

123I-meta-iodobenzylguanidine in patients with chronic heart failure: technical aspects, conceptual issues and future prospects

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Heart failure

Chronic heart failure (CHF) is a complex clinical syndrome characterized by abnormal function of the ventricles and neurohormonal regulation and caused by any cardiac disorder that impairs the ability of the left ventricle to fill or eject blood. The cardinal manifestations of CHF are shortness of breath (dyspnoea) and fatigue, which may limit exercise tolerance, and fluid retention that results in peripheral oedema and pulmonary congestion. The severity of clinical symptoms may vary substantially during the course of the disease process and may not correlate with changes in underlying cardiac function.

In Europe, the prevalence of CHF is estimated at about 1% (approximately 4 million patients in Western Europe), while in the United States (US), the number of CHF patients is approximately 5 million. About \$39 billion in costs, a million hospitalizations and 55,000 deaths are directly attributed to CHF in the US annually. In the Western industrialized world, coronary artery disease (CAD), hypertension and valvular heart disease are the main causes of CHF.

Cardiac sympathetic activity: ¹²³I-MIBG

In patients with CHF, increased sympathetic activity and cardiac sympathetic dysfunction are present and are related to an unfavourable outcome. In recent years, large scale clinical trials have documented the benefits of pharmacological therapies aimed at limiting left ventricular remodelling and even reversing this process. These beneficial effects were associated with an increase in myocardial uptake of ¹²³I-metaiodobenzylguanidine (¹²³I-MIBG), a radio-labelled norepinephrine analog. A large number of investigators have demonstrated decreased myocardial ¹²³I-MIBG uptake in patients with CHF and have shown that those patients with the lowest uptake tend to have the poorest prognosis. Abnormal myocardial ¹²³I-MIBG uptake has been reported to be correlated with an increased risk for ventricular arrhythmia and sudden cardiac death (SCD).

¹²³I-MIBG: procedure and acquisition parameters

One factor that has constrained acceptance of cardiac ¹²³I-MIBG imaging as a clinical diagnostic and prognostic tool in CHF has been the variability of technical aspects of the procedure. Although most publications have included the heart-to-mediastinum ratio (H/M) as the measure of myocardial uptake, the methods used to obtain this parameter show considerable variation. However, the influence of procedural and acquisition parameters on the reproducibility of the ¹²³I-MIBG semi-quantitative myocardial measurements have only occasionally been considered (1).

Procedure for planar ¹²³I-MIBG scintigraphy

In order to block thyroid uptake of free radioactive iodide either 500 mg potassium perchlorate or 200 mg potassium iodide (10% solution) is orally administered. Thirty minutes later approximately 185 MBq of ¹²³I-MIBG is administered intravenously. ¹²³I-MIBG is internalized by pre-synaptic nerve endings of postganglionic neuronal cells through the energy dependent norepinephrine transporter. A 15% energy window is usually used, centered on the 159-keV ¹²³I photo peak. Anterior planar scintigraphic images are obtained 15 min (early) and 4 hours (late) after injection and stored in a 128 x 128 matrix.

Semi- quantitative parameters

The commonly used myocardial ¹²³I-MIBG indices are the heart-to-mediastinum ratio (H/M ratio) and myocardial washout. On anterior planar images regions of interest (ROIs) are drawn over the heart (H) and the mediastinum (M). The mean count-density in each ROI is obtained and the H/M ratio (specific activity/nonspecific activity) is calculated. Myocardial ¹²³I-MIBG washout is calculated as the difference between the early and late H/M and expressed as a percentage of the early H/M:

The early H/M probably reflects the integrity of pre-synaptic nerve terminals and specific pre-synaptic uptake of ^{123}I -MIBG. The late H/M combines information on neuronal function from uptake to release through the storage vesicle at the nerve terminals. Myocardial ^{123}I -MIBG washout is an index of the degree of sympathetic drive. This implies that increased sympathetic activity is associated with high myocardial ^{123}I -MIBG washout and low myocardial ^{123}I -MIBG delayed uptake.

Influence of procedural and acquisition parameters

The most well validated influence on the measure of the late H/M is the collimator type. Because of the high energy photons emitted by ^{123}I , septal penetration influences late H/M. These effects are less for medium energy (ME) collimators. Although scatter correction increases H/M ratios, scatter correction does not improve the contrast between H/M ratios. For a straightforward implementation of semi-quantitative ^{123}I -MIBG myocardial studies, the use of ME collimators without scatter correction is recommended.

^{123}I -MIBG: prognosis

A number of studies have investigated the relationship between semi-quantitative myocardial ^{123}I -MIBG parameters (early H/M, late H/M and myocardial washout) and prognosis in CHF. However, estimates of the hazard ratio (HR) among studies differ considerably. The lack of consensus is reflected in the absence of ^{123}I -MIBG in any of the current guidelines regarding either heart failure or cardiac imaging. The data from a systematic review suggest that patients with heart failure and abnormal semi-quantitative myocardial ^{123}I -MIBG parameters have a significantly worse prognosis compared to those with relative normal semi-quantitative myocardial ^{123}I -MIBG parameters (2). More specifically, a decreased late H/M is associated with a higher incidence of cardiac events and is not associated with cardiac death. Furthermore, an increased myocardial washout is associated with both cardiac death and cardiac events. Therefore, semi-quantitative myocardial ^{123}I -MIBG uptake and washout are promising prognostic markers in patients with heart failure. However, due to heterogeneity between the various studies, the results were obtained from only a relatively small number of high quality studies. With these limitations in mind the ADMIRE-HF study was designed. This large multicenter study provided prospective validation of the independent prognostic value of ^{123}I -MIBG in patients with CHF: the hazard ratio for late H/M ≥ 1.60 was 0.40 ($p < 0.001$) (3).

Discussion and future perspectives

Despite the large number of studies on cardiac ^{123}I -MIBG imaging, methodological and limitations in the image analysis have hampered large scale implementation of this technique for the evaluation and management of individual patients. However, a prerequisite for large scale implementation of ^{123}I -MIBG imaging in clinical cardiology is adequate reproducibility, standardization and validation. ^{123}I -MIBG has been shown by individual centers to have both good reproducibility, acceptable variability, and to have prognostic value in CHF patients. These single-center experiences, however, do not necessarily allow for extrapolation of the obtained results to other centers. In spite of this, quantitative thresholds are often implemented without inter-institutional validation. Because there are differences between centers in hardware, acquisition parameters and post-acquisition processing, the extrapolation to other centers, or generalization of these single-center findings, is not per se justified. To improve uniformity in acquisition and analysis a proposal on standardisation of ^{123}I -MIBG myocardial scintigraphy has recently been formulated on behalf of the Cardiovascular Committee of the EANM and the European Council of Nuclear Cardiology (4).

In addition to the morbidity and mortality associated with ventricular dysfunction, there is also an increased incidence of sudden cardiac death (SCD) in CHF patients. Especially patients with severely reduced left ventricular ejection fraction (LVEF) ($<30\text{-}35\%$) are at risk. Although therapies for CHF have been successful in reducing morbidity and mortality, in recent years there has been rapid increase in the use of implantable cardioverter-defibrillators (ICD) as primary treatment for this condition. This development in therapeutic strategy has had an increasing impact on healthcare budgets in the USA and Europe and has stimulated interest in diagnostic tests capable of predicting future risk for heart failure progression and arrhythmic SCD.

The MADIT II study, however, showed that the actual reduction of fatal events for ICD compared to conventional medical therapy was 5.6 percentage points (from 19.8 to 14.2) (5). In addition, the SCD-HeFT trial showed that the annual rate of ICD shock was 7.1% and of appropriate shock for rapid ventricular tachycardia or ventricular fibrillation was 5.1%, with a total of 21% patients receiving appropriate shocks over 5 years (6). Since the majority of patients in these studies did not experience life-threatening arrhythmias, it is of the utmost importance to find better tools for risk stratification and thus the identification of patients most likely to benefit from ICD. The implantation of ICDs is costly (estimated number of ICDs needed to be implanted to save 1 life is 18) and, in addition, may have negative effects on quality of life. The degree of impairment of LVEF is used as the main indication for the need of implantation of ICDs in patients post myocardial infarction. However, LVEF is far from an ideal risk-stratification test on which to base prophylactic ICD therapy. Multiple factors

interact with LVEF to influence mortality of patients with similar degrees of left ventricular dysfunction.

Increased cardiac sympathetic activity is often present in patients with chronic heart failure and may play a role in the development of ventricular arrhythmias. High sympathetic activity has been demonstrated in CHF patients with ventricular arrhythmias. On the other hand, β -receptor antagonists have shown to reduce the incidence of ventricular arrhythmias in CHF patients. Therefore, cardiac sympathetic nervous function and activity may serve as parameters that can be used to identify CHF patients who are at risk for life-threatening arrhythmias. Some small clinical studies have already shown that cardiac sympathetic activity as assessed by the use of ^{123}I -MIBG scintigraphy in combination with other clinical parameters is related to sudden cardiac death and appropriate ICD discharge. If these findings are confirmed by larger studies, ^{123}I -MIBG might become an important tool to select CHF patients for ICD.

Conclusions

Sympathetic myocardial activity as assessed with ^{123}I -MIBG has powerful prognostic value in heart failure patients. Those patients with CHF with the lowest myocardial ^{123}I -MIBG uptake tend to have the poorest prognosis. However, additional studies will be needed to determine whether ^{123}I -MIBG can assist in triage of patients being considered for ICD placement.

References

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