^{123}I-Metaiodobenzylguanidine Imaging in the Era of Implantable Cardioverter Defibrillators: Beyond Ejection Fraction

Sudden cardiac death (SCD) due to lethal arrhythmia represents an important health-care problem in many developed countries. In the United States, for example, the annual death rate of SCD is reportedly much greater than that of AIDS, lung cancer, breast cancer, or stroke (*1*). Therefore, numerous efforts have been made to develop therapeutic options to reduce SCD mortality, including new antiarrhythmic drugs such as amiodarone and catheter ablation of arrhythmic substrates. Implantable cardioverter defibrillators (ICDs) have emerged as novel devices to prevent SCD (*2*). Large clinical trials, such as The Sudden Cardiac Death in Heart Failure Trial, have demonstrated that ICD therapy is more effective than any antiarrhythmic medications including amiodarone and can reduce the mortality rate by as much as 23% (*3,4*). Thus, ICD therapy has gained wide clinical acceptance and is therefore increasingly used together with the development of newer ICD devices.

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CURRENT INDICATION FOR ICD THERAPY AND PROBLEMS

Current indications for ICD therapy (*5,6*) have been based on the results of large randomized trials mainly involving heart failure (HF) patients with depressed left ventricular ejection fraction (LVEF); observational studies including patients with ICD; and observational studies or expert opinion based on scientific viewpoints, particularly in less common arrhythmogenic diseases such as hypertrophic cardiomyopathy, Brugada syndrome, arrhythmogenic right ventricular dysplasia (ARVD), and long QT syndromes, for which a large-scale prospective trial is difficult to perform (*7*). Generally accepted criteria for ICD therapy include severely depressed LVEF (<30%–40%) in patients with coronary heart disease, history of cardiac arrest due to ventricular arrhythmias, sustained ventricular tachycardias, positive electrophysiologic testing, and the like (*5,6*). However, the current criteria for ICD therapy in the guidelines are frequently updated (*6*), at least in part because these criteria are still not satisfactory in view of clinical benefit, efficacy, or risk balance. In fact, most patients who die from SCD actually have a low-risk profile and are missed for diagnosis by the current criteria (*1,7,8*). Unfortunately, SCD is often the first manifestation of the underlying disease in such patients. Furthermore, the current LVEF-based criteria inherently miss the diastolic HF patients with preserved LVEF, whose prognosis is not necessarily benign (*9*). Conversely, there are several patients with ICD placement in whom appropriate ICD shocks were never delivered during the observation period of years or who died from progression of pump failure and not from lethal arrhythmic events (*1,7,8*). In addition, the harmful effects of ICD (*8*)—such as unnecessary ICD shocks, hardware malfunction, and a higher risk for anxiety and depression (*10*), resulting in degradation of overall quality of life—are important as well. Thus, we still need a better strategy to identify high-risk patients for SCD who are most likely to benefit from ICD therapy (*11*).

THE ROLE OF NUCLEAR IMAGING

From a pathophysiologic viewpoint, nuclear imaging techniques are acknowledged as indispensable diagnostic tools for risk stratification (*12*). Using such imaging techniques, we can measure, for example, myocardial perfusion, left ventricular function by electrocardiogram gating, myocardial viability, metabolism, and cardiac sympathetic neuronal integrity. To date, much of our experience has been focused on myocardial perfusion SPECT. Numerous studies (*13,14*) have consistently demonstrated that an abnormal myocardial perfusion SPECT result is predictive for future cardiac death, including SCD. In particular, the total amount of scar tissue and ischemic myocardium, as reflected by summed stress score on stress myocardial perfusion SPECT, is related to SCD, as demonstrated in a study by Piccini et al. (*15*). From a pathologic viewpoint, a viable but hibernating myocardium is also a strong substrate for lethal ventricular arrhythmias (*16*).

SYMPATHETIC NEURONAL IMAGING

A strength of nuclear imaging over structural imaging such as CT is that it can touch on biologic and molecular

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process at a cellular level. Radiolabeled catecholamine analogs—such as ^{123}I-metaiodobenzylguanidine or ^{11}C-hydroxyephedrine—are taken up into the cardiac sympathetic neurons mainly via uptake-1, in a manner similar to that for norepinephrine; are not metabolized; and thus mark the location of functioning nerve terminals. Hence, the assessment of tracer uptake allows the unique characterization of alterations in cardiac sympathetic nerve function.

There is a general agreement that the autonomic nervous system plays an important role for the pathogenesis of HF (*17*) and lethal ventricular arrhythmias (*18*). In this regard, noninvasive sympathetic nerve imaging of the heart is expected to provide important prognostic information in such patients. Using planar ^{123}I-metaiodobenzylguanidine imaging, Merlet et al. were the first to describe its predictive value in HF patients in 1992 (*19*). In that study, a late ^{123}I-metaiodobenzylguanidine heart-to-mediastinum ratio (HMR) of less than 1.2 as an index reflecting cardiac sympathetic neuronal integrity and sympathetic drive (*20*) was the most powerful predictor of cardiac death beyond LVEF. Since then, several studies have shown that low ^{123}I-metaiodobenzylguanidine HMR or accelerated washout rate, as an index of cardiac sympathetic nerve tone, was associated with poor prognosis in HF patients (*20–23*). In particular, a recent large multicenter study (ADMIRE-HF) (*24*) involving 961 patients with HF (LVEF $\leq$ 35%) demonstrated that the low ^{123}I-metaiodobenzylguanidine HMR was the predictor of not only cardiac death but also lethal arrhythmic events, suggesting the potential use of ^{123}I-metaiodobenzylguanidine imaging for better selection of ICD candidates. The value of ^{123}I-metaiodobenzylguanidine for prediction of lethal arrhythmia has also been tested in patients with ICD placement, in whom detailed information on arrhythmic events is easily available. Nagahara et al. (*25*) demonstrated that ^{123}I-metaiodobenzylguanidine HMR combined with plasma brain natriuretic peptide were predictive for arrhythmic events.

In this issue of *The Journal of Nuclear Medicine,* Nishisato et al. (*26*) introduce a new strategy using the combination of planar ^{123}I-metaiodobenzylguanidine and myocardial perfusion SPECT for the prediction of lethal arrhythmic events in patients with ICD placement. They consecutively recruited 60 patients, and the endpoint was set as an appropriate ICD shock with an average follow-up period of 29 mo. The major finding of this study was that, among various clinical and scintigraphic variables tested, the impaired uptake of both ^{123}I-metaiodobenzylguanidine (late HMR $\leq$ 1.9) and ^{99m}Tc-tetrofosmin (summed defect score $\geq$ 12 on resting SPECT) was the most predictive for ICD shock, whereas the preserved uptake of both ^{123}I-metaiodobenzylguanidine and ^{99m}Tc-tetrofosmin was predictive for benign prognosis. Surprisingly, when ^{123}I-metaiodobenzylguanidine and ^{99m}Tc-tetrofosmin variables were considered, neither LVEF nor plasma brain natriuretic peptide level was any longer the determinant of ICD shock, indicating that the imaging-based strategy of Nishisato et al. (*26*) may be of clinical significance beyond LVEF or brain natriuretic peptide measurements. As compared with other published data on the use of ^{123}I-metaiodobenzylguanidine imaging, this study is unique in at least 2 aspects. First, unlike most of the prior ^{123}I-metaiodobenzylguanidine or ICD studies, this study mainly involved patients with relatively preserved LVEF (mean, 49%). Nevertheless, the overall event rate was high (50%), indicating that ICD was really necessary in this cohort. The ^{123}I-metaiodobenzylguanidine–perfusion combination worked well also, even when the patients with normal LVEF (>50%) were separately analyzed. Second, unlike most of the prior studies involving rather homogeneous patient cohorts, the study of Nishisato et al. (*26*) involved patients with various underlying diseases including coronary heart disease, dilated cardiomyopathy, Brugada syndrome, and arrhythmogenic right ventricular dysplasia, reflecting real-world clinical practice, as the authors acknowledge. Thus, if the results were validated in further studies, the imaging-based strategy could be applied irrespective of underlying diseases or LVEF.

QUESTIONS TO BE ADDRESSED AND CONCLUSION

There are several issues to be addressed before this new imaging method for planning ICD placement can come into widespread clinical use. First, the cost required for ^{123}I-metaiodobenzylguanidine and myocardial perfusion SPECT should be justified in light of the benefits of this method. According to the data presented in this study (Fig. 2 in the study of Nishisato et al. (*26*)), the patients with a summed defect score of 12 or greater on ^{99m}Tc-tetrofosmin SPECT are likely to be associated with low ^{123}I-metaiodobenzylguanidine HMR, suggesting that ^{123}I-metaiodobenzylguanidine imaging may not be necessary in this group. Furthermore, more easily accessible and less costly testing such as an electrocardiogram-based strategy should be established for selecting patients undergoing the imaging-based strategy. Second, although an appropriate ICD shock is considered a surrogate marker for SCD, it does not necessarily represent actual SCD, as demonstrated by Ellenbogen et al. (*27*). Third, regional heterogeneity in sympathetic innervation was not assessed in the study of Nishisato et al. (*26*) because of low cardiac ^{123}I-metaiodobenzylguanidine uptake in some patients, in whom high-quality SPECT images are difficult to obtain. It has been shown that myocardial infarction creates sympathetic neuronal damage exceeding the area of necrosis (*28*), and such denervated area may be related to electrical instability (*29,30*). Such regional variation of presynaptic sympathetic function may be better addressed by PET using tracers for sympathetic innervation (*31*).

Despite these unresolved questions, the study of Nishisato et al. (*26*) provides a rationale for further studies investigating the role of nuclear imaging for better selection of ICD candidates beyond LVEF measurements.

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