VILNIUS UNIVERSITY

Donatas Vajauskas

CARDIAC ADRENERGIC INNERVATION IMAGING FOR PREDICTION HEART FAILURE

Summary of doctoral dissertation

Biomedical science, Medicine (07 B)

Vilnius, 2014

Doctoral thesis was performed at Vilnius University in 2010–2014

Scientific supervisor: Prof. Ph.D. Algirdas Edvardas Tamosiunas (Vilnius University, biomedical sciences, medicine – 07 B)

Doctoral thesis will be defended at the Scientific Council of Medical Sciences of Vilnius University:
Chairman:

Prof. Dr. Habil. PhD. Aleksandras Laucevičius

Members:

Prof. PhD. Nomeda Rima Valevičienė
Prof. PhD. Algidas Basevičius
Prof. PhD. Saulius Lukoševičius
Asoc. Prof. PhD. Helle Westergren Hendel

The public defense of doctoral thesis will be held at the open meeting of Scientific Council of Medical Sciences on January 16, 2015, at 2 PM in the conference hall of Vilnius University Hospital Santariškių klinikos.
Address: 2, Santariškių str., Vilnius, LT-08661, Lithuania.

The summary of the doctoral thesis was sent on November , 2014
The doctoral thesis is available in the Library of Vilnius University.
Address: 3, Universiteto str., LT-01122, Vilnius, Lithuania.

ABBREVIATIONS

AF – atrial fibrillation

BNP – brain natriuretic peptide

CRT – cardiac resynchronization therapy

HF – heart failure

H/M – heart to mediastinum ratio

ICD – implantable cardioverter-defibrillator

EF – ejection fraction

LV – left ventricle

LVEDD – left ventricle end diastolic diameter

LVESD – left ventricle end systolic diameter

MIBG – metaiodobenzylguanidine

NA – noradrenaline

OMT – optimal medical therapy

ROC – receiver operating characteristic

SPECT –single photon emission computed tomography

VO_2 max – maximum rate of oxygen consumption as measured during incremental exercise

WR – washout ratio

INTRODUCTION

Relevance of the study

Heart failure (HF) remains large clinical cardiologic problem, as the annual morbidity of HF increases in Lithuania and worldwide. Heart failure is diagnosed in 10 of 1000 patients older than 65 years. Overall prevalence of heart failure in Europe accounts for 2 to 3 percent, and it corresponds to world's population trends. In addition, prevalence of HF increases proportionally to the aging of population. Incidence of heart failure in 70–80 years patients accounts up to 10–20 percent. Despite a wide choice of therapeutic measures – as optimal medical treatment (beta blockers, renin, angiotensin and aldosterone inhibitors), treatment with implantable cardiac devices (biventricular cardiac stimulators), drastically reducing cardiac deaths [1] heart failure has reached epidemic levels, and mortality form the HF remains high (19 percent annually) [2]. For this reason HF prognostic markers, which allow predicting adverse cardiac events, sudden cardiac death, or therapeutic response, are gaining the similar value as the diagnostic methods of HF.

Sudden cardiac death is the dominant cause of mortality in the developed countries and accounts for 300.000–350.000 annual deaths in the USA [3]. It is crucial to identify HF patients with high probability of sudden cardiac death [4]. Dysfunction of autonomic nervous system, which can be evaluated with cardiac metaiodobenzylguanidine (MIBG) imaging, pays important role in the development of ventricular arrhythmia [5, 6]. The overview studies states that ventricular tachyarrhythmia has close relationship with impairment of cardiac adrenergic system [7,8]. However there are little data on cardiac MIBG imaging value predicting ventricular arrhythmias [9]. Reduction of left ventricular ejection fraction (EF) below 35 percent is the most popular marker in prediction of ventricular arrhythmias, however it is not

suitable in recognising patients with sudden cardiac death [10]. Furthermore sudden cardiac death can occur for the patients with relatively normal EF [11].

Left ventricular EF and maximal oxygen consumption (VO_2 max) are functional markers of HF, which can stay longer in a normal range for the heart failure patients [12]. This statement is reflected in registry data, confirming that more than 50 percent of patients admitted to the hospital due to acute HF, had normal or relatively normal left ventricular EF (40–50 percent) [13]. According to a recent registry data, HF can occur at any left ventricular EF. Another biochemical marker of HF is serum brain natriuretic peptide (BNP), however it does not reflect intracellular or regional cardiac denervation.

^{123}Iodine labeled metaiodobenzylguanidine (123I-MIBG) is an analog of norepinephrine, and it is actively transported into noradrenaline granules of myocardial sympathetic nerve terminals [14,15]. 123I-MIBG and norepinephrine shares the same pathways with the norepinephrine – uptake, storage and release mechanisms at sympathetic nerve endings [16]. Increased myocardial sympathetic activity is an indicator of HF, accompanied with heart remodelation, reduction of left ventricular EF and worsening of clinical status [17–19]. Impairment of myocardial sympathetic nerve activity has big influence in development of ventricular arrhythmias and sudden cardiac death [5,20].

Noninvasive evaluation of activity of cardiac sympathetic innervation is possible using MIBG [21]. Cardiac 123I-MIBG imaging allows direct assessment of global cardiac sympathetic innervation, norepinephrine uptake and release processes from presynaptic nerve endings [22].

Scientific novelty

1. Cardiac adrenergic innervation imaging with 123I-MIBG, evaluation of global and regional cardiac adrenergic innervation on a basis of conducted and described study in Vilnius University Hospital Santariskiu klinikos first applied in Lithuania. Cardiac adrenergic innervation imaging with 123I-MIBG in neighboring countries has not been performed yet.

2. Published single centers studies, includes small patient samples, and are conducted using not optimal for ^{123}Iodine, low energy, high resolution collimators, which are convenient for most nuclear medicine centers. We could not find published studies, where for calculation of prognostic cardiac adrenergic innervation markers, medium energy collimators were used.

3. Most studies published in a world medicine literature studies report on HF markers reflecting global cardiac adrenergic innervation. There are not many studies which evaluate prognostic value of regional cardiac adrenergic innervation, acquired using single photon emission computed tomography (SPECT). Furthermore, no studies were done using ^{123}Iodine optimal medium energy collimators.

4. To our knowledge, there are no reports on prognostic value of integral planar and SPECT cardiac adrenergic innervation imaging with 123I-MIBG, as well as prediction of postherapeutic adverse cardiac events and clinical outcome.

5. Results of this study help us to assess prognostic value of global and regional cardiac adrenergic innervation markers:

- Predicting probability of adverse cardiac events and sudden cardiac death;
- Predicting clinical outcome after applied therapeutic measure;

6. These results are relevant for daily clinical practice assessing severity of HF in cellular level. This knowledge could allow earlier selection of more aggressive HF treatment measures expecting improved clinical course of HF and better disease control.

The aim of the study

Explore prognostic value of cardiac adrenergic innervation 123I-MIBG imaging predicting risk of adverse cardiac events, cardiac death and predicting clinical outcome after applied therapeutic measure.

Objectives

1. To determine global and regional indexes of 123I-MIBG uptake and release from cardiac sympathetic nerve terminals for HF patients, predicting adverse cardiac events and sudden cardiac death.
2. To determine global and regional indexes of 123I-MIBG uptake and release from cardiac sympathetic nerve terminals for HF patients, predicting outcome of applied therapeutic measure.
3. To determine relationship of conventional clinical HF markers – cardiovascular ultrasound parameters (left ventricle ejection fraction, measurement of functional capacity – VO_2 max), biochemical blood markers – BNP, and changes in cardiac adrenergic innervation system.

Principal statements for defense

1. A global and regional cardiac adrenergic innervation 123I-MIBG imaging markers for the HF patients predicts adverse cardiac events and cardiac death.
2. A global and regional cardiac adrenergic innervation 123I-MIBG imaging markers for the HF patients predicts clinical outcome of the applied therapeutic measure.
3. A global and regional cardiac adrenergic innervation 123I-MIBG imaging markers correlate with conventional clinical HF markers.

MATERIALS AND METHODS

Described study – cardiac adrenergic innervation 123I-MIBG imaging with cardiac planar and SPECT imaging is a prospective study, for the prediction of heart failure course and prediction of outcome after therapeutic measure. Evaluation of prognostic value of cardiac adrenergic innervation 123I-MIBG imaging was accomplished defining global and regional cardiac adrenergic innervation markers were analyzed: early and late heart to mediastinum (H/M) ratio, washout ratio (WR), early and late denervation score, denervation score difference, early and late denervation extent (percent of left ventricle), and denervation extent difference. Evaluation of clinical HF course was based on – BNP, functional cardiac markers – left ventricle EF, left ventricle end diastolic diameter (LVEDD), left ventricle end systolic diameter (LVESD), VO_2 max and their changes during observation, and changes of NYHA functional class.

This study corresponds to principles of the declaration of Helsinki (www.wma.net/e/policy/pdf/17c.pdf). For this biomedical study authorization was received form Lithuanian Bioethics Committee No. 158200-06-342-83.

Patients

The study involved Vilnius University Hospital patients who met inclusion criteria. Cardiac 123I-MIBG imaging was performed and clinical data was collected in Radiology and Nuclear Medicine Center starting from October 2010 till May 2014. Cardiac adrenergic innervation 123I-MIBG imaging was performed for 116 patients: 92 heart failure patients, and 24 control group patients.

Inclusion criteria:

1. II–IV NYHA functional class heart failure patients.

2. Patients in a stable heart failure state at the time of cardiac adrenergic innervation.

3. Patients with impaired systolic function (left ventricle EF < 45 %) and (or) impaired diastolic function, and conventional HF treatment algorithm is intended to apply.

4. Patient is capable to prepare for the investigation and is able to lay steady in gamma camera for 40 min.

5. The written consent to participate in this study was obtained.

Exclusion criteria:

1. Patients after heart transplantation.

2. At the time of investigation patient is diagnosed with decompensated or unstable HF.

3. Known Lewy body dementia.

4. Patient refused to participate in the study and did not sign written consent.

5. Allergy to radiopharmaceutical.

Patients of the control group

Patients for whom under clinical indications whole body 123I-MIBG imaging was performed in Vilnius University Hospital for detection of suspected pheochromocitoma.

Inclusion criteria

1. The written consent to participate in this study was obtained

2. Patients without cardiac diseases and a history of cardiovascular complaints.

3. After whole body 123I-MIBG imaging the suspicion of pheochromocitoma was denied.

Exclusion criteria

1. Patient refused to participate in the study and did not sign written consent.
2. Patient has cardiac disease.
3. Known Lewy body dementia.
4. After whole body 123I-MIBG imaging the diagnosis of pheochromocitoma was confirmed.

Patient preparation

Before the procedure the patient was instructed about the investigation, its duration, and the means to be used. Blockage of the thyroid was performed for protection from free 123 Iodine in 123I-MIBG solution. Thyroid blockage was performed according to EANM guidelines – with the potassium perchlorate (500mg), or with Lugol's solution (130 mg of iodine equivalent) for the patients without allergy to iodine.

Injection of radiopharmaceutical

123I-MIBG solution through intravenous catheter with slow injection (1-2 min.) was injected in to the peripheral vein. The average 123I-MIBG activity for the patient was 225 ± 17 MBq.

Imaging acquisition

Early images were acquired 15 min. after 123I-MIBG injection. First anterior planar images of the chest was acquired, with the patient lying on a back, afterwards SPECT of the chest was acquired. Delayed planar images of the chest and SPECT of the chest were acquired 4 hours after 123I-MIBG injection.

Anterior planar images of the chest were acquired for the 10 min., patient lying on the back. Image matrix of 256x256 was used.

SPECT of the chest was acquired immediately after the planar scan. Detectors of the gamma camera were set to “L” configuration (90° angle). Rotation of gamma camera detectors started at 45° left anterior oblique

position, and rotating 180° till 45° left posterior oblique position. Image matrix of 64x64 was set. Total SPECT scanning time was up to 25 min.

Medium energy collimators were chosen because ^{123}iodine emitted minor portion of high energy γ photons.

Attenuation correction with CT was not used.

Reconstruction

Cardiac 123I-MIBG early (15 min. after injection) and late (4 hours after injection) anterior planar images of the chest does not require further reconstruction.

Cardiac 123I-MIBG SPECT images were reconstructed using *Cedars Sinai QPS* reconstruction protocols for further analysis.

Iterative reconstruction algorithm OSEM/MLEM was used for the reconstruction of cardiac SPECT images

Manual reconstruction of three standard cardiac plains (short axis, long horizontal and long vertical axis) of the left ventricle was done.

Reconstructed SPECT images of LV were presented in polar maps for further analysis.

Analysis

Sequential analysis of planar and SPECT cardiac adrenergic innervation scintigraphic images, is essential for proper interpretation:

1. Analysis of nonreconstructed images, evaluating quality of the images, size of LV, uptake of 123I-MIBG in adjacent organs (liver, lungs).
2. Calculation of heart to mediastinum (H/M) ratio in anterior planar images.
3. Semiquantitative analysis of cardiac SPECT images from LV three standard planes and polar maps images.

Quantification of H/M and wash out ratio (WR) from anterior cardiac 123I-MIBG images was done using formulas: H/M average uptake ratio (Equation 1).

Equation 1. H/M quantification:

$$H/M = \frac{H}{M}$$

(H/M – heart and mediastinum count ratio, H – cardiac counts, M – mediastinum counts)

H/M ratio was calculated on early and late planar images.

Region of interest of the left ventricle is drawn on anterior planar chest images (H) and upper mediastinum center line 7x7 pixel region of interest is drawn (M) for the calculation of H/M ratio. Average counts of 123I-MIBG uptake in each region were used for the calculation of H/M ratio.

Using early and late H/M ratios, WR was calculated, 123Iodine decay and background uptake was taken in to account (Equation 2).

Equation 2. WR quantification:

$$WR = \frac{(H\ early - M\ early) - ((H\ late - M\ late) \times 1{,}21)}{(H\ early - M\ early)} \times 100$$

(WR – wash out ratio, H – cardiac counts, M – mediastinum counts)

Regional cardiac adrenergic impairment was evaluated using 17 segments LV model. Impairment of adrenergic innervation in segment of LV was assessed according to recommendations of American heart association (AHA) semiquantitatively using 5 point scale: 0 – no impairment of adrenergic innervation, 1 – mild impairment of adrenergic innervation, 2 – moderate impairment of adrenergic innervation, 3 – severe impairment of adrenergic innervation, 4 – absent adrenergic innervation. Early and late

cardiac denervation scores were calculated adding all scores in all 17 segments, respectively for early and late SPECT images. Denervation scores difference is calculated subtracting late denervation score from early denervation score. Early and late denervation scores were converted to percentage of denervated LV, this conversion includes extent of denervated myocardium (in segments) and severity of denervation (scores). The calculation of percentage of denervated LV was made according to equation 3.

Equation 3. Calculation percentage of denervation extent:

$$\text{Denervation extent \%} = \frac{\text{denervation score}}{68} \times 100\%$$

(68 maximal denervation score = 4 scores × 17 segments)

Clinical investigation

Clinical course of HF patients was evaluated in the period of 2 weeks, at the time of cardiac 123I-MIBG imaging.

Serum BNP concentration was evaluated at the time of cardiac 123I-MIBG imaging and 6 months later. Repetitive measures were done depending on clinical demand. According to serum BNP levels patients were divided into the following groups: less than 100 pg/ml, 101–300 pg/ml, 301–600 pg/ml, 301–600 pg/ml, 601–900 pg/ml and more than 900 pg/ml.

Echocardiogpraphy was done to evaluate left ventricle EF and LVEDD. According to left ventricle EF patients for subsequent analysis of the variables were divided in to two groups: left ventricle EF ≥ 40% and < 40%. Cardiopulmonary exercise test was performed and defining VO2 max. All above mentioned tests were repeated 6 months later, and repetitive tests were done depending on clinical demand.

Heart failure functional class according to NYHA was set at the time of cardiac 123I-MIBG imaging, and 6 months later.

Additional cardiac tests for control group patients were not performed. Clinical course was observed from the records of electronic health records system.

Statistical analysis

Statistical analysis was performed using SPSS 17 software (*version for Windows*). Descriptive statistics was presented as mean ± standard deviation (SD) and discrete data was presented as numbers (N) and percentage (%). Analyzed data had normal distribution. Averages of quantitative variables of two independent groups were compared using Student t test, comparison of the three groups - one factor analysis of variance ANOVA and LSD post hoc test.

Comparison of discrete (qualitative) variables was accomplished using Chi-square independence ($\chi 2$) test.

Relationship of cardiac adrenergic innervation markers and clinical cardiovascular tests markers was evaluated using Pearson's correlation coefficient.

P value less than 0.05 was considered statistically significant.

ROC (*Receiver Operating Characteristic)* curve analysis under optimal sensitivity and specificity of the relationship, was determined the critical values of different parameters in predicting whether a patient will have cardiac events.

Adverse cardiac events and cardiac death curves were based on Kaplan-Meier method, and groups being compared by log-rank test.

RESULTS

MIBG imaging data comparison of heart failure and control group patients

Characteristics of HF patient's global and regional cardiac adrenergic innervation data and clinical cardiovascular tests data presented in table 1.

Table 1. HF patient's cardiac adrenergic innervation and clinical cardiologic tests data

Variable	Average	Standard deviation
Early H/M ratio	2,28	0,44
Late H/M ratio	2,04	0,48
WR ratio	42,49	20,49
Early denervation extent (%)	19,68	14
Late denervation extent (%)	33,48	16,48
Denervation extent difference	9,52	9,68
Early denervation score	15,38	11,46
Late denervation score	26,75	13,25
Denervation extent difference	7,84	8,63
Patients age	60,2	12,1
NYHA functional class		
II	9 (10,3 %)	
III	65 (74,7 %)	
IV	13 (14,9 %)	
BNP (pg/ml)	489,66	598,09
LVEDD (mm)	6,53	0,94
EF (%)	30,2	8,0
QRS duration (ms)	156,8	39,0
VO_2 max (kg/cm/bm)	17,44	4,49
VO_2 max (%)	60,15	15,98

(H/M – heart to mediastinum ratio, WR – washout ratio, BNP – brain natriuretic peptide, LVEDD – left ventricle end diastolic diameter, EF – ejection fraction; VO_2 max – maximum rate of oxygen consumption)

Totally 11 (12,6%) patients died at the time of study. 57 (65,5%) patients were hospitalized for adverse cardiac events. Throughout the study there were 80 cardiac events, for which patients were hospitalized for stabilization of heart failure clinical course and optimization of the treatment.

Control group (without cardiac pathology) patients global cardiac adrenergic innervation data is presented in table 2.

Table 2. Control group patient's cardiac adrenergic innervation data

Variable	Average	Standard deviation
Early H/M ratio	3,00	0,72
Late H/M ratio	2,97	0,38
WR ratio	14,08	11,59

(H/M – heart to mediastinum ratio, WR – washout ratio)

Global adrenergic innervation data for all three variables (early and late H/M ratios, WR ratios) showed statistically significant differences between control group and HF group ($p < 0,001$).

During whole observation time, there were no cardiac events and no patient died in control group.

Global cardiac adrenergic innervation differences were assessed to define the causes of unsuccessful attemps to reconstruct and (or) evaluate cardiac 123I-MIBG SPECT data for HF patients. Analysis is presented in table 3.

Table 3. Cardiac adrenergic innervation imaging with 123I-MIBG, global adrenergic innervation data for the patients with quantified SPECT data and for the patients without quantified SPECT data

Variable	SPECT data was quantified		SPECT data was not quantified		p
	Average	Standard deviation	Average	Standard deviation	
Early H/M ratio	2,38	0,39	2,04	0,46	0,001
Late H/M ratio	2,21	0,42	1,67	0,38	< 0,001
WR ratio	36,37	13,55	56,08	26,32	< 0,001

(H/M – heart to mediastinum ratio, WR – washout ratio)

ROC curves of global adrenergic innervation rate, presented cutoff values of early H/M ratio 2,10 and late H/M 1,85 (p 0,001 and < 0,001 respectively), which help to predict the ability to reconstruct and (or) to evaluate the 123I-MIBG SPECT images. WR cutoff value 42,7 ($p < 0,001$) presents the threshold when WR value is higher the ability of reconstruction and (or) evaluation the SPECT images will no longer probable.

Prognostic value of cardiac adrenergic innervation imaging for adverse cardiac events and cardiac death

ROC curves of global and regional cardiac adrenergic innervation data were used, in order to find out cardiac adrenergic innervation 123I-MIBG imaging data cutoff value for prediction of cardiac events generally and separately adverse cardiac events and cardiac death. Statistically significant results were obtained for global adrenergic innervation early H/M ratio (figure 1), late H/M ratio (figure 2), and WR (figure 3). Area under the curve, cutoff value, sensitivity, and specificity are presented in table 4.

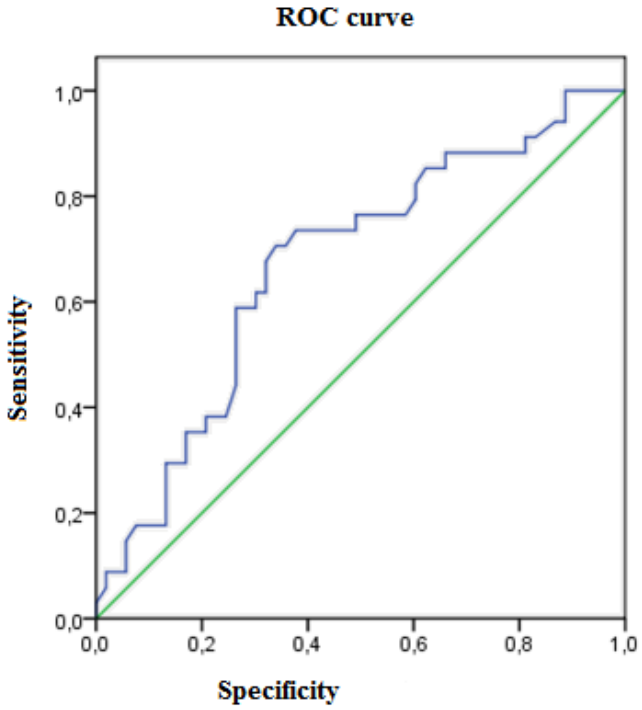

Figure 1. ROC curve of early H/M ratio predicting cardiac events generally

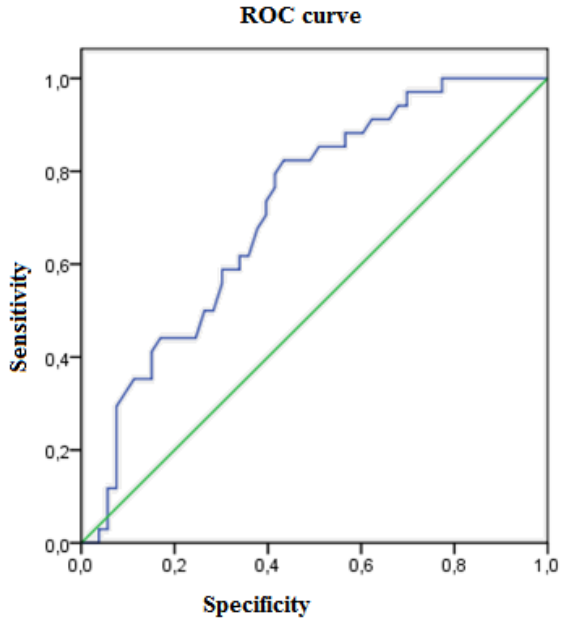

Figure 2. ROC curve of late H/M ratio predicting cardiac events generally

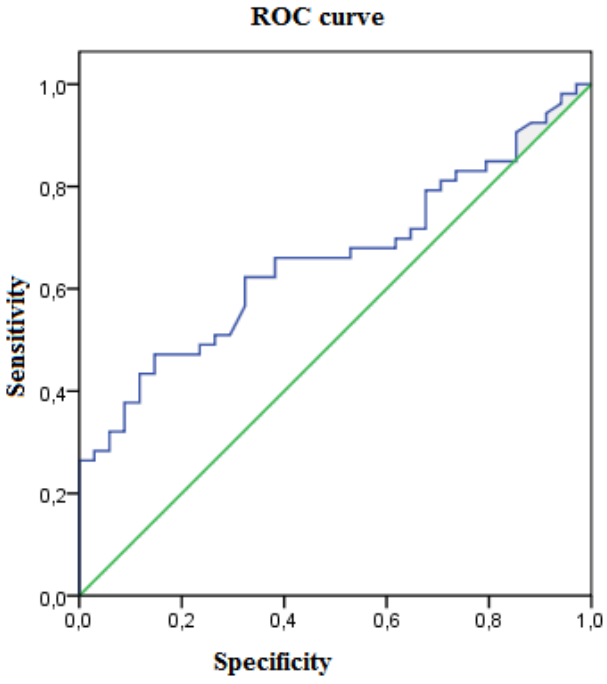

Figure 3. ROC curve of WR predicting cardiac events generally

Table 4. ROC analysis data of early and late H/M ratios and WR

Variable	Threshold	Are under the curve (95 % CI)	p	Sensitivity	Specificity
Early H/M ratio	2,26	0,672 (0,556;0,788)	0,007	0,706	0,340
Late H/M ratio	1,95	0,717 (0,610;0,823)	0,001	0,735	0,396

WR	40,55	0,658 (0,545;0,771)	0,013	0,623	0,324

ROC curves of regional cardiac adrenergic innervation data, presented statistically significant cutoff value of late denervation extent (figure 4) and late denervation score (figure 5) for prediction of cardiac events generally. Area under the curve, cutoff value, sensitivity, and specificity are presented in table 5.

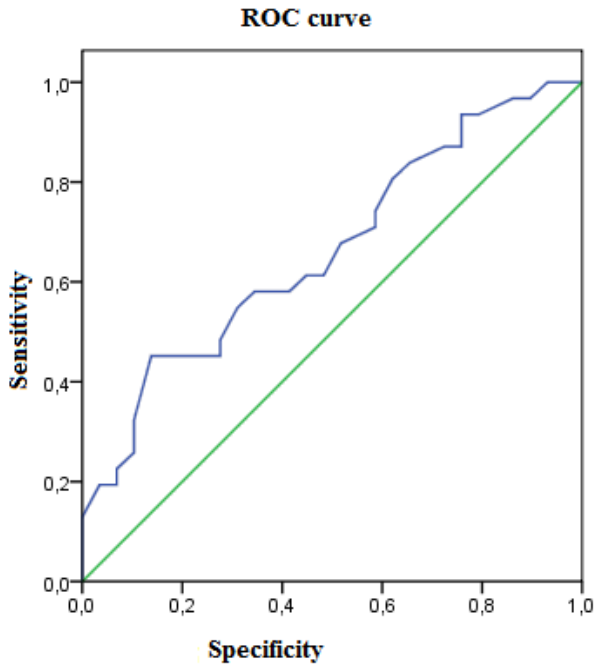

Figure 4. ROC curve of late denervation extent predicting cardiac events generally

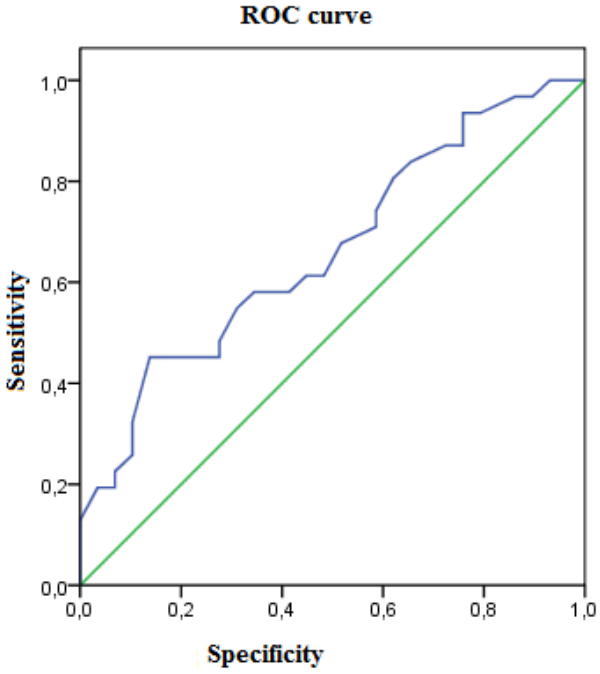

Figure 5. ROC curve of late denervation score predicting cardiac events generally

Table 5. ROC analysis data of late denervation extent and denervation score

Variable	Threshold	Are under the curve (95 % CI)	p	Sensitivity	Specificity
Late denervation extent %	33,5	0,664 (0,527; 0,800)	0,03	0,613	0,448
Late denervation score	26,5	0,664 (0,527; 0,800)	0,03	0,613	0,448

(CI – confidence interval)

We could not find statistically significant cutoff value for the rest of regional cardiac adrenergic innervation data, predicting cardiac events.

Prognostic value assessment of cardiac adrenergic innervation 123I-MIBG imaging data was made with Kaplan-Meier method. Kaplan-Meier curves for all events (adverse cardiac events and cardiac death) for global adrenergic innervation early H/M ratio are presented in figure 6.

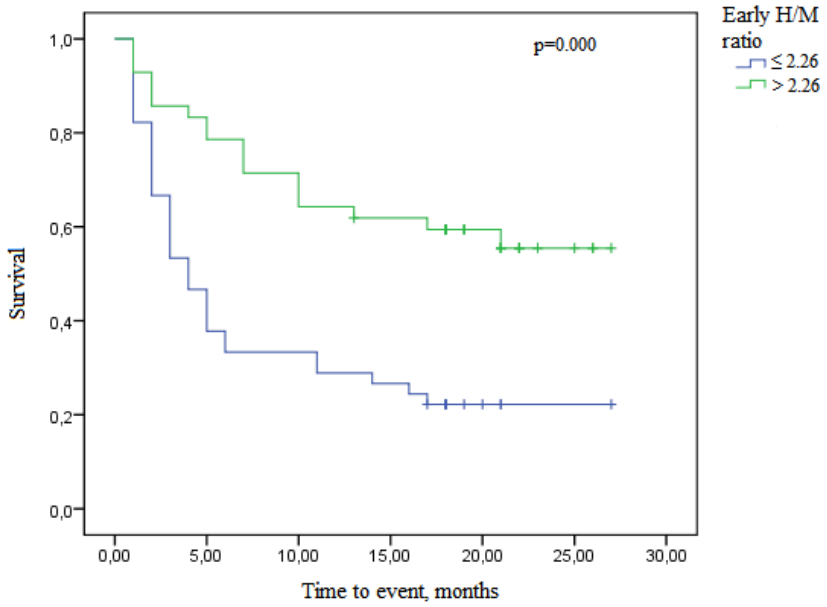

Figure 6 . Kaplan-Meier curve for all events in patients group when early H/M ratio > 2,26 and ≤ 2,26. + last data of the patient, till this time no events occurred

(H/M – heart to mediastinum ratio)

Kaplan-Meier curves for all events (adverse cardiac events and cardiac death) for global adrenergic innervation late H/M ratio are presented in figure 7.

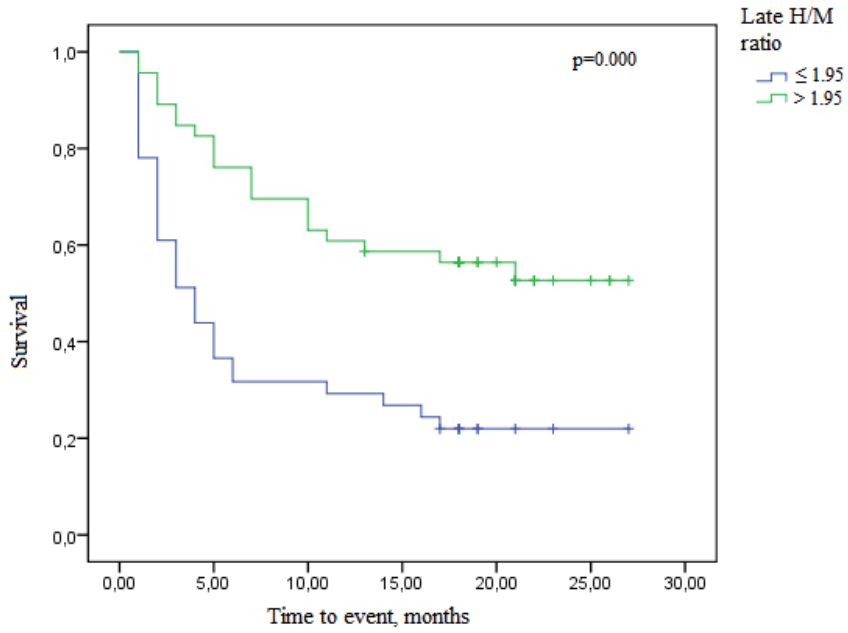

Figure 7. Kaplan-Meier curve for all events in patients group when late H/M ratio > 1,95 and ≤ 1,95. + last data of the patient, till this time no events occurred

(H/M – heart to mediastinum ratio)

Kaplan-Meier curves for adverse cardiac events for global adrenergic innervation early and late H/M ratio are presented in figure 8 and figure 9.

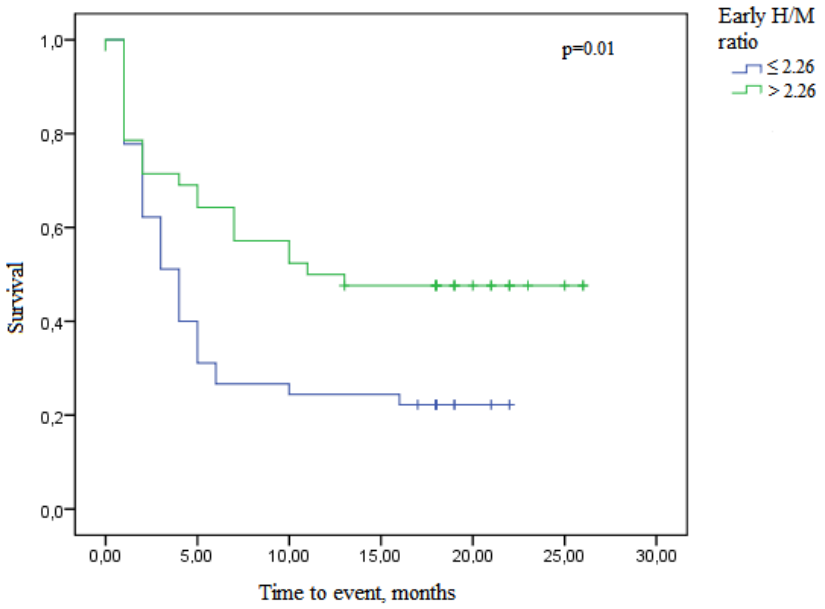

Figure 8. Kaplan-Meier curve for adverse cardiac events in patients group when early H/M ratio > 2,26 and ≤ 2,26. + last data of the patient, till this time no adverse cardiac events occurred

(H/M – heart to mediastinum ratio)

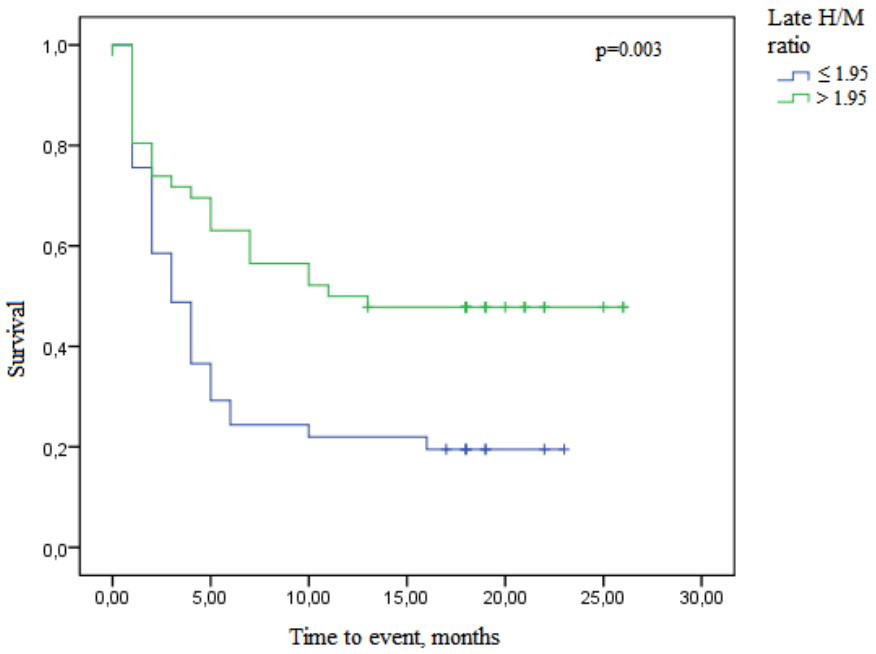

Figure 9. Kaplan-Meier curve for adverse cardiac events in patients group when late H/M ratio > 1,95 and ≤ 1,95. + last data of the patient, till this time no adverse cardiac events occurred

(H/M – heart to mediastinum ratio)

Kaplan-Meier curves for cardiac death for global adrenergic innervation early H/M ratio are presented in figure 10.

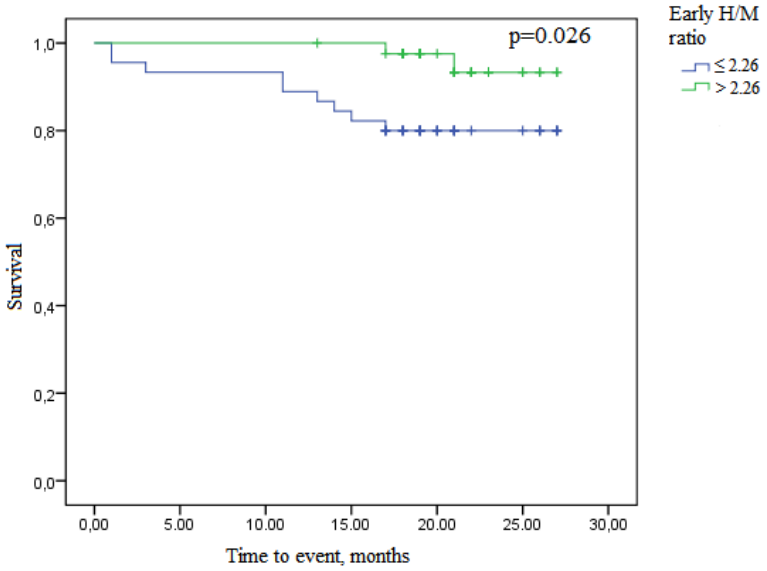

Figure 10. Kaplan-Meier curve for cardiac death in patients group when early H/M ratio > 2,26 and ≤ 2,26. + last data of the patient, till this time no cardiac death occurred

(H/M – heart to mediastinum ratio)

Predicting cardiac death using late H/M ratio in patient groups > 1,95 and ≤ 1,95, was not statistically significant.

Kaplan-Meier curves for adverse cardiac events for global adrenergic innervation WR are presented in figure 11.

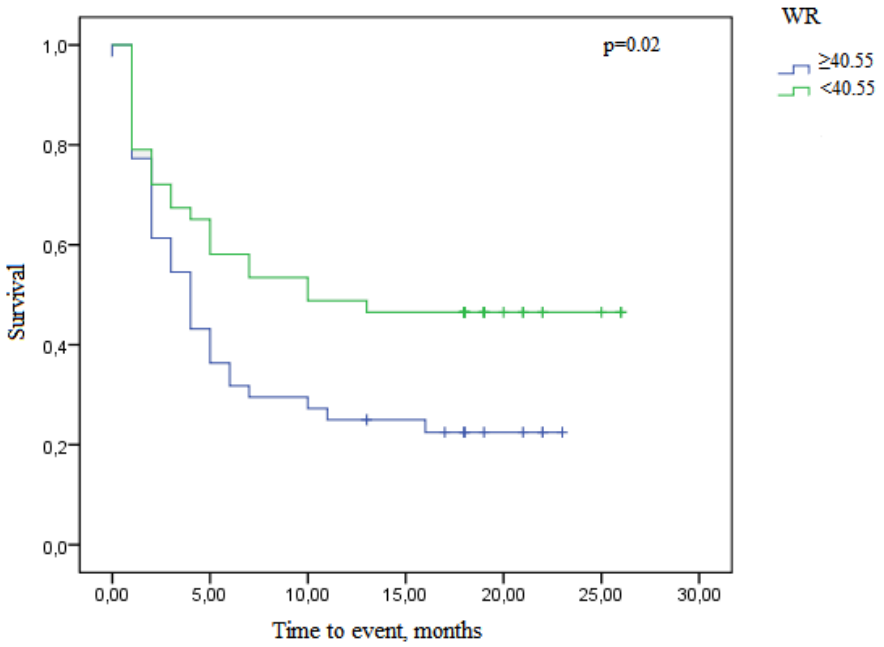

Figure 11. Kaplan-Meier curve for adverse cardiac events in patients group when WR < 40,55 and ≥ 40,55. + last data of the patient, till this time no adverse cardiac events occurred

(WR – washout ratio)

Prognostic value of cardiac adrenergic innervation imaging for therapeutic effect

The main characteristics of clinical cardiovascular and cardiac adrenergic innervation markers are presented in table 6. Patients depending on prospective application of therapeutic measures were divided in to: CRT

(cardiac resynchronization therapy) group (implanting biventricular cardio stimulator) and OMT (optimal medical therapy) group assigning patient to most effective medical therapy according to recent cardiovascular guidelines. CRT group patients considering NYHA functional class, left ventricle EF, few patients with sinus rhythm, clinical status of patients were considered more severe, and this fact confirmed the suitability of clinical decision to apply the CRT therapy. Despite above mentioned differences in the clinical patient groups, cardiac adrenergic innervation 123I-MIBG imaging data differed insignificantly.

Table 6. Main cardiac 123I-MIBG imaging and clinical cardiac test data of the patients assigned to CRT and OMT

Variable	CRT patients (N 36)		OMT patients(N 31)		p
Patient's age (years)	62,2 ± 10,80		57,7 ± 11,15		0,102
Gender					
Male	25	52,1 %	23	47,9 %	0,667
Female	11	57,9 %	8	42,1 %	
NYHA functional class					
II	1	14,3 %	6	85,7 %	0,026
III	29	54,7 %	24	45,3 %	
IV	6	85,7 %	1	14,3 %	
QRS duration (ms)	180,7 ± 38,9		169,0 ± 19,8		0,132
Rhythm					
Sinus	10	35,7 %	18	64,3 %	0,012
AF	26	66,7 %	13	33,3 %	
LVEDD (mm)	6,7 ± 1,1		6,6 ± 0,9		0,595
LVESD (mm)	5,6 ± 1,1		5,3 ± 0,9		0,330
Left ventricle EF (%)	27,3 ± 6,9 %		30,9 ± 7,1 %		0,042
BNP (pg/ml)	713,2 ± 826,4		402,6 ± 439,2		0,069
Early H/M ratio	2,21 ± 0,43		2,32 ± 0,45		0,307
Late H/M ratio	1,95 ± 0,43		2,10 ± 0,55		0,228
WR (%)	43,8 ± 14,5		44,5 ± 28,3		0,898
Early extent (%)	19,76 ± 17,04		19,71 ± 13,00		0,991
Late extent (%)	35,90 ± 19,80		32,25 ± 14,58		0,481
Extent % difference	16,14 ± 10,29		12,54 ± 6,18		0,156
Early denervation score	14,4 ± 11,83		16,00 ± 10,62		0,641
Late denervation score	28,67 ± 16,00		25,75 ± 11,67		0,485
Denervation score difference	14,24 ± 10,86		9,75 ± 4,55		0,071

(CRT – cardiac resynchronization therapy; OMT – optimal medical therapy; AF – atrial fibrillation; LVEDD – left ventricle end diastolic diameter; LVESD – left ventricle end systolic diameter; EF – ejection fraction; BNP – brain natriuretic peptide, H/M – heart to mediastinum ratio, WR – washout ratio)

All NYHA IV functional group patients had larger LVESD, smaller LV EF, larger concentration of BNP in blood, smaller H/M ratio table 7.

Table 7. Differences of cardiac adrenergic innervation imaging and clinical cardiovascular tests data within NYHA functional class

Variable	NYHA functional class			p
	II	III	IV	
LVESD (mm)	5,4 ± 1,1	5,3 ± 0,9	6,4 ± 0,99	0,029 (III and IV)
LV EF (%)	33,0 ± 7,3	29,4 ± 6,9	21,7 ± 4,9	0,007 (II and IV, III and IV)
BNP (pg/ml)	281,8 ± 294,4	509,4 ± 600,2	1294,8 ± 1121,3	0,008 (II and IV, III and IV)
Late H/M ratio	2,38 ± 0,38	2,01 ± 0,50	1,74 ± 0,26	0,046 (II and IV)
Denervation score difference	11,00 ± 6,78	11,11 ± 6,89	28,00 ± 24,04	0,016 (II and IV, III and IV)

(LVESD – left ventricle end systolic diameter; LV EF – left ventricle ejection fraction; BNP – brain natriuretic peptide, H/M – heart to mediastinum ratio)

Cardiac adrenergic innervation 123I-MIBG imaging data differed insignificantly for the patients with atrial fibrillation or sinus rhythm at the time of investigation, for the patients with permanent cardiac stimulation or without it, for the patients with different cause of the HF (dilative cardiomyopathy, ischemic cardiomyopathy, hypertensive/tachiarrhythmic cardiomyopathy, valvular cardiomyopathy).

Responders to therapeutic measure had much larger early H/M ratio than non-responders – respectively 2,35 ± 0,41 and 2,00 ± 0,44 (p = 0,004), larger late H/M ratio – respectively 2,11 ± 0,44 ant 1,72 ± 0,54 (p = 0,005). Responders had significantly lower WR than non-responders – respectively 40,2 ± 13,8 and 56,8 ± 35,2 (p = 0,007). However there was no statistically significant difference of the regional cardiac adrenergic innervation data for the responders and non-responders to therapeutic measure.

Similar results were obtained for sub analysis in the therapeutic measure groups – CRT and OMT. CRT group patients responders had higher early H/M ratio than non-responders – respectively 2,00 ± 0,44 and 1,63 ± 0,16 (p = 0,041). OMT group patients responders had higher early H/M ratio 2,47 ± 0,32

than non-responders 2,02 ± 0,55 (p = 0,006), and higher late H/M ratio – respectively 2,25 ± 0,41 and 1,78 ± 0,67 (p = 0,023). WR for the OMT group patients responders was lower than for the non-responders to therapeutic measure –37,53 ± 14,14 and 59,21 ± 43,46 respectively (p = 0,045).

ROC curves of cardiac adrenergic innervation 123I-MIBG imaging data presents statistically significant cutoff value of early and late H/M ratios (Figure 12 and 13), predicting effect of therapeutic measure (response to therapy and non-response to therapy) table 8.

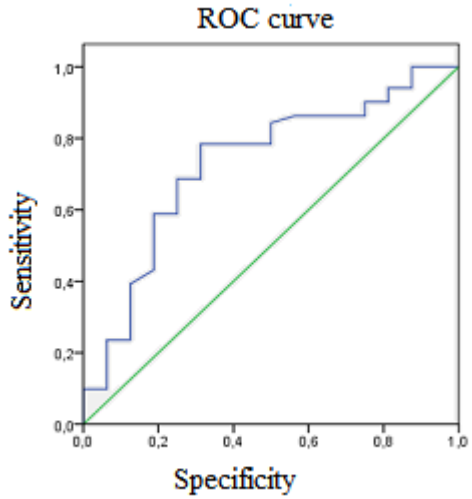

Figure 12. ROC curve of early H/M ratio

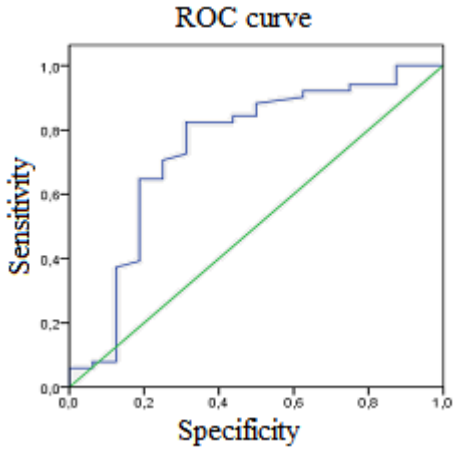

Figure 13. ROC curve of late H/M ratio

Table 8. ROC analysis data of cardiac adrenergic innervation 123I-MIBG imaging early and late H/M ratio

Variable	Cutoff value	Area under the curve (95 % CI)	P	Sensitivity	Specificity
Early H/M ratio	2,00	0,729 (0,583–0,874)	0,006	0,784	0,687
Late H/M ratio	1,77	0,743 (0,586–0,900)	0,004	0,824	0,687

(CI – confidence interval)

CRT group patients – responders and non-responders had significantly different left ventricle EF and QRS duration. Responders had higher left ventricle EF than non-responders –28,53 ± 6,69 and 21,17 ± 4,26 respectively (p = 0,015). Responders had significantly shorter QRS duration, than non-responders –174,47 ± 30,61 and 212,17 ± 60,95 respectively (p = 0,028).

Relation of cardiac adrenergic imaging with clinical heart failure markers

Main characteristic of cardiac adrenergic innervation 123I-MIBG imaging data and clinical cardiovascular tests data are presented in table 1.

Correlation of cardiac adrenergic innervation 123I-MIBG imaging data with clinical cardiovascular tests data was analysed using Pearson's correlation coefficient.

Week negative correlation was found between left ventricle EF and WR -0,3 ($p < 0,01$), early and late denervation score, $r = -0,347$, $r = -0,356$ respectively ($p < 0,01$). These results suggest that there is a relationship between the decreasing left ventricle EF and increasing WR – showing that WR increase responds to global cardiac adrenergic innervation overdrive; increasing of early and late denervation scores – these scores represents severity of regional cardiac adrenergic denervation. Week positive correlation was found between left ventricle EF and late H/M ratio $r = 0,356$ ($p < 0,01$). During the decrease of left ventricle EF there is decrease of late H/M ratio too,

representing global cardiac adrenergic innervation disorder. The lower the value of the late H/M ratio, the higher cardiac adrenergic innervation impairment.

Week positive correlation was found between BNP and late H/M ratio, r = -0,241 ($p < 0,05$) – increasing BNP rates to decreasing late H/M ratio; week positive correlation between BNP and WR, r = 0,246 ($p < 0,05$) – increasing BNP relates to increasing WR; BNP and early denervation score, r = 0,282 ($p < 0,05$) – increasing BNP relates to increasing WR and early denervation score.

Week negative correlation between VO_2 max and early and late denervation scores was found, respectively r = -0,361 ($p < 0,05$) and r = -0,420 ($p < 0,05$) – decreasing VO_2 max increases early and late denervation extent; week negative correlation between VO_2 max and WR r = -0,335 ($p < 0,05$) – decreasing VO_2max increases WR.

Average positive correlation between QRS duration and late denervation score ws found, r = 0,436 ($p < 0,01$) – increasing QRS duration relates to increasing late denervation score; week positive correlation between QRS duration and early denervation score was found, r = 0,349 ($p < 0,01$) – increasing QRS duration relates to increasing early denervation score.

Mean scores of a cardiac 123I-MIBG imaging variables with reference to NYHA functional class were compared using independent samples t-test. Significant difference comparing late H/M ratio variables between II and IV NYHA functional class was found –2,32±0,29 and 1,81±0,45 respectively (p=0,044).

Significant difference comparing WR variables between II and IV NYHA functional class was found –34,33±11,56 and 57,45±29,53 respectively (p=0,01), and between III and IV NYHA functional class –40,63±18,04 and 57,45±29,53 respectively (p=0,01).

Other cardiac adrenergic innervation 123I-MIBG imaging data variables with reference to NYHA functional class differed insignificantly.

Comparing mean scores of cardiac adrenergic innervation 123I-MIBG imaging data variables with reference to left ventricle EF ≥ 40% and < 40%, significant difference was found for late H/M ratios –2,36±0,50 and 1,98±0,45 respectively (p=0,008); WR –30,74±14,02 and 44,55±20,81 respectively (p=0,024); early denervation scores –7,50±8,25 and 16,96±11,42 respectively (p=0,016), and late denervation scores –18,9±9,79 and 28,32±13,37 respectively (p=0,039).

When grouping patients according to BNP concentration in blood, five groups were set: first group < 100 pg/ml, second group 101–300 pg/ml, third group 301–600 pg/ml, fourth group 601–900 pg/ml and fifth group > 900 pg/ml. Significant difference were obtained between late H/M ratios in first and fifth groups, 2,24±0,52 and 1,80±0,39 respectively (p=0,005); second and third group –2,19±0,47 and 1,82±0,43 respectively (p=0,005); second and fifth group –2,19±0,47 and 1,80±0,39 respectively (p=0,005); first and third group –2,24±0,52 and 1,82±0,43 respectively (p=0,005).

WR variables significantly differed in first and third group –35,57±31,00 and 52,41±19,88 respectively (p=0,018); second and third group –35,88±13,38 and 52,41±19,88 respectively (p=0,018); second and fifth group –35,88±13,38 and 50,08±12,08 respectively (p=0,018); first and fifth group –35,57±31,00 and 50,08±12,08 respectively (p = 0,018).

Other cardiac adrenergic innervation 123I-MIBG imaging variables, with reference to BNP concentration in blood differed insignificantly.

Practical recommendation

Considering results of our study, we propose the following suggestions for daily clinical practice, which could assist cardiologist for more accurate assessment of HF patient and referring further treatment.

Prognostic global cardiac 123I-MIBG imaging indicators values established in this study, and set threshold values of early H/M ratio – 2,26, late H/M ratio – 1,95, and WR ratio – 40,55%, in clinical practice could be use as selection criteria, helping to prognosticate the probability of cardiac events for HF patients. This would be relevant for the dividing patients in to low and high cardiac events risk groups before therapeutic strategy.

Decision of ICD treatment for the HF patients with ischemic cardiomyopathy, obtained in this study late H/M ratio threshold value – 1,95 could be combined with myocardial perfusion scintigraphy imaging, summed stress score value – 12 [23]. When late H/M ratio is < 1,95, and myocardial perfusion scintigraphy summed stress score is > 12, probability of cardiac events is very high (94%). For those patients the choise of ICD treatment modality would be defined as appropriate.

Other clinical applicability of our study results is prognostication of treatment modality effectiveness for HF patients with long QRS duration (> 120 ms). Quantified cutoff values of early and late H/M ratio – respectively 2,00 and 1,77, could help to predict effectiveness of planned treatment modality. If early H/M ratio is < 2,00, and late H/M ratio is < 1,77, we could expect that effectiveness of planed therapy measures would not result in positive effect.Specifically for clinical practice we could propose clinical decision algorithm, based on obtained cardiac adrenergic innervation 123I-MIBG imaging prognostic data (Figure 14).

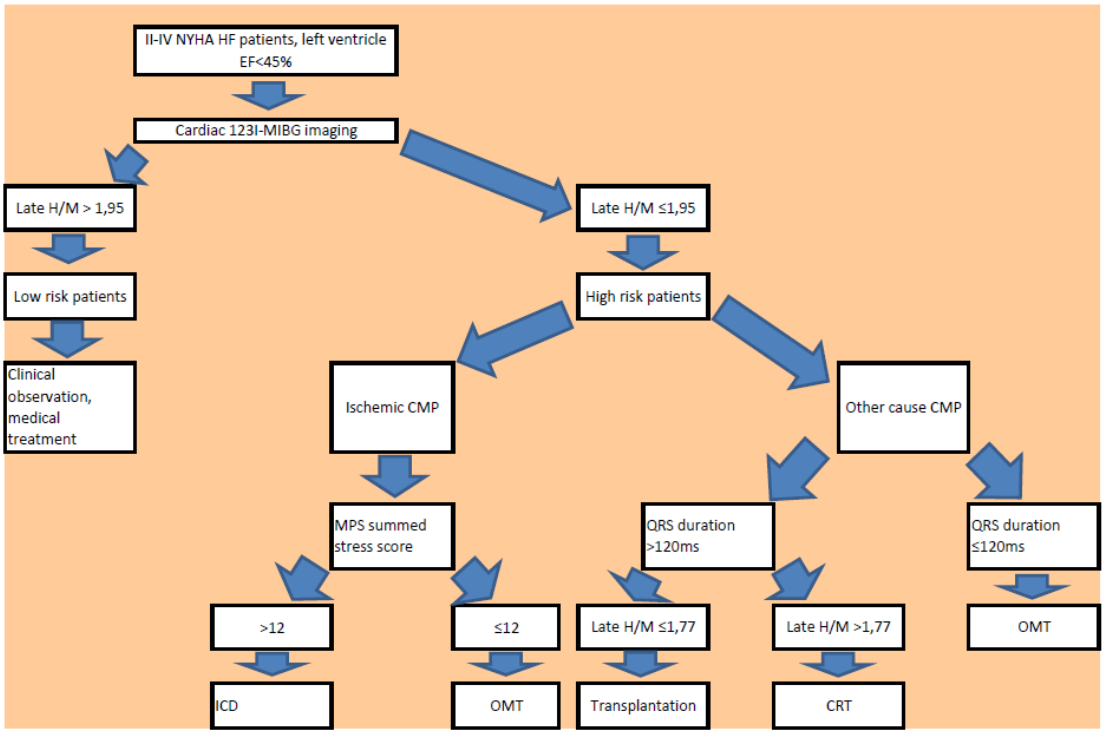

Figure 14. Algorithm of clinical decisions, based on global cardiac adrenergic innervation 123I-MIBG imaging late H/M ratio

(MIBG – metaiodobenzilguanide, H/M – heart to mediastinum ratio, MPS – myocardial perfusion scintigraphy, CMP – cardiomyopathy, ICD – implantable cardioverter-defibrillator, OMT – optimal medical therapy, CRT – cardiac resynchronization therapy)

In addition to cardiac adrenergic innervation 123I-MIBG imaging data, clinical cardiovascular tests, left ventricle EF, QRS duration, could add more precision for selecting patients (with severe impairment of left ventricle EF (approximately < 25%) and long QRS duration (approximately >200 ms)), who already have reached irreversible remodelation and our planned CRT therapeutic measure would not effective. For such patients the only lifesaving option remains cardiac transplantation.

CONCLUSIONS

1. Global cardiac adrenergic innervation 123I-MIBG imaging indicators (early and late H/M ratio, WR) were found to have prognostic value in predicting cardiac events (adverse cardiac events, cardiac death), and could be used in clinical practice assigning patients to the risk groups.
2. Global cardiac adrenergic innervation 123I-MIBG imaging indicators were found to have prognostic value in predicting clinical outcomes for the proposed treatment measure.
3. Based on our study data, regional cardiac adrenergic innervation 123I-MIBG imaging indicators (early and late denervation score, denervation score difference and their derivate indicators) does not have significant prognostic value, predicting cardiac events and prognosticating response to therapeutic measure.
4. Cardiac adrenergic innervation 123I-MIBG imaging data have week correlation with clinical cardiovascular tests data; however have additional value determining severity of HF.

LIST OF PUBLICATIONS

1. **Donatas Vajauskas,** Vytė Valerija Maneikienė, Algirdas Edvardas Tamošiūnas, Kęstutis Ručinskas, Raminta Lukšaitė, Evelina Balčiūnaitė. Correlation of Cardiac 123I-MIBG Imaging with Conventional Markers of the Heart Failure. Seminars in Cardiovascular Medicine 2014; 20:1-4.
2. Vytė Valerija Maneikienė, **Donatas Vajauskas**, Audrius Aidietis, Algirdas Edvardas Tamošiūnas, Kęstutis Ručinskas, Eglė Skiauterytė, Germanas Marinskis. Prognostic value of cardiac iodine-123 metaiodobenzylguanidine imaging in patients with indications for cardiac resynchronization therapy. Lithuanian Academy of Sciences jounal „Acta Medica Lithuanica“, 2014. Vol. 21. No. 2:81-90.

Abstracts and presentations

1. Poster presentation: Donatas Vajauskas, Algirdas Edvardas Tamošiūnas „IAEA-CN-202/ Cardiac adrenergic innervation imaging assessed with SPECT: imaging beyond planar cardiac adrenergic innervation scan“ International conference on integrated medical imaging in cardiovascular diseases (IMIC 2013) Vienna, Austria.
2. Methodic recommendation: Donatas Vajauskas, Algirdas Edvardas Tamošiūnas, Kęstutis Ručinskas, Vytė Valerija Maneikienė „Širdies adrenerginės inervacijos vaizdinimas“, 2012, Vilnius.
3. Presentation: Donatas Vajauskas, Algirdas Edvardas Tamošiūnas „Cardiac adrenergic innervation SPECT imaging” International conference „Evolutionary medicine: new solutions for the old problems“, 2012, Vilnius.
4. Presentation: Donatas Vajauskas, Algirdas Edvardas Tamošiūnas „Cardiac adrenergic innervation imaging: added value of MIBG SPECT imaging” International conference „The 4th Baltic Congress of Radiology“, 2012, Vilnius.

5. Presentation: Donatas Vajauskas, Algirdas Edvardas Tamošiūnas „Cardiac MIBG imaging“ International conference „Baltic nuclear medicine congress“, 2011, Vilnius.

6. Vaišnytė Birutė, Vajauskas Donatas, Palionis Darius, Nevidomskytė Daiva, Misonis Nerijus, Bilkis Valdas, Sučila Marius, Gutauskas Marijus. Complicated Congenital Gluteal Arteriovenous Malformation with Hemorrhage in Pregnancy. Ann Vasc Surg. 2013 May 22.

7. Vaišnytė Birutė, Vajauskas Donatas, Palionis Darius, Misonis Nerijus, Kurminas Marius, Nevidomskytė Daiva, Matačiūnas Mindaugas, Gutauskas Marijus, Laucevičius Aleksandras. Diagnostic methods, treatment modalities, and follow-up of extra cranial arteriovenous malformations. Medicina (Kaunas). 2012; 48(8): 388–98.

8. Instructional book „Branduolinė kardiologija“, Eglė Sadauskienė, Eglė Čiburienė, Mindaugas Matačiūnas, Dontas Vajauskas, 2011, Vilnius.

9. Kaladytė-Lokominienė Rūta, Vajauskas Donatas, Sakalauskaitė-Juodeikienė Eglė. Ioflupane I-123 SPECT in diferential diagnosis of extrapyramidal disorders (Ioflupane I-123 radionuklidinės kompiuterinės tomografijos vaizdinimo taikymo galimybės ekstrapiramidinių sutrikimų ir demencijų diferencinėje diagnostikoje). Neurology seminars 2011; 15(50): 253–60.

LITERATURE

1. 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; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA Guideline for theManagement of Heart Failure: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines. Circulation. 2013; 62: 147–239.

2. Korczyk D, Marwick TH, Kaye G. Fast facts: Heart failure. „Health press limited“, Elizabeth house, Queen street, Abingdon, Oxford, Great Britain 2012.

3. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol 2006; 48: 247–346.

4. Kioka H, Yamada T, Mine T, Morita T, Tsukamoto Y, Tamaki S, Masuda M, Okuda K, Hori M, Fukunami M. Prediction of sudden death in patients with mild-to-moderate chronic heart failure by using mild-to-moderate chronic heart failure by using imaging. Heart 2007; 93: 1213–8.

5. Podrid PJ, Fuchs T, Candinas R. Role of the sympathetic nervous system in the genesis of ventricular arrhythmia. Circulation 1990; 822 Suppl: I103–13.

6. Zipes DP. Sympathetic stimulation and arrhythmias. N Engl J Med 1991; 325: 656–7.

7. Mitrani RD, Klein LS, Miles WM, Hackett FK, Burt RW, Wellman HN, Zipes DP. Regional cardiac sympathetic denervation in patients with ventricular tachycardia in the absence of coronary artery disease. J Am Coll Cardiol 1993; 22: 1344–53.

8. Bax JJ, Kraft O, Buxton AE, Fjeld JG, Parízek P, Agostini D, Knuuti J, Flotats A, Arrighi J, Muxi A, Alibelli MJ, Banerjee G, Jacobson AF. 123-MIBG scintigraphy to predict inducibility of ventricular arrhythmias on cardiac electrophysiologic testing. A prospective multicenter pilot study. Circ Cardiovasc Imaging 2009; 1: 131–40.

9. Boogers MJ, Borleffs CJ, Henneman MM, van Bommel RJ, van Ramshorst J, Boersma E, Dibbets-Schneider P, Stokkel MP, van der Wall EE, Schalij MJ, Bax JJ. Cardiac Sympathetic Denervation Assessed With 123-Iodine Metaiodobenzylguanidine Imaging Predicts Ventricular Arrhythmias in Implantable Cardioverter-Defibrillator Patients. J Am Coll Cardiol. 2010 Jun 15; 55: 2769–77.

10. Goldberger JJ, Cain ME, Hohnloser SH, Kadish AH, Knight BP, Lauer MS, Maron BJ, Page RL, Passman RS, Siscovick D, Stevenson WG, Zipes DP; American Heart Association Council on Clinical Cardiology; American Heart Association Council on Epidemiology and Prevention; American College of Cardiology Foundation; Heart Rhythm Society scientific statement on noninvasive risk stratification techniques for identifying patients at risk for sudden cardiac death: a scientific statement from the American Heart Association Council on Clinical Cardiology Committee on Electrocardiography and Arrhythmias and Council on Epidemiology and Prevention. J Am Coll Cardiol 2008; 52: 1179–99.

11. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death. Structure, function, and time-dependence of risk. Circulation 1992; 851 Suppl: I2–10.

12. Takeishi Y, Sukekawa H, Sakurai T, Saito H, Nishimura S, Shibu T, Sasaki Y, Tomoike H. Noninvasive identification of anthracycline cardiotoxicity:

Comparison of 123I-MIBG and 123I-BMIPP imaging. Ann Nuc Med 1994; 8: 177–82.

13. Koprowski A, Gruchala M, Rynkiewicz A. Management of left ventricular diastolic heart failure: is it only blood pressure control? Current Opinion in Cardiology 2009, 24: 161–6.

14. Wieland DM, Brown LE, Rogers WL, Worthington KC, Wu JL, Clinthorne NH, Otto CA, Swanson DP beierwaltes WH. Myocardial imaging with a radioiodinated norepinephrine storage analog. J Nucl Med 1981; 22: 22–31.

15. Sisson JC, Shapiro B, Meyers L, Mallette S, Mangner TJ, Wieland DM, Glowniak JV, Sherman P, Beierwaltes WH. Metaiodobenzylguanidine to Map Scintigraphically the Adrenergic Nervous System in Man. J Nucl Med 1987; 28: 1620–4.

16. Nakajo M, Shapiro B, Copp J, Kalff V, Gross MD, Sisson JC. Beierwaltes WH. The normal and abnormal distribution of the adrenomedullary imaging agent m-[I-131]iodobenzylguanidine (I-131MIBG) in man: evaluation by scintigraphy. J Nucl Med 1983; 24: 672–82.

17. Brunner-La Rocca HP, Esler MD, Jennings GL, Kay DM. Effect of cardiac nervous activity on mode of death in congestive heart failure. Eur Heart J 2001; 22: 1136–43.

18. Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, Simon AB, Rector T. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984; 311: 819–23.

19. Leimbach WN Jr., Wallin BG, Victor RG, Aylward PE, Sundlof G, Mark AL. Direct evidence from intraneural recordings for increased central sympathetic outflow in patients with heart failure. Circulation 1986; 73: 913–9.

20. Paul M, Schäfers M, Kies P, Acil T, Schäfers K, Breithardt G, Schober O, Wichter T. Impact of sympathetic innervation on recurrent life-threatening arrhythmias in the followup of patients with idiopathic ventricular fibrillation. Eur J Nucl Med Mol Imaging 2006; 33: 866–70.

21. Patel AD, Iskandrian AE. MIBG imaging. J Nucl Cardiol 2002; 9: 75–94.

22. Hein J. Verberne, Lizzy M. Brewster, G. Aernout Somsen, Berthe L.F. van Eck-Smit. Prognostic value of myocardial 123Imetaiodobenzylguanidine (MIBG) parameters in patients with heart failure: a systematic review. European Heart Journal 2008; 29: 1147–59.

23. Estorch M, Flotats A, Serra-Grima R, Mari C, Prat T, Martín JC, Bernà L, Catafau AM, Tembl A, Carrió I. Impairment of cardiac sympathetic innervation and myocardial perfusion is related to lethal arrhythmic events: quantification of cardiac metaiodobenzylguanidine and tetrofosmin activities in patients treated with implantable cardioverter defibrillators. J Nucl Med 2010; 51: 1241–9.