DE GRUYTER OPEN

Seminars in Cardiovascular Medicine, 2014; 20:5–9 e-ISSN 1822-7767

Original paper

Correlation of cardiac 123I-MIBG imaging with conventional markers of the heart failure

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Received 5 May 2014; accepted 1 July 2014

Summary

Objectives: Quantitative values of cardiac iodine-123 metaiodobenzylguanidine (123I-MIBG) global and regional adrenergic innervation showed promising results in predicting clinical course of heart failure. Nevertheless data is lacking how global and regional cardiac 123I-MIBG imaging parameters correlate with patient's clinical data and conventional heart failure markers.

Patients and methods: Eighty-six patients with class II–IV New York Heart Association (NYHA) heart failure were investigated. Patients underwent early and late cardiac 123I-MIBG planar and single photon emission computed tomography (SPECT) scanning. Global and regional cardiac 123I-MIBG scores were calculated and compared to conventional heart failure markers (left ventricular ejection fraction (LVEF), B-type natriuretic peptide (BNP) and maximum rate of oxygen consumption (VO_2 max)), followed by NYHA functional class clinical assessment at the time of investigation.

Results: Weak statistically significant correlation was noted between LVEF and global and regional cardiac adrenergic denervation scores, between BNP and VO_2 max and global cardiac adrenergic denervation scores. Global and regional cardiac adrenergic denervation scores significantly differed within LVEF ranges. Global cardiac adrenergic denervation scores significantly differed within BNP levels and NYHA functional class.

Conclusions: Conventional cardiac heart failure markers had weak correlation with global and regional cardiac 123I-MIBG imaging parameters. Cardiac 123I-MIBG imaging markers differed significantly depending on LVEF and BNP levels, and NYHA functional class.

Seminars in Cardiovascular Medicine 2014; 20:5–9

Keywords: 123I-MIBG, SPECT, heart failure, nuclear cardiology

Objectives

A well-known feature of failing heart to compensate reduced cardiac output is to increase myocardial sympathetic activity. These compensatory mechanisms become injurious in chronic heart failure (HF) and cause myocardial hypertrophy, fibrosis and cardiac remodeling. The increased sympathetic activity at the cellular level causes increased neuronal release of norepinephrine (NE). This leads to a significant reduction in presynaptic NE uptake. Metaiodobenzylguanidine is an analog of the adrenergic neuron-blocking agent guanethidine, and shares the same uptake, storage and release mechanisms as norepinephrine in sympathetic nerve endings [1,2]. Radionuclide imaging with the most frequently used modality for assessment of cardiac sympathetic nervous system activity – 123-iodine labelled NE analogue metaiodobenzylguanidine (123I-MIBG) can non-invasively assess decreased NE uptake. Sympathetic overactivity and parasympathetic withdrawal contribute to the progression of HF and are associated with unfavorable prognosis [3,4]. The main purpose of cardiac 123I-MIBG imaging modality is the HF risk stratification [5–8]. Its prognostic value is shown by global markers of myocardial nerve

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integrity and sympathetic overdrive – early heart to mediastinum (H/M) ratio reflects the myocardial adrenergic nerve integrity, late H/M and washout ratio (WR) reflects the sympathetic overdrive. Recently regional cardiac sympathetic nervous system integrity markers, acquired from 123I-MIBG single photon emission tomography (SPECT), showed superiority for prediction of arrhythmic events compared to the global H/M ratio [9], and HF risk stratification [10,11]. Cardiac 123I-MIBG imaging could also be applied for evaluation of severity of HF, as rapid changes of cardiac 123I-MIBG imaging data could reflect current status of sympathetic activity. Numerous studies compared conventional cardiac heart failure markers with cardiac 123I-MIBG imaging as well as heart failure New York Heart Association (NYHA) functional class with cardiac 123I-MIBG. Some of these studies suggest that cardiac 123I-MIBG imaging correlate with these markers [12,13], other studies suggest that correlation is weak, or there is no correlation at all [14].

We could not find any literature data comparing regional cardiac sympathetic nervous system imaging markers, acquired from 123I-MIBG SPECT, with conventional cardiac heart failure markers. Also there is no data comparing 123I-MIBG planar and SPECT imaging markers within NYHA functional class, and implementing these markers in to the evaluation of the heart failure severity.

The objectives of our study were to compare cardiac 123I-MIBG imaging global and regional nerve integrity and overdrive markers with conventional heart failure markers. The second aim was to check whether 123I-MIBG planar and SPECT data differs significantly between NYHA functional classes. This could be relevant to more precise description of the severity of the heart failure.

Patients and methods

Patients

The patient population consisted of advanced heart failure patients undergoing cardiac 123I-MIBG imaging for heart failure risk stratification. Eighty-six subjects – 20 female and 66 male patients, aged 29 to 78 years (58 ± 12), with NYHA class II–IV heart failure were included. The patients were referred for cardiac 123I-MIBG imaging to assess cardiac sympathetic innervation. Planar early and late cardiac 123I-MIBG scans were performed followed by early and late cardiac 123I-MIBG SPECT.

The investigation conforms to the principles outlined in the Declaration of Helsinki. This study protocol was approved by regional biomedicine investigation ethics committee and informed consent was obtained from each patient.

123I-MIBG imaging

All patients were pretreated with potassium perchlorate 500 mg to block uptake of free 123-iodine by the thyroid gland. Potassium perchlorate was given orally 60–90 minutes before intravenous administration of 123I-MIBG [15]. Each subject received 225 ± 17 MBq of 123I-MIBG.

Planar and SPECT 123I-MIBG scans were performed in a supine position. The 123I-MIBG planar images of the thorax were acquired 15 minutes (early image) and 4 hours (late image) after injection. The acquisition time for planar imaging was set to 10 minutes in the anterior view and stored in a 128×128 matrix. Medium-energy, parallel hole collimator [16], 20 percentage energy peak was centered on the 159-keV energy peak of 123-iodine for planar and for SPECT acquisition.

SPECT images were acquired immediately after planar scans: early planar (15 minutes post injection), and late planar (4 hours post injection) 123I-MIBG scans. Images were acquired with a dual-detector gamma camera with a detector set in a 90° configuration (GE Infinia, Wisconsin, USA). Rotation of 180° was used (64 projections), starting at 45° right anterior oblique projection and proceeding to the 45° left posterior oblique projection. The time per projection was 35 seconds, overall acquisition time 19 minutes. A 64×64 matrix was used for SPECT imaging.

Reconstruction and quantification

H/M ratio was calculated semi-quantitatively from planar imaging using regions of interest placed over the entire heart and upper mediastinum (7×7 pixels). Average counts per pixel in the myocardium were divided by average counts per pixel in the mediastinum. Myocardial 123I-MIBG WR from initial to late images was calculated and expressed in percentage. The decay and background correction was taken into account.

Cardiac 123I-MIBG SPECT images were processed with iterative reconstruction – the ordered subsets expectation maximization. Reorientation of the reconstructed trans-axial data into the three standard image planes and polar maps was done using automated reorientation method – Cedars-Sinai QPS/QGS software algorithm [17]. The cardiac SPECT image set of each patient was divided into 20 segments. The short axis images at the basal, middle, and apical ventricular levels were divided into six segments each. The apical

segment of the vertical long axis image was divided into two segments.

Regional tracer uptake was scored semi-quantitatively using a four-point scoring system (0 – normal uptake; 1 – mildly reduced uptake; 2 – moderately reduced uptake; 3 – severely reduced uptake). The denervation score (defect score) was calculated by the summation of segmental tracer uptake scores. The 123I-MIBG SPECT defect score was calculated for early and late SPECT imaging. Denervation scores were described with respect to denervation severity and extent. Denervation score difference was determined semi-quantitatively using arithmetic difference between early and late denervation scores. LVEF, VO_2 max and BNP levels were measured ±2 weeks at the time 123I-MIBG imaging was performed.

Statistics

Data was expressed as a mean ± standard deviation and compared using Pearson's correlation coefficient and linear regression. Mean scores of a cardiac 123I-MIBG imaging variables with reference to conventional markers of heart failure were compared using independent samples *t*-test. For all tests, a *p*-value less than 0.05 was considered as significant. Statistical analysis was performed using SPSS 19 software.

Results

Baseline variables of cardiac nerve integrity and sympathetic overdrive global and regional markers are presented in Table 1.

Pearson's correlation analysis demonstrated a weak negative correlation between LVEF and WR ($r = –0.3$, $p < 0.01$); between LVEF and early denervation score ($r = –0.347$, $p < 0.01$); between LVEF and late denervation score ($r = –0.356$, $p < 0.01$); weak positive correlation between LVEF and late H/M of ($r = 0.356$, $p < 0.01$).

Weak negative correlation was noted between BNP and late H/M ($r = –0.241$, $p < 0.05$); also weak positive correlation between BNP and WR ($r = 0.246$, $p < 0.05$); between BNP and early denervation score ($r = 0.282$, $p < 0.05$).

Weak negative correlation was noted between VO_2 max, early and late denervation score – respectively $r = –0.420$ ($p < 0.05$) and –0.361 ($p < 0.05$); between VO_2 max and WR ($r = –0.335$, $p < 0.05$).

Using independent samples *t*-test we compared the mean scores of a cardiac 123I-MIBG imaging variables between different levels of conventional heart failure markers and NYHA functional classes. Significant difference was found comparing late H/M variables between NYHA II and IV classes, respectively 2.32 ± 0.29 and 1.81 ± 0.45 ($p = 0.044$); WR variables, between NYHA II and IV classes, respectively 34.33 ± 11.56 and 57.45 ± 29.53 ($p = 0.01$), and NYHA III and IV classes, respectively 40.63 ± 18.04 and 57.45 ± 29.53 ($p = 0.01$). No significant differences were found comparing regional cardiac 123I-MIBG SPECT imaging markers variables between NYHA classes.

Significant differences were found comparing late H/M variables between LVEF > 40% and <40%, 2.36 ± 0.50 and 1.98 ± 0.45 respectively ($p = 0.008$); comparing WR variables between LVEF > 40% and <40%, 30.74 ± 14.02 and 44.55 ± 20.81 respectively ($p = 0.024$); comparing early and late denervation scores between LVEF > 40% and <40% to early denervation scores, 7.50 ± 8.25 and 16.96 ± 11.42 respectively ($p = 0.016$), to late denervation scores – 18.9 ± 9.79 and 28.32 ± 13.37 ($p = 0.039$).

Significant differences were found comparing late H/M variables between BNP levels: <100 pg/ml and >900 pg/ml – 2.24 ± 0.52 and 1.80 ± 0.39 ($p = 0.005$); 101–300 pg/ml and 301–600 pg/ml – 2.19 ± 0.47 and 1.82 ± 0.43 ($p = 0.005$); 101–300 pg/ml and >901 pg/ml – 2.19 ± 0.47 and 1.80 ± 0.39 ($p = 0.005$); <100 pg/ml and 301–600 pg/ml – 2.24 ± 0.52 and 1.82 ± 0.43 ($p = 0.005$).

Comparing WR variables showed significant differences between BNP levels: <100 pg/ml and 301–600 pg/ml – 35.57 ± 31.00 and 52.41 ± 19.88 ($p = 0.018$); 101–300 pg/ml and 301–600 pg/ml – 35.88 ± 13.38 and 52.41 ± 19.88 ($p = 0.018$); 101–

Table 1.
Cardiac 123I-MIBG imaging variables

	Minimum	Maximum	Mean	Std. deviation
Early H/M	1.17	3.24	2.27	0.44
Late H/M	0.89	3.03	2.04	0.48
WR	1.2	148.4	42.5	20.5
Early defect score	0	61	19.7	14.9
Late defect score	3	76	33.5	16.5
Defect score difference	2	46	13.8	8.7

H/M – heart to mediastinum ratio, WR – washout ratio.

300 pg/ml and >900 pg/ml – 35.88 ± 13.38 and 50.08 ± 12.08 ($p = 0.018$); <100 pg/ml and >901 pg/ml – 35.57 ± 31.00 and 50.08 ± 12.08 ($p = 0.018$). Other cardiac 123I-MIBG markers variables differ insignificantly, with reference to BNP levels.

Discussion

It is well known that adrenergic nervous system plays a major role in the pathophysiology of heart failure. With the HF progression increased hyperactivity of sympathetic nervous system with an increase in plasma norepinephrine supports cardiovascular system by increasing heart rate, contractility and venous return. As the HF progression goes on such hyperactivity is unfavorable and this may result on desensitization and down-regulation of myocardial β-adrenoceptor with further impairment of cardiac performance and poor outcome [18]. Assessment of cardiac sympathetic nerve activity besides providing prognostic information in patients with HF, also represents the severity of HF, which further with impairment of the functional parameters may lead to unfavorable course of the disease. Severity of congestive heart failure can be evaluated based on parameters determined by measuring cardiac sympathetic activity with cardiac 123I-MIBG imaging.

Weak, statistically significant correlation between cardiac 123I-MIBG imaging and conventional cardiac HF biochemical and imaging data (LVEF, BNP, VO_2 max) strengthens the value of cardiac adrenergic innervation imaging parameters to predict HF severity. Our study results indicate that late H/M ratio decreases and WR increases with the decreasing LVEF. These data reflect that increasing cardiac sympathetic system overdrive is related to poorer LVEF, thus expressing severity of HF. The same relation was found with the decreasing late H/M ratio and increasing WR – in both circumstances BNP levels increase. The biggest difference between these methods is that LVEF is functional cardiac marker and the BNP is biochemical marker representing cardiac overload. However despite relatively inert nature of LVEF changes with the progression of HF and wide variation of BNP levels in blood for different patients age, gender, body mass index, renal function and the range of cardiological status (hypertension, myocardial ischemia), they both had relation to the cardiac sympathetic innervation status, which was assessed directly measuring adrenergic innervation integrity and sympathetic overdrive. These data support the assumption that for the stable patients cardiac adrenergic innervation imaging with 123I-MIBG data provides information regarding HF severity. Furthermore for the patient with progressive disease, or for the patients who receive effective treatment of HF, changes of cardiac adrenergic innervation status could indicate progression or regression of the disease more sensitively [19].

These assumptions are supported by our data measuring the difference of the global and regional cardiac 123I-MIBG scores between different LVEF levels (>40% and <40%), and between different BNP ranges. Established significant differences of late H/M ratios and WR ratios between different LVEF levels and BNP levels confirm the link between cardiac sympathetic innervation, LVEF and BNP, as the more pronounced global adrenergic denervation patients have lower LVEF and higher BNP.

The link between cardiac sympathetic innervation and cardiac HF status is confirmed by the difference of late H/M ratios and WR ratios between different NYHA functional classes. NYHA functional class integrates clinical expression of HF. Established statistically significant difference of late H/M ratios and WR ratios between NYHA II and IV, and III and IV functional classes, allows us to state that for the stable HF patients global cardiac 123I-MIBG imaging data can be used to assess functional status of HF.

To our knowledge this is the first attempt to look at correlation between conventional cardiac HF markers and 123I-MIBG SPECT data of regional sympathetic innervation.

Controversial results have been obtained for the correlation of VO_2 max with the cardiac 123I-MIBG imaging data, as in opposite to LVEF and BNP, only the regional cardiac sympathetic innervation markers (early and late denervation scores) correlated with VO_2 max. Increased early and late denervation scores, representing denervation extent in the left ventricle lead to decreased functional capacity reflected by VO_2 max. Probable explanation of such relation could be inhomogeneity of selected patients group, as one third of the patients had ischaemic cardiomyopathy. Functional capacity for these patients decreases more than for non-ischaemic patients who had more uniform/diffuse loss of sympathetic nerve integrity. For non-ischaemic HF patients, global cardiac sympathetic innervation assessed with 123I-MIBG imaging was affected more than regional cardiac sympathetic innervation, and for HF patients with ischaemic cardiomyopathy the opposite is true – cardiac sympathetic innervation was affected more regionally than globally. Inhomogeneity of selected patients group including ischaemic cardiomyopathy could be the limitation

of our study. Future investigations could include more homogeneous patient groups.

Conclusions

According to the study results, conventional cardiac heart failure markers (LVEF, BNP levels, VO_2 max) showed statistically significant weak correlation with global and regional cardiac 123I-MIBG imaging parameters. Cardiac 123I-MIBG imaging markers differed significantly depending on LVEF and BNP levels, and NYHA functional class. Therefore changes of cardiac sympathetic system activity determined by cardiac 123I-MIBG imaging can be used to determine the severity of HF.

Acknowledgement

This study is a part of Research council of Lithuania funded, 2010–2011 National science program – "Noncommunicable diseases", project "Cardiac adrenergic innervation imaging for prognostic assessment of heart failure and sudden cardiac death" No. LIG-29/2010.

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