and artifacts, the reader should be able to make all the necessary steps to limit the sources of error, and more importantly to interpret the results of a study by taking into account their relative influence.

Keywords: Artifacts, Attenuation artifacts, Breast attenuation, Cardiac imaging, Diaphragmatic attenuation, Myocardial perfusion imaging, Pitfalls, Single photon emission computed tomography.

INTRODUCTION

Single Photon Emission Computed Tomography (SPECT) has been proven to be a very important tool in the management of patients suffering from cardiovascular

* **Corresponding author Ioannis C. Tsougos:** Department of Medical Physics, University of Thessaly, Larissa, Greece; Tel: +30 6977 78 3833; Fax: +30 2413 50 1863; E-mail: tsougos@med.uth.gr.

disorders. SPECT myocardial perfusion imaging (MPI) has the unique ability to provide evidence, at the cellular level, regarding myocardial perfusion under peak stress conditions, hence providing information regarding myocardial viability [1].

However, MPI is a multifactorial imaging procedure; hence it may suffer from a number of pitfalls and artifacts related to both patient and technical factors. In fact, potential artifacts and pitfalls may be related to any stage of imaging procedure, as depicted in Fig. (**1**). It is evident that various usual imaging artifacts may be linked to the acquisition process and/or the reconstruction method, but more importantly there is considerable overlap. By recognizing the sources of such artifacts, both the radiation technologists and the nuclear medicine physicians can minimize their effect on the study, thus improving the specificity of the method and contributing to the optimization of patient treatment.

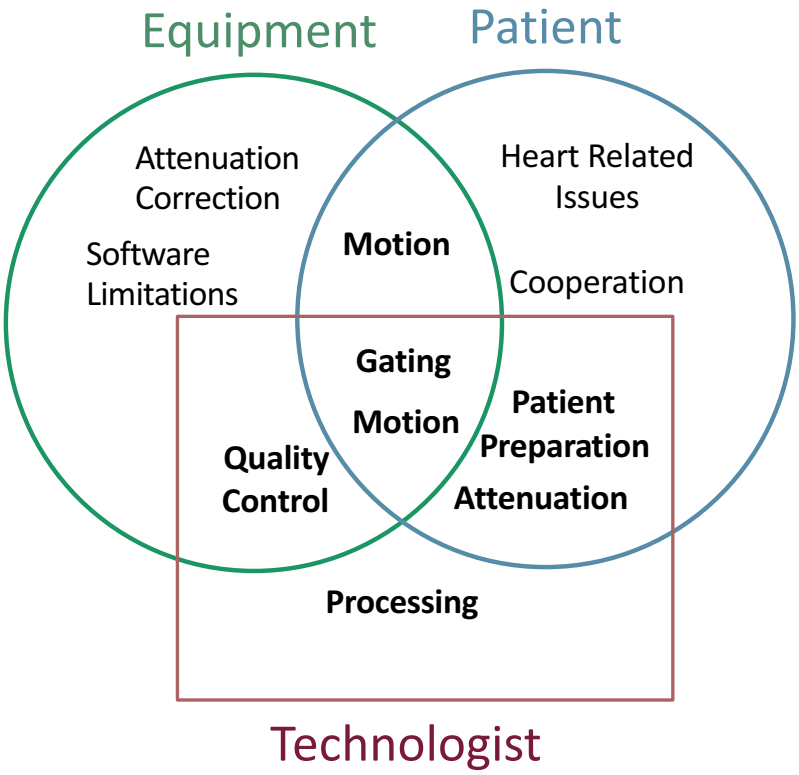

Fig. (1). Basic causes of artifacts and pitfalls in MPI SPECT, and their overlap.
MPI: myocardial perfusion imaging; SPECT: single photon computed tomography

A high degree of technical expertise, which improves image quality and minimizes the incidence of false positive and false negative results, is a crucial parameter for the successful clinical utilization of myocardial perfusion SPECT.

This chapter aims to review these artifacts, either related to the patient or several technical factors that may influence MPI findings and their interpretation.

QUALITY CONTROL (QC) PROCEDURES

In order to ensure the excellent performance of the camera, which is strongly required for the optimal diagnostic utility of MPI SPECT, a number of QC procedures, beyond that required for routine planar imaging, are necessary. Particularly, the proper performance of a camera for planar imaging does not exclude the presence of artifacts in the SPECT imaging, which may significantly compromise both diagnostic and therapeutic decisions [2].

Hence, additional QC tests and image correction are needed for MPI SPECT, in comparison to the routinely performed testing. Center of rotation, multi-head registration and tomographic uniformity represent SPECT corrections that may lead to the most important negative consequences on reconstructed data [2]. Moreover, QC tests for SPECT imaging should include pixel size calibration, tilt angle check and SPECT phantom reconstruction [3].

The QC testing should be performed at the recommended frequency according to the camera manufacturer guidelines and in accordance with the National Electrical Manufacturers Association (NEMA) recommendations for implementing SPECT instrumentation QC [3].

The most fundamental corrections and evaluations, that are absolutely necessary to be performed, are the uniformity and center of rotation (COR) corrections and the performance evaluations, with the use of special manufactured phantoms.

Uniformity Correction

The concentric ring or “bull’s eye” artifacts are associated with regional sensitivity variations in the projection images, and represent very common and severe reconstruction artifacts [3]. Collimator septum disparities, variations in

CHAPTER 15

Basics of Radiation Protection in Cardiac Imaging Studies

Constantin Kappas* and **Kiki Theodorou**

Department of Medical Physics, University of Thessaly, Medical School, Larissa, Greece

Abstract: Cardiology is responsible for a large part of the radiation exposures that every person receives per year from all medical sources. Fluoroscopically guided and other cardiology procedures are increasing in number and complexity. Catheterization PCI, interventional electrophysiology procedures and repeated procedures can result in patient skin doses high enough to cause deterministic skin injuries. Cancer risk from a single NST is small, but projected on a population level, NSTs may result in thousands of radiation-attributable cancers annually. Several epidemiological studies involving various levels of radiation exposure all show increased cancer risk, and allow risk projection. The occupational radiation exposure of cardiologists and nuclear cardiology staff must be considered; exposure of interventional cardiologists and cardiac electrophysiologists can be two to three times higher than that of diagnostic radiologists. In recent years, intensive efforts have been initiated to reduce the radiation dose associated with cardiology. Staff radiation protection is related to patient protection, as radiation received is mainly the scattered radiation from patients. The correlation between occupational and patient doses is very dependent on equipment, the specialist, and protocols followed throughout the procedure. Radiation data collection and documentation procedures, QA programmes, application of Diagnostic Reference Levels (DRLs), research, training and education are among the very basic tools also to enhance radiation protection and exploit all the advantages of radiation imaging and therapy in Cardiology.

Keywords: Cancer risk, Deterministic effects, Dosimetry, Medical imaging, Occupational risk, Radiation biology, Radiation dose, Radiation exposure, Radiation protection, Stochastic effects.

* **Corresponding author Constantin Kappas:** Department of Medical Physics, University of Thessaly, Medical School, Larissa, Greece; Tel: +30 2413 50 2052; Fax: +30 2413 50 1013; E-mail: kappas@med.uth.gr.

Panagiotis A. Georgoulias (Ed.)

INTRODUCTION

Cardiac Nuclear Medicine, Cardiac CT, Fluoroscopy (including Cine-Angiography), Percutaneous Coronary Interventions and Electrophysiology procedures are increasing in number and account for an important share of patient and occupational radiation exposure in medicine [1 - 5]. These modalities differ in the frequency with which they are performed, in patient absorbed doses, and in radiation dose to operators and staff.

POPULATION – COLLECTIVE EXPOSURE

40% of the entire Cumulative Equivalent Dose (except for Therapy purposes) that every person receives per year from all medical sources is due to Cardiology [6]. This is resulted from a variety of acts, unequally contributing to the total radiation burden:

- Among adult cardiology patients (study in Pisa, Italy), fluoroscopically guided diagnosis and intervention account for 12% of all radiological examinations performed, and 48% of their total collective dose [7].
- Among the nuclear medicine studies (USA, whole country), cardiac imaging accounted for 57% of the all procedures but contributes to 85% to the collective dose [8, 9].
- Among paediatric cardiology (worldwide study) patients with congenital heart disease, fluoroscopically guided diagnosis and interventions account for 3.5% of all radiological examinations performed and 84% of their total collective dose [10].

PATIENTS' EXPOSURE

The powerful data provided by cardiac diagnostic and therapeutic procedures are essential in clinical cardiology and have contributed to the decrease in morbidity and mortality from coronary heart disease. Procedures that utilize ionizing radiation should be performed in accordance with the As Low As Reasonably Achievable (ALARA) principle.

Patient radiation dose increases as procedure complexity increases [11 - 14]. These procedures can result in patient skin doses high enough to cause radiation injury and, in children, an increased probability of late effects [15].

Fluoroscopically Guided- Procedures

Despite the continuing development of non-invasive cardiac imaging techniques, Cardiologists perform a variety of fluoroscopically guided invasive cardiac diagnostic and therapeutic procedures. In Europe, North America, China and in developing countries, there was a substantial increase of coronary angiographies (CA) and percutaneous coronary interventions (PCI) between 1992 and 2001, primarily due to the introduction of coronary stents [9, 16 - 18]. Some procedures may involve long fluoroscopy times [19]. There is little literature concerning the safety issues of these new devices to be used in infants and children [20].

Patients undergoing interventional procedures in cardiology face radiation exposure in the order of a thousand or more times than that involved in conventional radiography [21]. In contemporary imaging practice, doses > 50–100 mSv are sometimes reached after cumulative exposures in a single hospital admission and sometimes by a patient in multiple examinations and diagnostic or interventional procedures for a single imaging technique or even in a single examination [7, 22 - 28].

Cardiac Computed Tomography (CT)

With the introduction of multi-slice CT scanners, cardiac CT angiography (CCTA) has emerged as a useful diagnostic imaging tool for many cardiac conditions [29 - 34]. Even if use of computed tomography (CT) for cardiac diagnostic evaluation has increased significantly after 2000, many clinicians and researchers working with patients with cardiovascular diseases may yet be unfamiliar with the radiation doses that are received during cardiac CT imaging [35]. The fact that radiation dose estimates for CT examinations of the heart can be expressed in many different ways [as volume CT dose index ($CTDI_{vol}$), dose length product (DLP), or effective dose] makes it difficult to compare doses that have been reported for specific CT applications in the published literature [29, 32, 36 - 41].

CHAPTER 16

Technical Advances in Hybrid Cardiac Imaging: Potential Applications in Heart Failure

George K. Loudos*

Department of Biomedical Engineering, Technological Educational Institute of Athens, Athens, Greece

Abstract: Hybrid molecular imaging has changed diagnostic medical imaging over the past fifteen years. The ability to combine anatomic and functional modalities in a single exam has opened new perspectives in personalized diagnosis and therapy. Although the first applications were focused in oncological and brain domains, hybrid cardiac imaging gains continuous interest due to the advantages that multimodal techniques offer, in terms of improved technical performance and diagnostic value. This chapter reviews the role of the well-established SPECT/CT and PET/CT in heart failure, as well as the potential of the rapidly evolving PET/MRI and the promising, yet only experimental, SPECT/MRI. To better understand the value of these hybrid technologies compared to the standard nuclear medicine (SPECT and PET), emphasis is given on the opportunities that the combination of anatomical and functional information can offer, in terms of image corrections and quantification, so that the reader can understand not only the added value of the current applications, but also envisage new, future possibilities.

Keywords: Attenuation correction, Bimodal agents, Computed tomography, Coronary artery disease, Functional imaging, Heart failure, Hybrid imaging, Magnetic resonance imaging, Motion correction, Multimodal imaging, Single photon emission tomography.

INTRODUCTION

While the value of nuclear and anatomic imaging in heart failure (HF) is undoubt-

* **Corresponding author George K. Loudos:** Department of Biomedical Engineering, Technological Educational Institute of Athens, Athens, Greece; Tel: +30 210 538 5376; Fax: +30 210 538 5302; E-mail: gloudos@teiath.gr.

Panagiotis A. Georgoulias (Ed.)

ful, the rapidly evolving hybrid imaging techniques can only have a positive influence. Hybrid imaging relies mainly on merging a functional (single photon emission computed tomography - SPECT or positron emission tomography - PET) with an anatomical (computerized tomography - CT or magnetic resonance imaging - MRI) technique. However, as it is often stated in hybrid imaging domain "*one plus one equals more than two*" and the actual benefits of hybrid imaging are far beyond the fusion of a functional image on an anatomical map. In oncology, the exact localization of a tumor can strongly influence the diagnostic procedure, thus treatment strategy. On the contrary, in cardiology the location of the organ of interest is known and the value of functional imaging lies on the quantification of radiotracers' biodistribution, which is indicative of the disease stage. Thus, the added value of hybrid imaging is clearly in quantification improvement, which is mainly achieved through accurate attenuation and motion correction. The recent advent of bimodal agents, including radiolabelled nanoparticles, is likely to have a strong impact in the role of hybrid cardiac imaging, especially in the case of PET/MRI and SPECT/MRI.

SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT) / COMPUTED TOMOGRAPHY (CT)

Basics of Single Photon Emission Computed Tomography (SPECT) / Computed Tomography (CT) Technology

SPECT imaging has still the largest share in cardiac imaging, due to the relatively low cost of the gamma camera, the availability of different tracers that do not require a cyclotron and the wide variety of radiotracers, which are based on different isotopes, have different energy and can cover different cardiac applications. SPECT is based on the rotation of a gamma camera around the patient body. The technical description of a gamma camera can be found in many references and very briefly it consists of i) a parallel hole lead collimator, which is used to filter the orbit of the photons which are emitted by the injected radionuclide, ii) a NaI(Tl) scintillator, which converts gamma photons to optical photons of lower energy, iii) a matrix of photomultiplier tubes (PMTs), which detect the light emitted from the scintillator, iv) electronics for amplifying, digitizing and transferring the detected signals to the computer and finally v) one or more computers for data visualization, correction and reconstruction in the case of camera rotation [1].

Although this is the basic gamma camera design, which is also used for various SPECT applications, the fact that heart is an organ associated with different diseases causing significant social impact, justifies the continuous research in SPECT instrumentation, which has resulted to dedicated cardiac SPECT systems. They can offer improved performance in terms of spatial and energy resolution due to the selection of improved detector modules and components, as well as due to the optimized geometry, which in many cases fits patient body and provides maximum information. These concepts are beyond the purpose of this chapter, but the reader is encouraged to read a nice review by Hutton *et al.* [2]. These new concepts, if combined with the decrease in systems cost, will change the tools that the physicist and physician will have in hand.

From a technical point of view, the main challenge for SPECT cardiac imaging is the quantification of tracer's biodistribution, which is strongly affected by the attenuation of photons in torso. Due to the non-symmetry of human body, the posterior projections suffer from strong attenuation and if no corrections are applied, the resulting SPECT images will have strong quantification artifacts, possibly leading to misdiagnosis. As an initial solution, the acquisition of only anterior positions was used in cardiac SPECT. The success of PET/CT and the benefits of CT-based attenuation correction (AC) inspired the introduction of SPECT/CT in clinical practice. Although the first SPECT/CT prototype was presented by Hasegawa in the early 90s, the first commercial systems were available in the late 90s, with a much slower acceptance compared to PET/CT [3]. Partially, this could be justified by the low cost of SPECT cameras, which significantly raises when adding a CT, compared to the relatively low cost that CT adds to the overall price of a PET system. In addition, there has been conscious for the additional radiation dose that a patient receives in a typical diagnostic cardiac SPECT, which needs to be better justified compared to the exams that target cancer patients in whom the diagnostic benefit superimpose dose considerations.

From an instrumentation point of view, a SPECT/CT consists of a standard SPECT camera, which is combined with a standard CT system [4]. The two studies are separately performed, with all limitations and concerns that one must have in mind for image fusion, correction and interpretation. The evolution of

SUBJECT INDEX

A

B

C

D

E

F

G

H

I

L

M

N

O

P

Q

R

S

T

U

V

W

X

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.