Influence of medical intervention on sympathetic activity in heart failure

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Chapter VII

Relationship between cardiac MIBG uptake and hemodynamic, functional and neurohormonal parameters in patients with heart failure

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Chapter VII

Abstract

Background: Sympathetic activation plays a pivotal role in heart failure attributing to the disease process and symptoms of the patient. Myocardial sympathetic activity can be visualized using radioiodinated metaiodobenzylguanidine $^{123}$I-MIBG, a structural analogue of norepinephrine (NE).

Aim of the study: We investigated whether a relation exists between myocardial MIBG uptake and different functional, hemodynamic and neurohormonal parameters in patients with chronic heart failure.

Methods and results:
The study comprised 52 patients with stable congestive heart failure functional class II or III and left ventricular ejection fractions of less than 35%. The heart/mediastinum ratio (H/M ratio) was calculated to quantify myocardial MIBG uptake. A significant correlation was found between peak oxygen consumption and maximal exercise duration as exercise parameters and H/M ratio of MIBG (R respectively 0.36 and 0.4. P<0.05). From all other measured parameters, only plasma NE showed a significant correlation with the H/M ratio of MIBG.

Conclusion: Cardiac sympathetic activity, as measured by myocardial MIBG uptake, is correlated with peak exercise parameters.
Heart failure frequently leads to progressive exercise intolerance. Several factors may attribute to this reduced exercise capacity including a decreased cardiac output, changes in skeletal muscle metabolism, wasted skeletal muscle, reduced baroreflex sensitivity, angina threshold and chronic sympathetic overactivity. The general activation of sympathetic function plays a key role in the syndrome of heart failure and can initially be considered as compensation but with progression of the disease it becomes pathological and even aggravates the disease process.

Radioiodinated metaiodobenzylguanidine (\(^{123}\)I-MIBG), an analogue of norepinephrine can be used to visualize and quantify myocardial sympathetic activity and integrity. Reduced myocardial MIBG uptake has been demonstrated in heart failure and a correlation exists between severity of disease and MIBG uptake. Recently, Atsumi showed a correlation between exercise capacity and myocardial MIBG uptake. The purpose of the present study was to investigate the relation between myocardial MIBG uptake and different functional, hemodynamic and neurohormonal parameters in patients with chronic heart failure.

Methods

Study patients

The study was approved by the review board and the ethics committee of both participating institutions. Written informed consent was obtained from all patients before they entered the study. The investigation conforms with the principles outlined in the Declaration of Helsinki.

We examined 52 patients with a history of chronic symptomatic heart failure, NYHA functional class II or III and an ejection fraction of less then 35% as assessed by radionuclide ventriculography. Both ischemic and non-ischemic cardiomyopathies were included. Patients were classified as ischemic if they had a history of a documented myocardial infarction and/or coronary angiography showed significant coronary artery disease.

Inclusion required stable disease for at least 4 weeks without change in medication before measurement of all functional, hemodynamic and neurohormonal parameters and myocardial MIBG uptake. Exclusion included obstructive airway disease, inability to exercise for other reasons than heart failure, objective signs of ischemia and angina pectoris as limiting factor during exercise.

Functional parameters

The six-minute walk test was conducted using a predefined course in the corridors of our hospital with small distance markers on the wall. Patients walked at their own pace and were allowed to stop during the test but were instructed to resume walking as soon as they were able to do so. They were unaware of the distance markers. A study nurse accompanied them but did not attempt to influence the patient. After 6 minutes they stopped walking and the total distance walked was...
measured. The course can be entered at different places to avoid patient bias when the test is repeated. A previous study with this course showed an excellent reproducibility of the test in our hospital. Peak oxygen consumption was measured on a bicycle ergometer according to previous defined standards. For the quality of life assessment the Minnesota living with heart failure questionnaire was used.  

**Neurohormones**

Blood samples for plasma catecholamines and atrial natriuretic factor (ANP) were drawn after 30 minutes of rest in supine position. An indwelling catheter in the antecubital vein inserted before the resting period was used. Blood samples were transferred immediately to ice-chilled tubes. The plasma was separated through centrifugation at 4°C and stored at −70°C until assay. Plasma NE concentration was determined by high performance liquid chromatography and electrochemical detection, after purification on Biorex 70 and concentration by solvent extraction. Atrial natriuretic peptide was determined by radio-immunoassay (Nichols Institute Diagnostics, Wychen, the Netherlands).

**123I-MIBG imaging**

123I-MIBG imaging was performed in the morning one hour after 100 mg potassium orally to block thyroid uptake of free 123I. 185 MBq 123I-MIBG (Cygne BV, Technical University Eindhoven, the Netherlands) was injected intravenously. Images were obtained 3 hours after injection (planar imaging, medium-energy collimator). A 20% energy window centered on the 159 keV photopeak of 123I was used. A region of interest was manually drawn around the left ventricle. Mediastinum activity was measured using a 7x7-pixel region of interest over the upper mediastinum. Cardiac MIBG uptake was quantified by calculating the heart to mediastinum ratio (mean counts per pixel in the heart divided by those in the mediastinum).

**Statistical methods**

Numeric values are expressed as means ± standard deviation. Correlations were calculated for all continuous variables. Pearson’s correlations were calculated using SPSS and considered significant at the 0.05 level (2-tailed).

**Results**

Initially, 52 patients were included. One patient was excluded from all analysis because (nor)epinephrine concentrations were far beyond the normal range. In retrospect, there was a highly significant uptake of MIBG in the renal region, suggesting apheochromocytoma. His progressive heart failure was probably related to this entity. He died shortly after inclusion in this
study. Baseline characteristics are summarized in table 1. Results of all measured parameters and their correlation with MIBG uptake are summarized in table 2. Mean H/M ratio of MIBG uptake was 1.8±0.45.

**Table 1. Baseline characteristics.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65 ± 10</td>
</tr>
<tr>
<td>Male, n</td>
<td>35</td>
</tr>
<tr>
<td>NYHA functional class, n</td>
<td>II: 27  III: 24</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy, n</td>
<td>31</td>
</tr>
<tr>
<td>Non-ischemic cardiomyopathy, n</td>
<td>20</td>
</tr>
<tr>
<td>Medication, n</td>
<td>ACE-inhibitor: 48, Digoxin: 16, Atrial fibrillation: 4</td>
</tr>
</tbody>
</table>

**Table 2. Correlation between measured parameters and H/M ratio of MIBG.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Included patients (n=51)</th>
<th>H/M ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>64.7 ± 10.2</td>
<td>-0.06</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic bloodpressure (mm Hg)</td>
<td>130.4 ± 18.9</td>
<td>0.18</td>
</tr>
<tr>
<td>Diastolic bloodpressure (mm Hg)</td>
<td>74.3 ± 10.0</td>
<td>0.24</td>
</tr>
<tr>
<td>Mean heart rate day (bts/min)</td>
<td>90.0 ± 13.0</td>
<td>-0.13</td>
</tr>
<tr>
<td>Mean heart rate night (bts/min)</td>
<td>77.3 ± 13.2</td>
<td>-0.03</td>
</tr>
<tr>
<td>Mean heart rate 24 hours (bts/min)</td>
<td>84.5 ± 11.5</td>
<td>-0.13</td>
</tr>
<tr>
<td>Maximal heart rate (bts/min)</td>
<td>140.4 ± 20.4</td>
<td>0.23</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>26.5 ± 6.5</td>
<td>0.04</td>
</tr>
<tr>
<td>End diastolic diameter (mm)</td>
<td>73.0 ± 10.0</td>
<td>-0.06</td>
</tr>
<tr>
<td>Functional parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO,max (ml/kg/min)</td>
<td>15.2 ± 4.3</td>
<td>0.36*</td>
</tr>
<tr>
<td>Exercise duration (min)</td>
<td>7.5 ± 7.3</td>
<td>0.4*</td>
</tr>
<tr>
<td>Six minute walking test (m)</td>
<td>408.2 ± 82.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Quality of life</td>
<td>26.6 ± 16.5</td>
<td>-0.09</td>
</tr>
<tr>
<td>Neurohormones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine (nmol/l)</td>
<td>3.9 ± 2.6</td>
<td>-0.35*</td>
</tr>
<tr>
<td>Epinephrine (nmol/l)</td>
<td>0.25 ± 0.24</td>
<td>0.04</td>
</tr>
<tr>
<td>ANP (pg/l)</td>
<td>189.1 ± 120.8</td>
<td>-0.25</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD

*Correlation is significant at the 0.05 level (two tailed)
Figure 1. Regression of heart/mediastinum ratio of MIBG uptake vs peak oxygen consumption (P<0.05).

Figure 2. Regression of heart/mediastinum ratio of MIBG uptake vs maximal exercise duration (P<0.05).
A significant correlation was found between H/M ratio and two clinically used exercise parameters: peak oxygen consumption and maximal exercise duration (R respectively 0.36 and 0.4, P <0.05, figure 1 and 2). This correlation was not found between total distance during the 6-minute walking test and MIBG uptake (R 0.2, P=0.2). No correlation could be found between heart rate, blood pressure, left ventricular ejection fraction, end-diastolic diameter and quality of life assessment and MIBG uptake. From the three measured neurohormones, only plasma NE showed a significant correlation with MIBG uptake (R =-0.35, P=0.01). In addition, a correlation was found between total distance during the 6-minute walking test and peak oxygen consumption (R 0.7, P=0.001) and between the total distance during the 6-minute walking test and duration of maximal exercise testing during peak VO$_2$ testing (R 0.7, P=0.001). Left ventricular ejection fraction was not correlated to any exercise parameter.

**Discussion**

Our study demonstrates a correlation between myocardial MIBG uptake and two important exercise parameters: peak oxygen consumption and maximal exercise duration. These results extend the observations of two recently published studies that also demonstrated a significant correlation between myocardial MIBG uptake and peak oxygen consumption in patients with mild to moderate heart failure.$^{2,3}$ In contrast, exercise duration during submaximal testing was not correlated to cardiac MIBG uptake.

**Sympathetic activity and peak VO$_2^*$.**

Exercise intolerance resulting in exertional fatigue and dyspnea is a key feature in patients with heart failure. Different mechanisms have been identified to explain these symptoms. First, there are cardiac limitations as a result of a decreased cardiac output. However, from clinical practice it is known that cardiac factors are not the sole mechanism by which exertional symptoms can be explained as demonstrated by the fact that a correlation between left ventricular ejection fraction and exercise capacity has never been demonstrated. Second, in addition to other peripheral factors, increased muscle sympathetic activity has been correlated to reduced exercise tolerance.$^{4}$ Results from our study and others$^{2,3}$ suggest however that the correlation between increased sympathetic tone and exercise impairment is not restricted to sympathetic tone at the level of the peripheral muscle but can also be demonstrated for cardiac sympathetic tone. It might well be possible that local and systemic increase of sympathetic activity (including for example baroreflex impairment) contributes to the observed decrease in exercise tolerance.

The fact that myocardial sympathetic activation as measured by MIBG uptake is correlated to
exercise capacity in contrast to several hemodynamic and functional parameters emphasizes the role of neurohumoral activation in heart failure. There is another explanation for the observed correlation between peak VO\(_2\) and myocardial MIBG uptake because both parameters have been related to disease severity and prognosis.\(^2\) The relation between peak VO\(_2\) and cardiac MIBG uptake thus represents two different parameters of the same phenomenon: disease severity without direct correlation. It can not be elucidated from our data whether this hypothesis is true.

**Maximal vs. submaximal exercise testing**

In contrast to peak exercise parameters (peak exercise duration and peak VO\(_2\)), the distance ambulated during the 6-minute walk test could not be correlated to cardiac MIBG uptake. The 6-minute walk test is an objective measure of submaximal exercise capacity in congestive heart failure and has been correlated both to prognosis and peak VO\(_2\).\(^{10-12}\) It reflects functional capacity during daily activity probably better than maximal exercise testing in laboratory conditions. Although the distance walked during the 6-min walk test correlated to both peak VO\(_2\) and maximal exercise duration in our study, no correlation could be found between the results of the 6-min walk test and myocardial MIBG uptake. The reason for this is not immediately obvious and can not be clarified from our data. In line with this observation is the fact that the assessment of quality of life and functional class were not correlated to cardiac MIBG uptake. Both quality of life assessment and functional class reflect functional capacity during normal daily life as is the case with the distance ambulated during the 6 minute walk test.

In conclusion, the results from our study indicate that a correlation exists between cardiac sympathetic activity as measured by myocardial MIBG uptake and peak exercise parameters (maximal exercise duration and peak oxygen consumption).

**Study limitations**

This study was conducted before β-blocker treatment became part of routine clinical practice in heart failure patients. Although β-blockers have an effect on sympathetic activity and myocardial MIBG uptake, the effect of β-blockers on exercise capacity seems to be marginal. It can, however not be predicted whether the observed correlation between peak VO\(_2\) and maximal exercise duration and myocardial MIBG also applies to patients with heart failure treated with β-blockers.

**Acknowledgments**

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References


