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# Chapter 1

General Introduction and Outline of the Thesis





## INTRODUCTION

Despite the remarkable development in our understanding of cardiovascular diseases, they are still responsible for about one-third of all deaths in Western societies<sup>1</sup>. The major contributor to mortality is coronary artery disease leading to acute myocardial infarction, causing 12% of all global deaths<sup>1</sup>. In the last decades coronary artery disease has reached endemic proportions, putting an enormous strain on health care economics, and with the aging population this is expected to increase in the future.

As a result, the patient population observed in cardiology practice is changing. Not only the number of patients with suspected and known coronary artery disease has increased, but also the population of chronic heart failure patients has grown and will continue to increase, due to the aging population and the improved survival after acute myocardial infarction<sup>2</sup>. In addition, due to the developments in cardiothoracic surgery, there is an increasing number of patients with congenital heart disease reaching adulthood and entering the adult cardiology outpatient clinic<sup>3</sup>. Those patients are not only at risk for late cardiac complication, but also for developing coronary artery disease as they are exposed to the same risk factors for cardiovascular disease as every other person living in a Western society.

For appropriate management and treatment of this growing and diverse patient population encountered in cardiology practice, the assessment of the proper diagnosis and the evaluation of the cardiac condition of the patient remains the first important step. Therefore, enormous efforts have been made over the past decades to improve invasive and non-invasive cardiac imaging<sup>4</sup>. As a result, a great variety of techniques is now available in daily clinical routine. According to the information that is provided by the different imaging techniques, they can be divided into two major groups: anatomical imaging and functional imaging. In anatomical imaging the focus is on visualizing the coronary artery tree, atherosclerotic plaques and myocardial structure. Functional imaging focusses on assessment of myocardial perfusion, myocardial contractile function and myocardial sympathetic innervation. At present, cardiac imaging not only has contributed to the applied diagnostic algorithms, it also had its impact on therapeutic strategies and prognostication of patients with cardiovascular disease.

Among the available anatomical imaging techniques, computed tomography coronary angiography (CTCA) has emerged as one of the most potent cardiac imaging technique for non-invasive evaluation of the presence of coronary arterial atherosclerosis. Because of high negative predictive value, CTCA has an excellent ability of ruling out significant coronary artery disease<sup>5</sup>. Moreover, in the presence of significant coronary artery disease, CTCA provides information about the type of atherosclerotic plaque that is causing the luminal narrowing, such as calcified plaques, mixed or soft tissue plaques. This information is valuable for further therapeutic decision making, as the type of atherosclerotic plaque

provides important prognostic information<sup>6</sup>. Importantly, other information that is always included and is easily assessed on CTCA is information about cardiac anatomy including coronary arterial dominance. Coronary arterial dominance is defined by the coronary artery that supplies the posterior descending artery (PDA) and posterolateral branches. Up till present, the value of this anatomical information may be underestimated. Coronary arterial dominance influences the relative contribution of the different coronary arteries to the total left ventricular blood flow<sup>7</sup>. Therefore, a significant coronary artery obstruction may jeopardize a large amount of myocardium in one patient, and less in the other patient, depending on the coronary anatomy. Subsequently, coronary arterial dominance may have prognostic value in patients with suspected or known coronary artery disease (PART I).

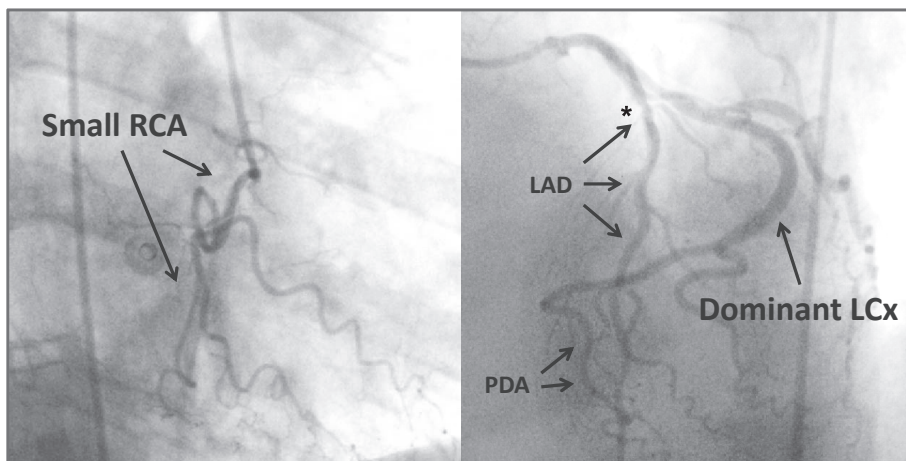
Another advantage of CTCA is that it provides the possibility to reconstruct the coronary arterial tree in three-dimensional view. Compared to conventional invasive coronary angiography, the three-dimensional view of CTCA makes it easier to determine the origin of the coronary arteries and the coronary course in relation to the great arteries. This can be of a particular value in patients with a higher risk of having anomalous coronary arteries, such as patients with congenital heart disease (PART I).

As a result of better primary prevention and early detection of the presence of significant coronary artery disease, the occurrence of an acute myocardial infarction can be prevented in many cases. Moreover, in case of an acute ST-elevation myocardial infarction (STEMI), survival has significantly improved due to the aggressive therapy with primary percutaneous coronary intervention<sup>8</sup>. On the other hand, as previously mentioned, this improved survival of STEMI patients in combination with an aging population, resulted in a growing number of patients with chronic ischemic heart disease<sup>2</sup>. Therefore, the role of secondary prevention in limiting the number of reinfarction and heart failure in post-STEMI patients has increased. Despite the therapeutic innovations over the last decades, a considerable number of patients develops heart failure post-STEMI. Unfortunately, the mortality rates of patients with heart failure remain high with an estimated 5-year mortality rate of 59 % in men and 45 % in women<sup>9</sup>. Therefore, interest has grown in the development of tests capable of providing insight into future risk for heart failure progression and arrhythmic sudden cardiac death. One potential area for such testing is the sympathetic innervation of the heart using 123-iodine metaiodobenzylguanide (<sup>123</sup>I-MIBG) scintigraphy. The recent developments in sympathetic nerve imaging with <sup>123</sup>I-MIBG imaging may be useful for the risk stratification of patients with chronic heart failure (PART II).

## IMPORTANCE OF CORONARY ARTERIAL DOMINANCE IN PATIENTS WITH SUSPECTED AND KNOWN CORONARY ARTERY DISEASE (PART I)

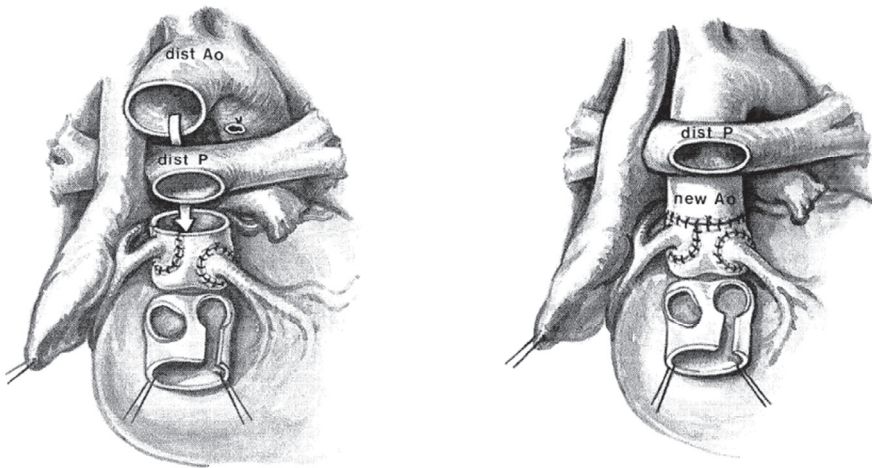
Variations in coronary circulation are common, particularly with regard to the supply of the posterior wall of the left ventricle. In approximately 88% of people in the general population the posterior descending artery (PDA) originates from the right coronary artery (RCA), defined as a right dominant coronary artery system<sup>10,11</sup>. A left dominant coronary artery system, with a PDA originating from the left circumflex artery (LCx), is far less prevalent with reported proportions between 7 and 10%. When the PDA originates from the RCA in combination with large posterolateral branches from the LCx artery, reaching near the interventricular groove, there is a balanced coronary artery system, as present in approximately 4% of people<sup>10</sup>.

In patients with a left dominant coronary artery system (Figure 1), around 60% of the left ventricular myocardium is supplied by the dominant LCx artery, making this the most important coronary vessel of the coronary artery tree in these patients. Not only the LCx artery is more important in patients with a left dominant coronary system, also the left anterior descending artery (LAD) is longer and wrapped around the apex of the heart in 87% of these patients<sup>12</sup>. Moreover, patients with a left dominant coronary system seem to have less ability to form adequate collateral circulation in case of significant coronary obstruction<sup>13</sup>. This inferiorly balanced coronary circulation may have negative influence on prognosis of patients with coronary artery disease.



**Figure 1.** Conventional coronary angiogram of a patient with a left dominant coronary artery system. In this patient the RCA is small, only supplying the right ventricle. The entire lateral and posterior wall of the left ventricle is supplied by the dominant LCx artery.

\*This patient had a subtotal occlusion of the proximal LAD artery, which was stented during primary PCI.



**Figure 2.** Schematic drawing of the arterial switch operation performed with the Lecompte manoeuvre for the correction of the transposition of the great arteries. Both big arteries are transected and the pulmonary root is completely clear for visualization of the coronary arteries arising from the pulmonary artery. The coronary arteries are then transferred to the aorta, using a 'button-technique'. This is the most challenging step during the operation. Reprinted from Thesis of J.M. Quaeghebeur, with permission.

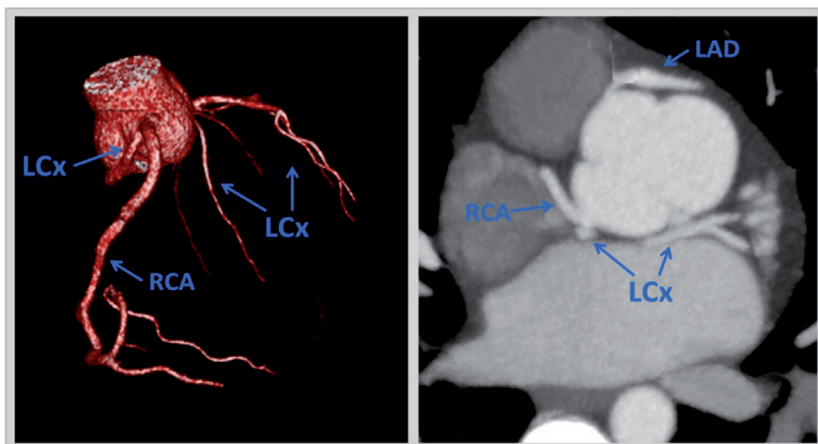
At present, little is known about the prognostic relevance of this anatomical variation. A study screening 1620 postmortem angiograms showed that the prevalence of a left dominant coronary artery system decreased with age, suggesting a higher death rate among patients with a left dominant coronary artery system<sup>14</sup>. An explanation could be the larger amount of myocardium that is at risk in these patients, resulting in more extensive myocardial infarction in case of a left coronary artery occlusion.

Data describing the prognostic value of coronary arterial dominance in patients with coronary artery disease are scarce. A previous study by Goldberg et al. in a large cohort of patients undergoing cardiac catheterization due to acute coronary syndrome, showed that the presence of a left dominant coronary artery system was a predictor of death<sup>15</sup>. In addition, a study by Ilia et al. showed that an acute occlusion of a proximal dominant LCx artery resulted in a higher proportion of patients presenting with cardiogenic shock and higher in-hospital mortality rate when compared with patients with a proximal LAD artery occlusion<sup>16</sup>.

Better awareness of the prognostic relevance of coronary arterial dominance may improve risk estimation of future adverse events in patients with coronary artery disease assessed on CTCA and in patients after STEMI.

### Abnormal coronary artery anatomy in adults with congenital heart disease

According to literature, coronary anomalies affect approximately 1% of the general population<sup>17</sup>. However, due to the interplay between cardiac malformation and coronary



**Figure 3.** Three-dimensional and axial image of the coronary artery tree of a patient with a variant coronary artery pattern. In this patient the LCx is arising from the RCA. The LAD forms the single left coronary artery. Using different post-processing procedures in the evaluation of the images, the coronary course can be appreciated nicely in relation to the great arteries.

morphogenesis, the incidence of coronary anomalies is much higher in patients with congenital heart disease. Different incidences for the presence of coronary artery abnormalities in patients with congenital heart disease are reported, ranging from 9-12%<sup>18</sup>. In these patients, knowledge about the coronary origins and their course is essential for optimal surgical repair shortly after birth, particularly when the coronary arteries need to be replaced as part of the correcting surgery. The presence of coronary anomalies in these patients can cause an increased risk of ischemic damage during surgical correction<sup>19</sup>. Moreover, coronary complications later in life are observed more often in patients with a variant coronary artery pattern<sup>20</sup>.

In patients with transposition of the great arteries an arterial switch operation is the preferred surgical approach. The principle step in the arterial switch operation is the transfer of the coronary arteries into the neo-aorta (Figure 2). The arterial switch operation was performed first in 1977 and more routinely in the years thereafter. Subsequently, most patients who underwent this type of surgery are now reaching adulthood. Late cardiac complications that are reported in patients with transposition of the great arteries corrected by arterial switch operation include dilation of the neo-aortic root and coronary obstructions<sup>21</sup>. Particularly patients with variant coronary artery anatomy seem to have a higher risk of developing significant coronary lesions during follow-up after the arterial switch operation. Importantly, due to perioperative sympathetic denervation, these patients often remain asymptomatic<sup>22</sup>. Therefore, the evaluation of the patency of the coronary arteries is of major importance in these patients. Because of its non-invasive nature and the advantage of three-dimensional imaging, enabling precise determination



of the origin and course of the coronary arteries in relation to the great arteries, CTCA is the preferred technique for the evaluation of the coronary arteries in these young adults (see example case in Figure 3).

With the increasing number of patients with congenital heart disease entering the adult cardiology outpatient clinic, it is of major importance that cardiologists become familiar with the spectrum of abnormal coronary findings that may be encountered in these patients.

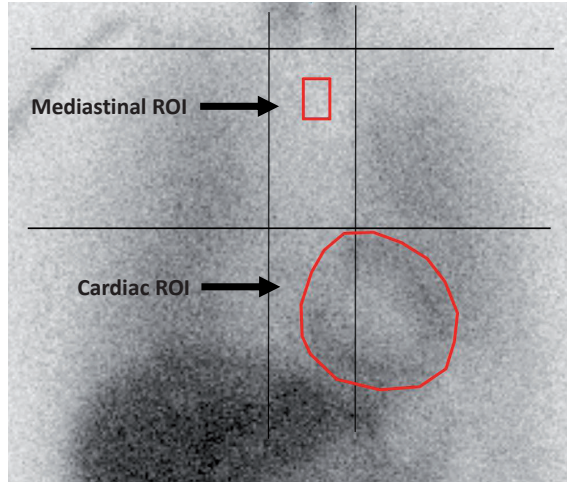
## **USE OF CARDIAC 123-IODINE META-IODOBENZYLGUANIDE IMAGING IN PATIENTS WITH CHRONIC HEART FAILURE (PART II)**

The heart is innervated by the autonomic nervous system, consisting of the sympathetic and parasympathetic system by which it controls the cardiac performance, such as contractility, conduction and heart rate. The sympathetic nervous system is dominant in the ventricles with norepinephrine as most important neurotransmitter. In heart failure patients, there is an increased myocardial sympathetic activity as the failing heart tries to compensate for the reduced cardiac output<sup>23</sup>. At the cellular level, the increased sympathetic activity causes increased neuronal release of norepinephrine. This increase in norepinephrine eventually leads to posttranscriptional downregulation of the cardiac norepinephrine transporters causing a significant reduction of presynaptic norepinephrine uptake<sup>24</sup>.

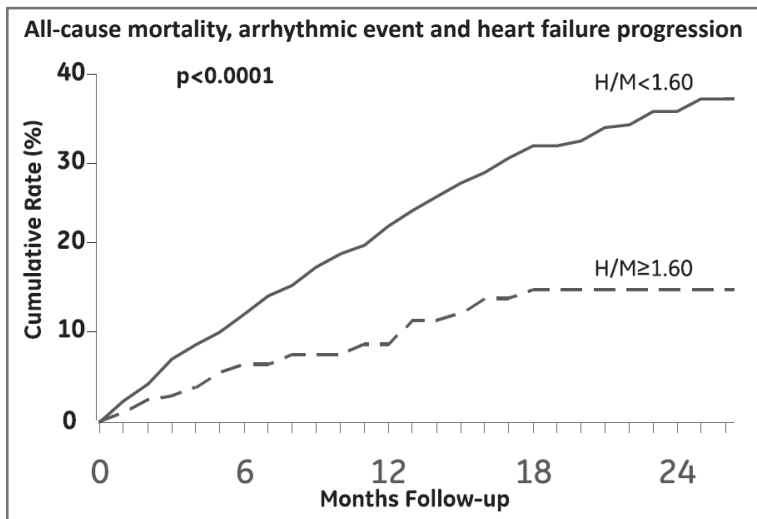
Meta-iodobenzylguanidine (MIBG) is a <sup>123</sup>I-labelled norepinephrine analogue allowing visualization of the myocardial sympathetic neuronal uptake. The amount of myocardial <sup>123</sup>I-MIBG uptake is expressed as the heart-to-mediastinum (H/M) ratio, with the very low amount of <sup>123</sup>I-MIBG uptake in the mediastinum as reference (Figure 4).

A large number of investigators have demonstrated decreased myocardial <sup>123</sup>I-MIBG uptake in patients with heart failure. This decreased uptake was shown to be related with future adverse events, while patients with the lowest uptake tend to have the poorest prognosis (Figure 5)<sup>25</sup>.

Despite the demonstrated prognostic value cardiac <sup>123</sup>I-MIBG imaging in chronic heart failure patients, clinical use of this procedure remains limited<sup>26</sup>. Potential reasons for the limited clinical impact of cardiac <sup>123</sup>I-MIBG imaging has been the variability in the technical aspects of the procedure. Most of the publications include the H/M ratio as the measure of myocardial uptake, however the methods used to obtain this parameter showed considerable variation. Subsequently, there is a need for standardization of this imaging technique to improve its usefulness as a prognostic tool in heart failure patients.



**Figure 4.** The mediastinal region of interest (ROI) and the manually drawn cardiac ROI on a planar  $^{123}\text{I}$ -MIBG image. In patients with severe heart failure the cardiac uptake of  $^{123}\text{I}$ -MIBG can be very low, making it harder to define the accurate location of the cardiac ROI.



**Figure 5.** Kaplan-Meier curve showing the cumulative event rate of the composite end-point all-cause mortality, arrhythmic event and heart failure progression in patients with high and low Heart-to-Mediastinum ratio (H/M). Patients with a low H/M ratio had significantly more adverse events during 2 years of follow-up. Reprinted with permission from Jacobsen et al.<sup>25</sup>

## OBJECTIVE AND OUTLINE OF THE THESIS

In current cardiology practice different cardiac imaging techniques are used to detect the presence of coronary artery disease, evaluate the cardiac performance in post-STEMI patients and guide therapeutic decision making in patients with heart failure. Yet, due to the vast array of choices, it is challenging for the cardiologists to take full advantage of the different cardiac imaging modalities. Therefore, the aim of this thesis was to use all information provided by the different imaging techniques and improve the clinical usefulness of cardiac imaging in different patient categories encountered in daily cardiology practice, with the purpose of improving risk estimation in patients with suspected coronary artery disease, patients who suffered from STEMI and heart failure patients.

In **Part I** of this thesis the prognostic importance of coronary artery anatomy in patients with suspected and known coronary artery disease is investigated. More specifically, **chapter 2** shows that the evaluation of coronary arterial dominance on CTCA, next to the assessment of the presence, severity and extent of coronary artery disease, can enhance risk stratification of patients with suspected coronary artery disease. **Chapter 3** describes the influence of coronary arterial dominance on short-and long-term outcome in post-STEMI patients, recognizing the presence of a left dominant system as one of the risk factors for future adverse events in patients after STEMI. In **chapter 4** the relation between coronary arterial dominance and echocardiographically assessed left ventricular ejection fraction in post-STEMI patients is evaluated. **Chapter 5** shows the usefulness of CTCA for the evaluation of coronary anatomy in adult patients late after arterial switch operation for the correction of the transposition of the great arteries. Moreover, it describes the relation between the observed variations in coronary anatomy, the presence of potential harmful abnormal coronary findings and the development of neo-aortic root dilation in these patients.

In **part II** of this thesis the clinical usefulness of cardiac  $^{123}\text{I}$ -MIBG imaging for the evaluation of sympathetic innervation of the myocardium in patients with chronic heart failure is investigated. In **chapter 6** the reproducibility of the clinically important parameters on planar  $^{123}\text{I}$ -MIBG myocardial scintigraphy is assessed, with the purpose of improving standardization of the method and therewith increase its usefulness in the clinical management and prognostication of patients with chronic heart failure.

## REFERENCES

- 1) World Health Organization. Cardiovascular diseases, fact sheet N°317.
- 2) Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013;128(16):1810-52.
- 3) Deanfield J, Thaulow E, Warnes C, Webb G, Kolbel F, Hoffman A, Sorenson K, Kaemmer H, Thilen U, Bink-Boelkens M, Iserin L, Daliento L, Silove E, Redington A, Vouhe P, Priori S, Alonso MA, Blanc JJ, Budaj A, Cowie M, Deckers J, Fernandez Burgos E, Lekakis J, Lindahl B, Mazzotta G, Morais J, Oto A, Smiseth O, Trappe HJ, Klein W, Blömstrom-Lundqvist C, de Backer G, Hradec J, Mazzotta G, Parkhomenko A, Presbitero P, Torbicki A; Task Force on the Management of Grown Up Congenital Heart Disease, European Society of Cardiology; ESC Committee for Practice Guidelines. Management of grown up congenital heart disease. *Eur Heart J* 2003;24(11):1035-84.
- 4) Gaemperli O, Marsan NA, Delgado V, Bax JJ. The year in cardiology 2014: imaging. *Eur Heart J* 2015;36(4):206-213.
- 5) Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, Paul N, Clouse ME, Shapiro EP, Hoe J, Lardo AC, Bush DE, de Roos A, Cox C, Brinker J, Lima JA. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med* 2008;359(22):2324-36.
- 6) Pundziute G, Schuijf JD, Jukema JW, Boersma E, de Roos A, van der Wall EE, Bax JJ. Prognostic value of multislice computed tomography coronary angiography in patients with known or suspected coronary artery disease. *J Am Coll Cardiol* 2007;49(1):62-70.
- 7) Leaman DM, Brower RW, Meester GT, Serruys P, van den Brand M. Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. *Circulation* 1981;63:285-299.
- 8) Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003;361(9351):13-20.
- 9) Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, Murabito JM, Vasan RS. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med* 2002;347(18):1397-402.
- 10) Cademartiri F, La GL, Malago R, Alberghina F, Meijboom WB, Pugliese F, Maffei E, Palumbo AA, Aldrovandi A, Fusaro M, Brambilla V, Coruzzi P, Midiri M, Mollet NR, Krestin GP. Prevalence of anatomical variants and coronary anomalies in 543 consecutive patients studied with 64-slice CT coronary angiography. *Eur Radiol* 2008;18:781-791.
- 11) Angelini P, Velasco JA, Flamm S. Coronary anomalies: incidence, pathophysiology, and clinical relevance. *Circulation* 2002;105:2449-2454.
- 12) Ilia R, Rosenshtein G, Weinstein J, Cafri C, Abu-Ful A, Gueron M. Left anterior descending artery length in left and right coronary artery dominance. *Coron Artery Dis* 2001;12:77-78.

- 13) Iliá R, Carmel S, Cafri C, Gueron M. Coronary collaterals in patients with normal and impaired left ventricular systolic function. *Int J Cardiol* 1998;63:151–153.
- 14) Knaapen M, Koch AH, Koch C, Koch KT, Li X, van Rooij PC, Tijssen JG, Peters RJ, van der Wal AC, Damman P, de Winter RJ. Prevalence of left and balanced coronary arterial dominance decreases with increasing age of patients at autopsy. A postmortem coronary angiograms study. *Cardiovasc Pathol* 2013;22:49–53.
- 15) Goldberg A, Southern DA, Galbraith PD, Traboulsi M, Knudtson ML, Ghali WA. Coronary dominance and prognosis of patients with acute coronary syndrome. *Am Heart J* 2007;154:1116–1122.
- 16) Iliá R, Cafri C, Weinstein JM, Gueron M. Acute myocardial infarction due to occlusion of the dominant left circumflex artery proximally. *Am J Cardiol* 2003;92:54–55.
- 17) Angelini P, Velasco JA, Flamm S. Coronary anomalies: incidence, pathophysiology, and clinical relevance. *Circulation* 2002;105(20):2449–54.
- 18) Koifman B, Egdell R, Somerville J. Prevalence of asymptomatic coronary arterial abnormalities detected by angiography in grown-up patients with congenital heart disease. *Cardiol Young* 2001;11(6):614–8.
- 19) Humes RA, Driscoll DJ, Danielson GK, Puga FJ. Tetralogy of Fallot with anomalous origin of left anterior descending coronary artery. Surgical options. *J Thorac Cardiovasc Surg* 1987;94(5):784–7.
- 20) Mayer JE, Jr., Sanders SP, Jonas RA, Castaneda AR, Wernovsky G. Coronary artery pattern and outcome of arterial switch operation for transposition of the great arteries. *Circulation* 1990;82(5 Suppl):IV139–IV145.
- 21) Losay J, Touchot A, Serraf A, et al. Late outcome after arterial switch operation for transposition of the great arteries. *Circulation* 2001;104(12 Suppl 1):1121–6.
- 22) Kondo C, Nakazawa M, Momma K, Kusakabe K. Sympathetic denervation and reinnervation after arterial switch operation for complete transposition. *Circulation* 1998;97: 2414–9.
- 23) Carrió I. Cardiac neurotransmission imaging. *J Nucl Med* 2001;42:1062–76.
- 24) Caldwell JH, Link JM, Levy WC, Poole JE, Stratton JR. Evidence for pre- to postsynaptic mismatch of the cardiac sympathetic nervous system in ischemic congestive heart failure. *J Nucl Med* 2008;49(2):234–41.
- 25) Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA, et al. Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. Results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. *J Am Coll Cardiol* 2010;55(20):2212–21.
- 26) Agostini D, Carrió I, Verberne HJ. How to use myocardial 123I-MIBG scintigraphy in chronic heart failure. *Eur J Nucl Med Mol Imaging* 2009;36(4):555–9.



