RISK STRATIFICATION IN HEART FAILURE USING 123I-mIBG.

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Abstract
Heart failure (HF) is a progressive, heterogeneous form of cardiovascular disease that requires treatment to be individualised depending on the presenting symptoms. A decision to use an implantable cardioverter/defibrillator (ICD) is based on chronic HF patients presenting with a New York Heart Association (NYHA) classification of II or III and a left ventricular ejection fraction (LVEF) less than or equal to 30-35%. A large percentage of ICD devices, however, never deliver therapy during their lifetime while as many as 33% of patients ineligible for an ICD (LVEF > 35%) die of SCD. $^{123}$I-<em>m</em>IBG scintigraphy identifies sympathetic nervous system dysfunction and has been shown to lead to better patient stratification. This article reviews the role of planar $^{123}$I-<em>m</em>IBG global quantitation in improving differentiation of HF, regardless of the LVEF, to better identify those in whom an ICD is more likely to reap benefits. It goes on to explore the potential incremental benefit of SPECT based regional quantitation to risk stratification and provides a case example where $^{123}$I-<em>m</em>IBG SPECT was used to inform a decision to not use an ICD in a patient eligible under the standard criteria.
Introduction
Heart failure (HF) is a progressive, heterogeneous form of cardiovascular disease that requires treatment to be individualised depending on the presenting symptoms. HF is the inability of the left ventricle (LV) to fill or eject enough blood to meet the requirements of the body (1) and might be viewed as a syndrome representative of a variety of cardiac diseases (2). Nonetheless, coronary artery disease (CAD) is the underlying pathology in 70% of HF patients (3). Chronic heart failure (CHF) involves both mechanical failure and autonomic nervous system dysfunction which can lead to sudden cardiac death (SCD). A number of therapies are, therefore, utilised including pharmaceutical and device options; for example the implantable cardioverter/defibrillator (ICD) device. Despite these options, the long term prognosis in HF is poor with 5 year mortality rates of 59% and 45% for men and women respectively (3). There is a clear need for improved stratification of patients based on risk yet there is a paucity of screening programs available for early detection (2).

A decision to use an ICD is based on CHF patients presenting with a New York Heart Association (NYHA) classification of II or III and a left ventricular ejection fraction (LVEF) less than or equal to 30-35%; depending on the country. A large percentage of ICD devices, however, never deliver therapy during their lifetime while as many as 33% of patients ineligible for an ICD (LVEF > 35%) die of SCD (4). Consequently, there is a pressing need for improved differentiation of CHF, regardless of the LVEF, to better identify those in whom an ICD is more likely to reap benefits. In the USA, scintigraphy with 123-iodine meta-iodobenzylguanidine ($^{123}$I-mIBG) has been used for risk stratification in CHF patients with low LVEF (< 35%). $^{123}$I-mIBG identifies sympathetic nervous system dysfunction and has been shown to lead to better patient stratification (4).

Heart Failure
HF has been described as the “Cinderella of health issues — hardly registering on the radar of key health care providers, regulators, relevant government bodies and the general public” (5). This is in a large part due to a lack of a universally recognised definition of HF and because varying degrees of left ventricular systolic dysfunction (LVSD) may be asymptomatic. Indeed, almost half of HF patients have preserved LV
function \((I)\). In the USA, there are more than 5 million people with HF \((I-3)\) while there are estimated to be more than 20 million HF suffers world wide \((I)\). In the USA, 550000 new HF cases are detected each year, there are more than 1 million HF related hospitalisations each year and HF currently costs $29 billion annually \((3)\). For developed countries, 1-2% of the population have HF \((I, 6, 7)\). Clarke et al. \((8)\) estimated that 325000 Australians had symptomatic HF and another 214000 had left ventricular systolic dysfunction (LVSD); in a population of just 20 million. The same investigators estimated that HF in Australia was responsible for 1.4 million hospital days and $1 billion in costs annually.

Age is a very good predictor of the incidence of HF. HF incidence is 10 per 1000 of the population for those over 65 years of age and 20% of hospitalisations are in those of 65 years of age \((2)\). For those 50-59 years of age, the prevalence is 8 per 1000 for both men and women, however, this sharply increases for those 80-89 years to 66 per 1000 and 79 per 1000 for men and women respectively \((I)\).

HF has a median survival of just 1.7 years and 3.2 years for men and women respectively \((I)\). It has a 10% mortality by 30 days, which highlights an early high risk period of disease. This high risk period is followed by a 5 year mortality rate of 54% and 40% for men and women respectively \((9)\). CHF is progressive in nature and ultimately fatal which makes early detection crucial for delaying progression. For patients with mild symptoms, the annual death rate is 5-10% and this increases sharply to 30-40% for those with more advanced symptoms \((10)\).

Although HF is generally classified according to the NYHA classification (table 1), there are other classification methods in use. The American College of Cardiology (ACC) and American Heart Association (AHA) offer an alternative classification (table 1) that has a number of advantages over the NHYA version. The NYHA classification is based on functional limitations of the HF patient, progressing from lesser through to greater limitation. Unlike the disease itself, the NYHA classification may regress if a patient’s functional status improves. Conversely, the ACC/AHA classification progresses from stage A through to D and can not reverse the order \((2)\). This is an important discussion
because the decision to provide or refuse an ICD in HF based on the NYHA classification of the patient may not reflect the patient’s actual disease stage. That is, functional status may improve from NYHA IV to III without an improvement in disease state or indeed risk. Stage D in the ACC/AHA classification, on the other hand, provides a consistent classification of disease state and risk.

Morbidity and mortality in CHF remain high, despite advances in treatment (8). There are a number of approaches to management of CHF and these generally relate to the severity of disease, symptoms and co-morbidity. The goal of therapy is to improve and prolong life and this is achieved using lifestyle modifications, pharmaceutical therapy, surgery, supportive devices management programs and palliative care (6). More recently, cardiac resynchronisation therapy has emerged as a good option for those patients presenting with class III/IV heart failure (11). The risk of arrhythmia and SCD is greater in patients with CHD. Consequently, ICD devices have been used in select patients for over a decade to protect against arrhythmia and SCD, and have been increasingly used in Australia; 2864 were implanted in 2005 which was up from 956 in 2001 (12). The ICD is a device that combines the functions of a traditional pacemaker, a Holter monitor and a defibrillator. The Cardiac Society of Australia and New Zealand has stated that ICDs are indicated in CHF patients with a LVEF less than 35% with NYHA class II or III symptoms (6). Medicare Australia provide coverage for CHF patients with NYHA class II or III symptoms, an LVEF of less than or equal to 35% and after receiving optimised medical therapy. Patients treated with an ICD have a 1-3% annual decrease in absolute mortality which equates to a 20-30% relative reduction in mortality each year. The VALIANT trial reported on 14609 patients with LVSD or HF after myocardial infarction (MI) and found a mortality rate of 6.2% after a median 24.7 month follow up (13). Analysis revealed that each decrease of 5 points of LVEF was associated with a 21% adjusted increase in risk of mortality (13). The MADIT-CRT trial recruited 1232 patients with previous MI and a LVEF less than 30% and reported that, compared to standard medical therapy, the addition of an ICD improved the 20 month follow up mortality rate from 19.8% to 14.2% (14).
Cardiac Autonomic Neuropathy in Heart Failure
The compensatory response of the autonomic nervous system to LV dysfunction in HF becomes part of the disease progress leading eventually to further deterioration of the disease. The sympathetic nervous system is part of this response. The ventricular innervation is characterised by a gradient from base to apex (15). Chronic impairment in cardiac output due to damage to the cardiac pump increases plasma noradrenaline levels released from sympathetic postganglionic nerves. This sympathetic overdrive, which is related to dysfunctional atrial baroreceptor reflex activity and sympatho-vagal balance, parallels the clinical severity of HF expressed by the NYHA functional class categories and is similar in ischaemic or non-ischaemic heart failure states (16).

$^{123}$I-$m$IBG in Heart Failure
Molecular imaging of the cardiac sympathetic neuronal system is possible with $^{123}$I-$m$IBG because it is a false adrenergic neurotransmitter that has a similar re-uptake mechanism as norepinephrine. Fortunately, $^{123}$I-$m$IBG is not metabolised and does not interact with post-synaptic receptors which allows scintigraphic imaging at early (15 minutes post administration) and delayed (4 hours post administration) phases (17). Impaired sympathetic innervation has been shown to increase ventricular arrhythmias because even in viable myocardium the impaired innervations results in abnormal chemical and electrical stimulation (18). Since the sympathetic nervous tissue is more sensitive to ischaemia than the myocardium, impaired innervations can cause arrhythmia but be insufficient to cause myocardial infarction (18). Clinical use is well established for $^{123}$I-$m$IBG and its safety profile is well documented to provide a useful non invasive tool to risk stratify patients with CHF. Greater deprivation of cardiac sympathetic innervation is associated with a worse prognosis in heart failure patients (19).

Generally speaking, the delayed uptake (H:M) has been shown to have predictive power although washout rate and defect score have also been reported to be clinical important. Nonetheless, the correlation between LVEF and H:M is weak ($r = 0.50$) (20). While CHF can show an initial compensatory increase in myocardial uptake of $^{123}$I-$m$IBG, low uptake is strongly correlated with a poor prognosis and predicts increased risk of arrhythmia and SCD (21). More recently, the washout rate of $^{123}$I-$m$IBG from the myocardium between
early and delayed images has shown promising predictive power (3). HF is associated with more rapid washout while even in the presence of HF, the washout rates of lung, liver and mediastinum appear uniform (21). Washout greater than 27% has been reported as a strong predictor of survival but not necessarily of cardiac events (22). One might consider the late uptake a marker for risk of SCD and washout a marker of survival independent of SCD risk (ie. death due to disease progression). Together, they might provide better stratification of those suitable for ICD with uptake identifying those likely to benefit and washout those less likely to benefit. Table 2 provides an overview of the key HF studies evaluating $^{123}$I-MAIBG.

There has been a broad range of research and reports in the medical literature highlighting the role $^{123}$I-MAIBG plays in risk stratification. Recently, a multi-national prospective open-label, multi-centre, phase 3 study evaluated the role of $^{123}$I-MAIBG imaging in identifying CHF patients who are likely to experience a major adverse cardiac event (ADMIRE-HF - AdreView Myocardial Imaging for Risk Evaluation in Heart Failure study) (23). The study included 961 patients with a NYHA II or III classification and a LVEF of 35% or less that followed them for two years. The results indicated that normal (using a delayed heart to mediastinum ratio [H:M] of 1.60 as the cut-off) $^{123}$I-MAIBG uptake was associated with an 85% event free two year period while abnormal $^{123}$I-MAIBG only had a 63% 2 year event free period. The investigation also showed that H:M less than 1.20 had a 10 fold increase in event rate over those greater than or equal to 1.60. Carrio et al (9) used a delayed H:M of 1.75 as the cut-off and improved sensitivity to 84% (specificity 60%) to predict events with a 95% event free survival for 2 years greater than or equal to 1.75 and 62% for those lower than 1.75 (9).

In a 2-year follow-up period in CHF patients, using $^{123}$I-MAIBG SPECT to show that appropriate ICD discharge was documented in 21% of patients and patients with greater defect scores showed a 10-fold higher likelihood of appropriate ICD discharge therapy (24). Boogers et al. (24) reported on 116 patients referred for ICD presenting with advanced heart failure to show that a high defect score (<26) determined by regional summation on SPECT was predictive of appropriate ICD discharge. The late MAIBG defect score was also independently predictive of appropriate ICD discharge. Indeed,
patients with a late mIBG SPECT summed defect score greater than 26 were associated with a 52% appropriate discharge rate compared to just 5% for those with lower defect scores (p < 0.01).

Clinical Case
A 77 year old male presented with dyspnoea on exertion and ischaemic cardiomyopathy secondary to a history of myocardial infarction in the inferior wall and coronary artery bypass graft (CABG) four years earlier; saphenous vein graft (SVG) to the first obtuse marginal artery (OM1) and second obtuse marginal artery (OM2), SVG to the posterior descending artery (PDA), and pedicled left internal mammary artery (LIMA) to the left anterior descending artery (LAD). The resting ECG demonstrated atrial fibrillation, left anterior hemiblock and poor R wave progression. Post surgical atrial fibrillation has been treated with sotalol. No significant ST deviation was noted on the stress ECG. Stress myocardial perfusion imaging was performed as dipyridamole pharmacologic stress in conjunction with hand grip exercise. Resting myocardial perfusion SPECT evaluation revealed a LV end diastolic volume of 195 mL at rest and 210 ml post stress. The LVEF was 32% at rest and 34% at post-stress. The myocardial perfusion SPECT study revealed a fixed perfusion defect in the inferior wall and in the inferolateral wall. A partially reversible perfusion defect was noted in the anterolateral wall. Wall motion was paradoxic in the septal wall, akinetic in the inferior wall and severely hypokinetic in the inferolateral wall. On the basis of this history, the patient was eligible for ICD implantation under Australian Medicare coverage.

The patient was administered with 185 MBq of $^{123}$I-mIBG IV and received 30mg of Lugol’s iodine daily from 2 days prior to $^{123}$I-mIBG administration until 2 days after $^{123}$I-mIBG administration. The early phase imaging commenced 15 minutes post IV using 600 second anterior planar chest images. A 256 matrix on a GE Healthcare Infinia Hawkeye 4 with medium energy general purpose collimation was employed. Planar imaging was followed by 180 degree SPECT (LPO45 to RAO45) using a 64 matrix, 60 projections at 25 seconds per projection. The patient was imaged supine with the arms extended above the head. The SPECT study was reconstructed using CT based attenuation correction. The planar and SPECT acquisitions were repeated 4 hours post IV. Global myocardial,
mediastinal, lung and liver regions of interest were applied to the planar images. Normalised (counts per pixel) H:M were calculated for both the early phase (2.15) and delayed phase (2.21) using previously described methods (25-27). Delayed image statistics were decayed corrected. The global washout rate from early to delayed phases was calculated for myocardium, mediastinum, lung and liver. Cardiac washout rate was determined as 35.0% by (25-27):

\[
\frac{\text{early phase counts per pixel} - \text{delayed phase counts per pixel}}{\text{early phase counts per pixel}} \times 100
\]

Regions were applied to the planar image as described by Verberne et al. (28) with the myocardium represented by a region that circumscribes the entire myocardium and the mediastinum region placed adjacent to the upper part of the lung on the midline of the chest (figure 1). High lung uptake of $^{123}$I-IBG is characteristic of HF and this represents a limitation of region of interest placement (21). Given the intense lung uptake in this patient and the potential for count contribution of the lung to the myocardial counts, a smaller region was also drawn to include representative myocardial activity with exclusion of lung superimposition (21). A duplicate mediastinum region was also drawn adjacent to the lower third of the lung. H:M and washout rates were determined using the various combinations to assess how robust calculations were (table 3). Regions of interest were also placed on the liver and each lung. Verberne et al (21) reported washout rates to be elevated for the myocardium and decreased in the liver in CHF patients compared to normal patients and those with hypertension. In this patient, liver washout was 0% while the right and left lung showed 46.7% and 48.4% washout respectively. While the global H:M, despite the poor LVEF, demonstrated a low risk of SCD (ratio well in excess of 1.75), the global washout rate was abnormal. The H:M reflects cardiac sympathetic activity while the washout rate reflects norepinephrine retention by sympathetic neurons. Thus, more rapid washout might be a marker for making a decision against an ICD.

Normalised (counts per pixel) regions of interest were drawn on mid short axis (SA) and vertical long axis (VLA) SPECT slices (26). On the SA slice, regions included anterior,
septal, lateral and inferior walls. One the VLA slice, the region included apex. Matsuo et al. (29) used 5x5 pixel regions in the basal and distal SA slice for anterior, lateral, septal and inferior walls plus apex on the VLA. Our approach was to use the mid SA slice and mid VLA slice to generate regions for each wall using larger regions that represented the entire territory (ie. anterior, lateral, septal, inferior and apex). The 4 hour data were decay corrected and regional washout rates (RW) and uptake index (MUP) were determined (table 4) using the method described by Zhao et al. (26) (table 5):

\[ \text{RW\%} = \frac{[\text{mean early segment counts} - \text{mean delayed segment counts}] \times 100}{\text{mean early segment counts}} \]

\[ \text{MUP} = \frac{\text{mean segment counts} \times \text{H:M}}{\text{maximum voxel counts in all myocardial regions}} \]

Polar maps were generated to demonstrate regional cardiac $^{123}$I-mIBG distribution at 15 minutes (left) and 4 hours (right) post IV administration (figure 2). The polar maps show the marked washout from the apex and moderate washout from the infero-lateral wall. The cascade of HF sympathetic dysfunction can be appreciated in the inferior wall progressing into the lateral and septal walls and sparing the anterior wall at this point in the disease. The areas of denervation correspond to similar regions of hypoperfusion on the end diastolic polar map in the $^{99m}$Tc-MIBI study (figure 3) but show thickening and motion (figure 4). Figures 3 and 5 provide a comparison of the innervation and perfusion to the myocardium. The inferior septum, with its paradoxical motion, has a more extensive $^{123}$I-mIBG defect than the perfusion. Similarly, the inferior lateral wall and the apex show discordance between $^{123}$I-mIBG and $^{99m}$Tc-MIBI perfusion. Indeed, both wall motion and wall thickening are noted in these regions on the perfusion study. The global $^{123}$I-mIBG findings reflect sympathetic change associated with infarct not just progression.
of HF. Interestingly, the non MI region of greatest $^{123}$I-IBG washout (apex) was also the region with the greatest thickening (apex).

Despite satisfying the criteria to receive an ICD under the Medicare scheme, an ICD was not implanted and the patient remains event free at 12 months follow-up.
Discussion

The cost effectiveness of ICD therapy remains controversial. While ICDs have proven value in reducing mortality in CHF, they remain expensive so identifying those patients who would benefit most from an ICD is crucial. SCD occurs more commonly in those with LVEF over 35% with 67% of SCD having a LVEF over 35% and only 33% of SCD patients having a LVEF less than or equal to 35% (4). This no doubt reflects the high number of patients with an LVEF under 35% who die of progressive HF rather than SCD. In addition, a substantial number of patients with an ICD and LVEF < 35% never see it deliver therapy during its lifetime. The ability to accurately stratify those patients with a low LVEF in whom an ICD is not indicated (discharge unlikely or CHF progression fatal) and those with a higher LVEF in whom it is (SCD likely) would minimise unnecessary health expenditure and decrease preventable deaths respectively. There is a paucity of literature examining the predictive capability of $^{123}$I-mIBG in the above 35% LVEF group.

Reliance on LVEF is a poor predictor of who does and does not need ICD. An LVEF greater than or equal to 30% with a delayed $^{123}$I-mIBG heart to mediastinum ratio greater than or equal to 1.60 is associated with zero deaths in the two year follow-up period (23). The same LVEF stratification, however, with a heart to mediastinum ratio less than 1.60 has a greater cumulative two year mortality than those with an LVEF less than 30% and a heart to mediastinum ratio greater than 1.60. Naturally, LVEF and a heart to mediastinum ratio lower than 30% and 1.60 respectively are associated with the greatest two year mortality. There is no specific line above or below which a decision can be made to use ICD or not. While the literature to date indicates $^{123}$I-mIBG to be a reliable and strong predictor of events, it does not provide sufficient discriminatory power to direct a decision to either offer ICD in those with a LVEF over 35% or to decline the ICD option in those with an LVEF below 35%. The discriminatory power is perhaps reduced due to the global approach to calculations. That is, cardiac autonomic neuropathy (CAN) progression begins in the inferior wall of the heart and progresses through adjacent myocardial walls (lateral and septal) before eventually reaching the anterior wall (30). Normal global uptake may reflect anterior wall uptake and fail to highlight early CAN in the inferior wall.
There is a need for further evaluation of the role of both planar and SPECT $^{123}$I-$m$IBG in stratification of heart failure patients. In particular, to more accurately identify patients with a LVEF less than 35% who are unlikely to benefit from the ICD and to identify those with an LVEF over 35% in whom ICD is likely to be life saving. This approach will result in a more cost effective heart failure management; both decreasing health care costs and increasing lives saved. This case highlights a patient eligible for ICD based on standard criteria but in whom the global and regional $^{123}$I-$m$IBG study suggest that ICD implantation is not ideal.

**Conclusion**

While $^{123}$I-$m$IBG imaging and global analysis provides a useful tool to direct appropriate HF treatment options in a patient eligible of ICD implantation, the discriminatory power of regional quantitation using SPECT data adds an important dimension that warrants further clinical investigation. While delayed H:M ratios provide improved stratification of HF patients over LVEF and HF classification, the washout rate provides an important marker for identifying more rapid disease progression and lower likelihood of a benefit from ICD. Further research is required for both global and regional quantitation in this patient group.
REFERENCES


Tables Legends

Table 1: NYHA and ACC/AHA classifications for heart failure. The arrows indicate the potential directions of stage progression for each. Horizontal alignment provides an indicator of corresponding stages between the two classifications.

Table 2: Global $^{123}$I-$m$IBG quantitative values from various studies.

Table 3: H:M and washout rates for optimistic and pessimistic approaches to region of interest placement. The tabulated data shows some variability, however, best and worst cases are consistent with a low risk H:M ratio and abnormal washout.

Table 4: Regional analysis on SPECT.

Table 5: Regional $^{123}$I-$m$IBG parameters determined by Zhao et al (26) using SPECT.
**Figures Legends**

Figure 1: Anterior lanar images demonstrating the global accumulation of $^{123}$I-mIBG in the myocardium at 15 minutes (A) and 4 hours (B) after injection. The red regions represent the standard global regions of interest while the blue regions are those modified and described above. Lung and liver regions are in purple. The images highlight the need for greater discriminatory power using SPECT. Nonetheless, it is apparent that the heart to mediastinum ratio is in the order of 2 and that there is marked washout at 4 hours.

Figure 2: Polar map demonstrating regional cardiac $^{123}$I-mIBG distribution at 15 minutes (left) and 4 hours (right) post IV administration. The arrows highlight areas of denervation that correspond to similar regions of hypoperfusion on the end diastolic polar map in the $^{99m}$Tc-MIBI study (figure 3) but show thickening and motion (figure 4).

Figure 3: Polar map demonstrating regional myocardial perfusion (%) at end diastolic (A) and end systolic (B). The polar maps show perfusion deficits in the inferior and inferolateral walls. The arrows highlight areas of decreased perfusion in the distal LAD region that correspond to similar regions of $^{123}$I-mIBG denervation (figure 3).

Figure 4: Polar map demonstrating regional myocardial thickening (A) and wall motion (B). The arrows highlight areas of decreased perfusion and denervation in the distal LAD region that show both thickening and motion. The septal paradoxical motion can be appreciated and the inferior and infero-lateral hypokinesia is also apparent.