I-123-MIBG cardiac innervation imaging in patients with atrial fibrillation

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Atrial fibrillation (AF) is a supraventricular tachyarrhythmia with uncoordinated atrial activation and consequently ineffective atrial contraction.[1] AF is one of the most important health problems in developed countries, with the prevalence of approximately 3% in adults aged 20 years or older, significantly increasing with advancing age. It is associated with an increased risk of stroke (five-fold), heart failure (three-fold), and dementia (two-fold). This arrhythmia is independently associated with nearly a two-fold increased risk of all-cause mortality, especially cardiovascular mortality due to sudden death, heart failure, or stroke.[1,2]

AF occurs when structural and/or electrophysiological abnormalities alter atrial tissue to promote abnormal impulse formation and/or propagation. A focal source in the pulmonary veins (PVs) can trigger AF, and ablation of this source can suppress recurrent AF, what led to the development of pulmonary vein isolation (PVI) as the foundation for radiofrequency catheter ablation methods. Although the PVs are the most common sites for ectopic focal triggers, experimental and clinical studies have shown that the intrinsic cardiac autononomic nervous system (CANS) plays an important role in the initiation and maintenance of AF. The system primarily includes thousands of autonomic neurons and nerves located in ganglionated plexuses (GPs), which are located in the epicardial fat pads. There are 7 major GPs, including 4 located in the left atrium (LA) around the PVs. However, the usefulness of ablation of autonomic ganglia as an initial or repeat ablation strategy for paroxysmal, persistent, and long-standing persistent AF is not well established. The effectiveness of ablation of GPs in patients with AF remains controversial and one of the major reasons can be the lack of an efficient method to localize the GPs. The standard approach is to apply high-frequency stimulation (HFS) to the presumed GP areas to induce their typical vagal reaction (i.e., elicit AV block). As HFS has low specificity and sensitivity, is invasive and time consuming, better methods for localization of GPs are needed.[1–3]

The adrenergic part of CANS can be evaluated with I-123-metaiodobenzylguanidine (MIBG), which is a norepinephrine analog and a tracer for sympathetic neuron integrity and function.[4] MIBG imaging has been performed to assess patients with AF, for: (1) the prognosis of patients with paroxysmal atrial fibrillation (PAF)[5,6]; (2) the prediction of outcome of catheter ablation of AF [7,8]; and (3) evaluation of denervation/renervation after AF ablation.[8,9]

In patients with PAF and without structural heart disease, CAS abnormality defined as reduced H/M ratio from planar MIBG delayed imaging was a predictor of vascular events (myocardial infarction, stroke, or heart failure) during a mean of 4.5 years follow-up. Therefrom, MIBG imaging in this group of patients could support clinical risk stratification.[5] In a group of patients with first occurrence of PAF, the same investigators identified a reduced H/M ratio as a predictor for the development of permanent AF during a mean of 4 years follow-up. Hence, MIBG imaging may be a useful modality for predicting the development of AF.[6] If the use of planar MIBG scintigraphy to risk stratify patients with PAF is wider validated, this widely available method can improve patient selection for AF ablation. The expensive and complicated ablation technique could potentially be avoided in patients who would derive little or no benefit.[10]

Arimoto et al. demonstrated that a high global washout rate of MIBG (calculated in a stable sinus

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rhythm condition 5 days after PVI) is an independent predictor of AF relapses during a mean follow-up period of 14 months in patients with either paroxysmal or permanent AF. These results indicate that excessive sympathetic nervous activation may be one of the mechanisms of AF recurrences, and the evaluation of the cardiac nerve activity using planar MIBG scintigraphy shortly after the AF ablation may be a promising tool to predict the patient's outcome.[7] Wenning et al. performed planar and SPECT MIBG imaging in a small group of 16 PAF patients before and 4 weeks after PVI. For the short-term follow-up (6 months), the results suggested that the presence of regional innervation defects after PVI on MIBG SPECT images may be indicative for the risk of AF relapses.[8]

MIBG SPECT allows assessment of the impact of AF ablation on ventricular myocardial innervation. The study performed by Wenning et al. showed the deterioration of left ventricular (LV) MIBG uptake after PVI, observed in SPECT images performed 4 weeks after the ablation procedure, in 10 of 16 (63%) PAF patients.[8] In the study performed by Lemery et al. on 5 patients (4 with PAF and 1 with persistent AF), radiofrequency ablation targeted LA GPs identified by HFS, in addition to PVI. The planar and SPECT MIBG imaging was performed before, early (1–8 days), and late (3–4 months) after ablation. Ventricular myocardial post-ablation denervation was documented in all patients and persisted at least 3–4 months post-ablation.[9] For AF ablation procedures it had been shown that successful elimination of AF usually involves various degrees of denervation of the LA. Association of catheter ablation, which is technically performed in the LA area (PVs ostia, GPs), with modifications of autonomic tone in the LV, is obvious: intrinsic CANS is a distributed network of ganglia and interconnecting nerves, and sympathetic postganglionic somata in each intrinsic cardiac GP project axons to widespread regions of the heart.[11] The studies by Wenning et al. and by Lemery et al. proved for the early stage after AF ablation that by conventional planar and SPECT MIBG imaging 'the autonomic footprint left by atrial ablation could be visualized in the ventricle'.[9] It was not explored by Wenning or by Lemery how long this effect is maintained over 4 months. Observing another serious intervention on the heart, LV adrenergic reinnervation appeared approximately 6 months after transmyocardial laser revascularisation (TMLR) in the assessment by MIBG SPECT. Although TMLR-induced impairment of CANS could contribute to the clinical improvement shortly after the procedure, the good clinical effect was lasting for years, what was linked to another involved process-increasing angiogenesis.[12] In patients after heart transplantation (HTx), sympathetic reinnervation of cardiac allografts was in large part evaluated by norephinephrine analogs scintigraphy and it proved to be partial, heterogeneous, occurring in some but not all recipients (mostly at around 2 years, but in some patients as early as 5-6 months after HTx), never reaching global cardiac reinnervation.[13] For AF ablation, in a randomized study it had been shown, that GP ablation can improve clinical outcomes (freedom from AF) up to 24 months after the sole procedure in 48% of patients and after the adjunct to PVI in 74%.[14] Effects of circumferential PVI on cardiac autonomic function were assessed by deceleration and acceleration capacity of heart rate and immediate decrease of autonomic function persisted after PVI for at least 1 year.[15] The long-term (> 2 years) clinical outcomes and innervation results of GPs ablation have not been studied and whether reinnervation causes recurrent AF post-ablation remains uncertain.[16] The dynamics of changes over time in LV innervation after AF ablation can be tracked with MIBG as it was shown by Wenning and Lemery[8,9] and it could be related to AF relapses.

The papers dedicated to AF disease and MIBG, as selected above, technically were not based on the measurements performed in the atrial region solely. They included planar studies of the global cardiac sympathetic activity and SPECT applied as a tool of LV and not atria sympathetic activity assessment. Similarly, a new generation of cardiology dedicated cadmium zinc telluride (CZT) SPECT cameras have been applied in patients with AF for global and LV cardiac assessment.[17] Solid-state technology offers significantly improved imaging parameters, including sensitivity and spatial resolution, allowing high quality SPECT imaging with spatial resolution approximately twice better than in SPECT based on classical Anger scintillation detector (about 5 mm vs $\geq$ 10 mm).[18] This suggests that CZT SPECT has the potential to identify the small structures, like GPs located on the atrial epicardium, which typically measure 5-10 mm. The results of CZT SPECT studies of atria, particularly in GP diagnostics in patients with AF, have not been published but few congress abstracts (always with involvement of Royal Brompton Hospital, London, United Kingdom, like in the case of discussed study), and a case report written by the other group.[19]

In this issue of the Journal, Stirrup et al. have addressed the usefulness of cardiac MIBG scintigraphy for non-invasive identification of LA GPs.[20] It would be of clinical importance for the ablation of the plexi, as a potential add-on to PVI in patients with PAF, if MIBG SPECT could replace invasive HFS technique with its well recognized limitations for GPS identification. The idea behind the presented method is that localization of GPs by invasive multi-site testing HFS, a process that identifies GPs by their typical parasympathetic response

of slowing atrio-ventricular nodal conduction, and non-invasive imaging of LA sympathetic innervation by MIBG, might identify the same areas, as sympathetic and parasympathetic fibers co-localize in GPs. The work of Stirrup et al. is a complex, all-encompassing approach to introduction of a relatively young technology (CZT SPECT-CT) to the new clinical applications (LA GPs ablation). Phantom studies of specific design preceded clinical studies to demonstrate feasibility of the technique and to establish the methods for image acquisition and interpretation. Thereafter, in the pilot group of 20 patients with AF, the validating assessment of the technique, including inter- and intra-observer variability and inter-study variability, was carried on. Finally, correlation with HFS was performed. The study is elegant and the achieved results are encouraging. The proposed diagnostic approach is built on demanding hardware and software supporting the CZT SPECT ('D-SPECT') imaging. First, high-resolution reconstruction was necessary for imaging GPs: a very good D-SPECT resolution (5.6 mm) yielded by standard iterative reconstruction, may be a borderline resolution for identification of subcentimeter size GPs (0.5-1 cm). Therefore, the high-resolution reconstruction algorithm was developed and validated on the NEMA resolution phantom for MIBG data, leading up to the resolution of 3.9 mm. Second, simultaneous cardiorespiratory gating using a dedicated device was needed as well as software upgrade to allow processing minimizing the effects of motion on spatial localization of MIBG uptake. Third, the necessary images and calculations were generated by a dedicated workstation (SUMO D-SPECT). SUMO optional application enables assessment of the sympathetic innervation of the heart by quantification of uptake ratios between regions of interest, identifying discreet uptake areas (DUAs) of MIBG. In SUMO, the nuclear data from D-SPECT can be effectively coupled with CT scans and with physiological signals. Following registration, the semi-automatically CT-derived LA segment is used as an anatomical constraint to define a region of search (ROS) around the LA endocardium to facilitate identification of focal MIBG uptake adjacent to the atria. Focal increased MIBG activity within the ROS is automatically overlaid on the CT-derived LA surface, generating a hybrid 3D image of LA innervation and anatomy. The results of the study showed, that MIBG solid-state SPECT LA innervation imaging identifies GPs verified by HFS with good accuracy and reproducibility, particularly when reconstructed with cardiorespiratory gating. However, DUAs identified over the lateral and inferior LA walls were less likely to be HFS positive, probably due to difficulty in distinguishing true LA epicardial activity from activities in neighboring structures.[20]

The usefulness of ablation of autonomic ganglia as an initial or repeat ablation strategy for AF is not well established, as the results of randomized studies are not unequivocal. Further studies are needed to better understand the role of GPs ablation for rhythm control. As timing and extent of reinnervation is dependent on the extent of denervation, and as reinnervation is not an isolated effect of the denervating intervention on the heart, long-term clinical benefits of GPs ablation are to be investigated. Regardless of a clinical settlement to the on-going dispute, the study by Stirrup et al. has shown the possibilities of CZT SPECT-CT using I-123-MIBG for a truly SPECT LA innervation imaging. The preliminary results are encouraging but need further validation in larger trials. It is possible, that the presented methodology will not replace invasive HFS in identification of GPs, as the predictive value of receiving HFS-positive response at DUA area was only 76%, mainly because of DUAs located either laterally/inferiorly on LA MIBG images or identified with less confidency. On the other hand, the criteria that define a positive response to HFS are still debated and MIBG results may help in better selection of LA regions to be submitted to ablation, beyond HFS results. Moreover, MIBG-CZT-SPECT-CT technique poses an innovative tool for the assessment of the extent of LA denervation and the dynamics of renervation, at least in some regions, after ablation. It should be stressed that the presented methodology is developed for a specific scintigraphic system with a dedicated application software for the fusion of D-SPECT scintigraphic images with CT scans and with electrophysiological signals, and for the identification of discreet uptake areas of MIBG.[20] The natural alternative for MIBG-CZT-SPECT-CT technique could be PET-CT. Taking into account its high sensitivity, spatial resolution, existing advanced software for reconstruction and fusion, proved ability to image small uptake areas within heart (for example, for identification of high-risk atherosclerotic plaques in coronary arteries[21]), and advanced development of new F-18 labeled tracers of cardiac innervation,[22] PET-CT has a high potential to apply to atrial diagnostics.

Disclosure

The author has no conflict of interest to disclose.

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