What will be the role of I-123 MIBG in improving the outcome of medically treated heart failure patients?

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Heart failure (HF) remains the most common cause for hospital admissions in the Medicare age population.¹ In recent decades, major advances in medical treatment of HF patients have resulted in longer survival and improved quality of life. Randomized clinical trials have documented that beta-adrenergic blockers (β -blockers), angiotensin-converting enzyme inhibitors (ACE-inhibitors), angiotensin receptor blockers (ARBs), and aldosterone inhibitors have provided improved outcomes for HF patients. Although widely used, these medications have frequently not been used in the doses validated in large clinical trials. This likely reflects concerns about using the full doses of β -blockers in patients with baseline bradycardia and/or using increasing doses of β -blockers, ACE-inhibitors, or ARBs in patients with low baseline systolic blood pressure. Maximum benefit of pharmacologic therapy is limited by inadequate data for drug selection for individual HF patients and inadequate data documenting the optimal therapeutic target for blood pressure and heart rate.

Excessive activity of the sympathetic nervous system is a major contributor to HF progression, by increasing cardiac work, promoting myocardial fibrosis, and causing down-regulation of post-synaptic adrenergic receptors.² The impact of the sympathetic nervous system in HF patients can be assessed non-invasively by imaging cardiac neuronal uptake and retention of the norepinephrine congener, I-123 *metaiodobenzylguanidine* (I-123 MIBG). A growing literature addresses the

potential role of I-123 MIBG for identifying HF patients at high risk for sudden cardiac death, in whom implantation of a cardioverter-defibrillator may be life-saving.³ Relatively little attention has been focused on the potential role of I-123 MIBG in guiding medical therapy of HF and avoidance of HF progression. Therefore, this review focuses on the question of whether sympathetic cardiac neural imaging with I-123 MIBG has the potential to guide medical therapy of properly selected patients with advanced HF, thereby improving symptoms and outcome.

TARGET DOSES OF β -BLOCKERS

Treatment with β -blockers has been shown to reduce cardiac work, up-regulate post-synaptic adrenergic receptors,⁴ and with carvedilol, for example, reduce proliferation, possibly through antioxidant properties.⁵ β -blockers reduce the risk of death in patients with chronic HF (CHF).⁶⁻⁹ They are a mainstay of HF management for patients with stages B, C, or D HF. According to the ACC/AHA 2005 guideline update for the diagnosis and management of chronic HF, there are few contraindications to their use.¹⁰ More than 20 placebo-controlled trials recruiting over 20,000 patients have demonstrated the benefit of long-term β -blockers in improving symptoms and quality of life in HF patients as well as reducing mortality and the frequency of hospitalization.

In most of these trials, the administered doses of β -blockers were either based on a pre-set minimum cutoff value for systolic blood pressure or clinical evidence of maximum benefit, regardless of the resultant minimum systolic blood pressure (Table 1). Evidence suggests that the favorable response to β -blockers in HF patients is dose dependent. In the Multicenter Oral Carvedilol HF Assessment (MOCHA) trial, Bristow et al¹⁵ described a dose-dependant effect of carvedilol on 6-month mortality in patients with mild to moderate HF (Figure 1). Similar dose-related positive effects were seen on left ventricular ejection fraction (LVEF) as well as cardiovascular rehospitalization.

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This study is funded in part by the John R. Strauss Fund for Research and Education in Cardiac Imaging, Cincinnati, Ohio.

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J Nucl Cardiol 2012;19:1198–205.

1071-3581/\$34.00

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doi:10.1007/s12350-012-9612-z

Table 1. Initiation, target and mean doses of various β -blockers in major trials

Study (investigation drug)	Initiation dose	Target dose	Mean dose (mg/day)
CIBIS I (bisoprolol) ¹¹	1.25 mg daily	5 mg daily	3.8
US CHFS (carvedilol) ⁶	6.25 mg BID	25-50 mg BID	45
CIBIS II (bisoprolol) ⁷	1.25 mg daily	10 mg daily	8.5
MERIT-HF (metoprolol CR/XL) ⁸	12.5-25 mg daily	200 mg daily	159
MDC (metoprolol) ¹²	5 mg BID	75 mg BID	108
CAPRICORN (carvedilol) ¹³	6.25 mg BID	25 mg BID	44
COPERNICUS (carvedilol) ¹⁴	3.125 mg BID	25 mg BID	37

CIBIS, The Cardiac Insufficiency Bisoprolol Study; US CHFS, US Carvedilol Heart Failure Study; MERIT-HF, Metoprolol CR/XL Randomized Intervention trial in Congestive Heart Failure; MDC, Metoprolol in Dilated Cardiomyopathy trial; CAPRICORN, the Carvedilol Post-Infarct Survival Control in LV Dysfunction trial; COPERNICUS, the Carvedilol Prospective Randomized Cumulative Survival study; BID, twice daily.

Figure 1. Six-month mortality among HF patients receiving placebo and incremental doses of carvedilol (Bristow et al.¹⁵). Used with permission from Circulation.

TARGET DOSES OF ACE-INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS

Pharmacologic inhibition of the renin-angiotensin system can be achieved via inhibition of conversion of angiotensin I to angiotensin II (ACE-inhibitors) or blockade of angiotensin receptors (ARBs). A meta-analysis of randomized, placebo-controlled trials, assessing over 7,000 patients with varying degrees of left ventricular (LV) dysfunction, showed improvement in cardiovascular outcome and mortality with the use of ACE-inhibitors.¹⁶ However, patients with low blood pressure (<90 mm Hg systolic) and/or impaired renal function (serum creatinine >2.5 mg/mL) were commonly excluded from these studies.¹⁷⁻²²

What are the target doses (Table 2) of ACE-inhibitors in treating HF? In most clinical trials studying ACE-inhibitors, the dose was not determined by a patient's therapeutic response but was increased until a pre-set target dose was reached.^{21,22,27} In clinical practice,

however, these drugs are often prescribed at lower than recommended maintenance doses. In the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial,²⁸ which is one of the few major studies comparing the effect of low and high doses of ACE-inhibitors on clinical outcome, a non-significant improvement in mortality but a significant decrease in hospitalization for worsening HF ($P = .002$) as well as improvement in combined end point of death or hospitalization ($P = .002$) was noted in the high-dose lisinopril group compared to the low-dose group. In another major trial, NETWORK,²⁹ low, medium, and high doses of enalapril showed similar effects on a combination of death, HF-related hospitalizations, and worsening HF symptoms as the primary endpoint. Other studies have compared low- and high-dose ACE-inhibitors but are substantially limited compared to ATLAS and NETWORK in terms of statistical power to assess mortality and outcome.³⁰⁻³² Overall, these trials demonstrate a potential advantage of higher doses in terms of improved symptoms and reduced frequency of hospitalizations, but do not provide conclusive proof that higher doses improve survival. These results may have led to less aggressive recommendations and guidelines regarding titration of ACE-inhibitors and ARBs in HF patients as compared to β -blockers.³³ As for ARBs, the candesartan in HF: Assessment of Reduction in Mortality and Morbidity (CHARM) study reported significant but similar improvement in outcome with low, medium, and high doses of candesartan.²⁶

From these and other studies, it is apparent that β -blockers, ACE-inhibitors, and ARBs have provided substantial benefits for HF patients in clinical trials. It is not clear that the full benefits of these agents are provided when they are used in reduced doses compared to the doses used in the major clinical trials. In a study of HF subjects treated in an outpatient setting, Peters-Klimm et al³⁴ found that 75% of patients received β -blockers and 80% received an ACE-inhibitor or ARB.

Table 2. Initiation, target and mean doses of various ACE-inhibitors and ARBs in major trials

Study (investigation drug)	Initiation dose	Target dose	Mean dose (mg/day)
SAVE (captopril) ²³	12.5 mg TID	50 mg TID	N/A
CONSENSUS (enalapril) ²²	2.5 mg daily	40 mg daily	18
SOLVD Prevention (enalapril) ²⁴	2.5 mg daily	20 mg daily	16
SOLVD Treatment (enalapril) ²¹	2.5 mg daily	20 mg daily	11
AIRE (ramipril) ²⁵	2.5 mg BID	5 mg BID	N/A
CHARM (candesartan) ²⁶	4 mg daily	32 mg daily	N/A

SAVE, The Survival and Ventricular Enlargement trial; CONSENSUS, the Cooperative North Scandinavian Enalapril Survival Study; SOLVD, Studies of Left Ventricular Dysfunction; AIRE, the Acute Infarction Ramipril Efficacy study; CHARM, the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity program.

Nevertheless, adherence to guideline recommendations for target therapeutic dose was only accomplished in 8% of patients for β -blockers and 16% for an ACE-inhibitor or ARB. Even with adjustment for contraindications for drug therapy, including chronic obstructive lung disease, hypotension, hyperkalemia, and renal dysfunction, only 46% of HF patients received β -blockers and 49% received ACE-inhibitors or ARBs in the targeted doses. Thus, inadequate HF drug dosing may be a common problem faced when trying to optimize HF therapy. This suggests a potentially important role for testing that could provide a metric to determine which drug is the most important to maximize in the patient with low baseline systolic blood pressure and what level of blood pressure lowering provides benefit, whereas further blood pressure lowering may be detrimental. Imaging the response of cardiac sympathetic nerve function to therapy may provide this type of metric.

I-123 MIBG UPTAKE IN HF PATIENTS REFLECTS CARDIAC SYMPATHETIC NERVE ACTIVITY AND IMPROVES FOLLOWING TREATMENT WITH β -BLOCKERS, ACE-INHIBITORS, AND ALDOSTERONE INHIBITORS

Background of I-123 MIBG-Based Imaging

Sustained hyperactivity of the cardiac sympathetic nervous system observed in HF is a consequence of increased central sympathetic outflow, altered neuronal norepinephrine (NE) reuptake, and facilitation of cardiovascular response to sympathetic stimulation by angiotensin II. Myocardial beta-adrenoceptor density is reduced in patients with HF. With progressive HF, there is reduced uptake of NE into presynaptic cardiac nerve storage vesicles via the NE uptake-1 transporter. Chronic over-exposure of post-synaptic beta-adrenergic receptors on the cardiomyocyte to NE in the synaptic

cleft results in beta-receptor desensitization and eventual catabolism and loss of beta-receptors.

I-123 MIBG is the most widely used imaging agent for studying cardiac sympathetic hyperactivity. Uptake of I-123 MIBG into presynaptic sympathetic neurons occurs through the same uptake-1 transporter mechanism responsible for the reuptake of NE. Reduced function of the uptake-1 mechanism may lead to abnormally high levels of catecholamine in the synaptic cleft.

After intravenous injection of I-123 MIBG, early (20 minutes) and late (4 hours) planar and SPECT images are obtained.³⁵ In addition to visual analysis of the images, a heart-to-mediastinum ratio (HMR) can be calculated as shown in Figure 2. The I-123 MIBG washout (WO) rate from the myocardium can be calculated using early and delayed images. The effective dose resulting from an administered activity of 10 MCi (370 MBq) is 4.8 mSv, so the activity from serial doses is consistent with dosing from a single rest/stress Tc-99m myocardial perfusion scan.

Imaging of Cardiac Adrenergic Activity as Predictor of Outcome

Many studies have demonstrated that impaired cardiac adrenergic innervation assessed by I-123 MIBG imaging is strongly related to adverse cardiac events and mortality in patients with HF.³⁶ The AdreView Myocardial Imaging for Risk Evaluation in HF (ADMIRE-HF) trial³⁷ evaluated 961 HF patients (NYHA class II-III, LVEF < 35), using a prospectively selected HMR of 1.6 to separate low- from high-risk patients. The combined adverse event rate was found to be 15% for patients with an HMR $\geq$ 1.6 and 37% for HMR < 1.6 (hazard ratio [HR] 0.40, $P < .001$). A late HMR $\geq$ 1.6 was independently associated with a reduced risk for HF progression (HR 0.49, $P = .002$), cardiac death (HR 0.14, $P = .006$),

Figure 2. Normal (A) and reduced (B) heart-to-mediastinum ratio (HMR).

and potentially life-threatening arrhythmic events (HR 0.37, $P = 0.02$).

Cardiac I-123 MIBG Imaging in Predicting Effect of Medical Therapy

As clinical status and LV function improve in response to β -blockers, ACE-inhibitors, ARBs, and/or aldosterone antagonists, there is a parallel improvement in cardiac sympathetic nerve function as assessed by I-123 MIBG. In 30 NYHA class II or III HF patients treated with 16 ± 4 mg/day of carvedilol for 12 ± 1 months, Kasama et al.³⁸ noted that an improvement from baseline in B-type natriuretic peptide from 270 ± 249 to 148 ± 125 ($P = .002$) and in LVEF from 33 ± 6 to 39 ± 6 ($P = .003$) was paralleled by an improvement in late I-123 MIBG HMR from 1.66 ± 0.16 to 1.88 ± 0.23 ($P < .001$). Similar concordant improvement in cardiac sympathetic nerve function with improvement in clinical status and/or LVEF has also been observed in response to treatment with metoprolol,³⁹ carvedilol,^{40,41} bisoprolol,⁴² enalapril,⁴³ candesartan,⁴⁴ and spironolactone.⁴⁵

Improvement in LVEF in response to β -blocker therapy has been documented in HF patients with a broad range of baseline sympathetic neural impairment.⁴⁶ For an individual HF patient, the cardiac sympathetic neural response to drug intervention may provide insight into the amount of benefit provided compared to other HF treatments. Neural imaging studies may have a role in differentiating patients likely to benefit from medical therapy from those that are likely to show poor long-term response and thus might be better candidates for non-medical therapy (e.g., device therapy and cardiac transplantation). Furthermore, neural imaging may help identify patients in whom aggressively increasing medical

therapy, despite mild hypotension or other mild side effects, might produce a more favorable clinical outcome.

WHAT IS THE LOWER LIMIT OF SYSTEMIC BLOOD PRESSURE THAT SHOULD BE TARGETED WITH β -BLOCKERS, ACE-INHIBITORS, AND ANGIOTENSIN RECEPTOR BLOCKERS?

The majority of HF trials have used arbitrary lower limits of systemic blood pressure (e.g., 85–100 mm Hg) to determine the target therapeutic dose, without clear evidence of poorer outcome at lower systolic blood pressures. On the other hand, evidence of worsened outcome with or without treatment in HF patients with low systolic blood pressure has been well established.⁴⁷

Because adrenergic stimulation plays an important role in maintaining both blood pressure and cardiac contractility in patients with impaired LV systolic function, the administration of adrenergic blocking drugs can cause both hypotension and worsening HF. The risk of these adverse circulatory reactions is most marked in patients with the lowest BP or most advanced disease before treatment.⁴⁸ Such patients have generally responded poorly to treatment and have frequently been excluded from participation in clinical studies using beta-blocking drugs.^{7,8} An important exception is the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study^{9,14} that evaluated the effects of carvedilol in patients with severe HF, including those with a very low SBP (85–100 mm Hg). This study demonstrated a reduction in the risk of death ($P = .0014$) and combined risk of death or hospitalization ($P < .001$) in these patients using carvedilol, but did not explore whether pretreatment BP influenced the presence or magnitude of these benefits. A follow-up

study by Rouleau et al.⁴⁷ confirmed that progressively lower systolic blood pressure is associated with progressively worse outcomes. Nevertheless, β -blocker therapy improved outcome significantly for patients across the range of baseline systolic blood pressures. The benefits of beta-blockade appeared to be the greatest in the patients with chronic stable HF with the lowest baseline blood pressure. Baseline systolic BP does not appear to be a determinant of the response to ACE-inhibitors¹⁶ or ARB's in large-scale trials. In the CHARM study, similar improvement in outcome with low, medium, and high doses of candesartan was observed regardless of baseline systolic blood pressure.²⁶

BY ASSESSING IMPACT ON SYMPATHETIC NERVOUS SYSTEM FUNCTION AS ASSESSED BY I-123 MIBG IMAGING, CAN AN OPTIMAL TARGET SYSTEMIC BLOOD PRESSURE BE IDENTIFIED FOR β -BLOCKER, ACE-INHIBITOR, AND ALDOSTERONE ANTAGONIST THERAPIES?

The benefits of therapies that ameliorate the effects of neurohormonal imbalance in the failing heart are well established. For patients who respond well to HF therapy with full therapeutic doses of β -blockers, ACE-inhibitors or ARBs, and aldosterone antagonists, there is currently no potential advantage to an addition of neural imaging to monitor the response to proven therapy. Yet, it is clear that a significant proportion of HF patients are not receiving full, proven-to-be-effective doses of these HF drugs due to concerns about resultant hypotension. Although it is known that low baseline systolic blood pressure portends an adverse prognosis in HF patients, it is not clear to what extent doses of proven HF drugs should be up-titrated to improve prognosis in these patients. In the patient with a baseline systolic blood pressure of 95 mm Hg, does the outcome improve or worsen when a β -blocker, ACE-inhibitor, or ARB is increased and the blood pressure falls to 85 mm Hg? The symptomatic response of the patient may determine the treatment endpoint in some patients, but in patients who remain asymptomatic or minimally symptomatic, the blood pressure endpoint on treatment is often undefined. Does cardiac sympathetic innervation and activity improve or worsen as HF drug therapy is maximized to relatively low (e.g., <90 mm Hg) systolic blood pressure levels? By identifying the target blood pressure that maximizes sympathetic nerve function, can HF outcome in response to medical therapy be optimized?

Alternative Methods for Assessment of Cardiac Sympathetic Neuronal Function in HF Patients

Elevated plasma norepinephrine levels are associated with increased sympathetic nervous system function and unfavorable outcomes in HF patients.⁴⁹ Serial measurements might provide a method for assessing the response of the sympathetic nervous system to selection and dosing of HF medications, but have not entered into wide clinical use. Plasma norepinephrine levels are altered by a wide variety of physical and emotional stimuli that affect norepinephrine release, as well as changes in cardiac output and regional blood flow that vary the rate of removal of norepinephrine from the plasma.⁵⁰ Heart rate variability is an indirect method for assessing cardiac sympathetic nerve activity and has been associated with HF outcomes in several studies.⁵¹ Reduced heart rate variability reflects sympathetic autonomic activity, but is also influenced by parasympathetic tone, chemoreceptor function, respiratory rate and tidal volume, mechanical factors (e.g., stretch of the atria from changes in cardiac filling and thoracic pressure), and level of physical activity. These multiple variables affecting heart rate variability, as well as the technical limitations in heart rate variability measurement, limit its potential to detect changes in cardiac sympathetic activity that may alter response to adjustment of medical therapy.^{52,53} In studies directly comparing heart rate variability to I-123 MIBG imaging, I-123 MIBG imaging was predictive of all-cause mortality⁵⁴ and for either cardiac death or hospitalization for HF,⁵⁵ whereas heart rate variability was not.

Cardiopulmonary exercise testing, with measurement of maximum oxygen consumption (VO_2 max), and the 6-minute walk do not focus specifically on cardiac sympathetic neuronal activity, but are well-validated and accepted procedures for measuring the functional response to HF treatment. These tests are important comparators for future studies to assess a potential role of serial neuronal imaging in the assessment of clinical response to modifications in HF therapy.

WHAT IS NEEDED TO VALIDATE A MEANINGFUL ROLE OF CARDIAC NEURONAL IMAGING IN THE SELECTION OF MEDICAL THERAPY AND OPTIMAL THERAPEUTIC DOSES IN HF PATIENTS?

- (1) It must be determined if the reproducibility of the I-123 MIBG HMR measurement is adequate to accurately identify a significant change in response to a selection of medication or dose adjustment. The

HMR is highly reproducible in normal subjects,⁵⁶ however, HF subjects have low I-123 MIBG cardiac count statistics and HMR reproducibility is not well established. Nevertheless, the studies cited earlier show an increase in HMR in response to known effective HF drugs, indicating that improvement in neural function by HMR is measureable with I-123 MIBG. Whether these demonstrable changes in HMR reported in populations of HF patients will be paralleled by demonstrable changes in HMR in response drug dose changes in individual HF patients remains to be proven.

- (2) The hypothesis requires testing that I-123 MIBG can identify differences in neuronal function in HF patients treated to moderate treatment goals (e.g., systolic blood pressure 95–105 mm Hg with no symptoms) versus aggressive goals (e.g., systolic blood pressure 85–95 mm Hg and/or mild symptoms).
- (3) The hypothesis also requires testing that patients with LVEF $\leq 35\%$ and NYHA class II or III HF randomized to I-123 MIBG guided medical treatment have improved survival compared to patients treated by guidelines-based conventional HF treatment alone.
- (4) Similarly, testing is needed to determine if severe HF patients with a poor versus favorable neuronal response to maximal medical therapy have a more favorable outcome with left ventricular assist devices compared to continued medical therapy alone.

With the growing burden of HF in our society, improving outcomes by optimizing HF medical therapy is a priority, and measuring the response of the cardiac sympathetic nervous system to treatment may help provide answers to difficult therapeutic questions.

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