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EDITORIAL

What future for the myocardial sympathetic innervation imaging?

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The myocardial sympathetic innervation plays a pivotal role in the progression of heart failure and in the occurrence of life-threatening arrhythmias. An impaired function of presynaptic sympathetic nerve terminals is considered to reflect impaired reuptake and thus impaired removal of the neurotransmitter from the synaptic cleft [1], resulting in overexposure of the myocardium to catecholamines and in a pre/post-synaptic signaling imbalance [2]. Consistent with this pathophysiologic model, prospective, large-scale clinical trials confirmed an excellent prognostic value of adrenergic imaging in patients with heart failure, both with single photon emission tomography (SPECT) and with positron emission tomography (PET) [3, 4].

Although extensively validated and embedded in clinical practice, the study of myocardial sympathetic innervation activity with standard SPECT suffers from evident limitations. In fact, its main prognostic parameters, i.e., the heart-to-mediastinum ratio and the cardiac washout rate, are generally derived from planar scans of the chest, thus allowing only for a semiquantitative evaluation of the global activity of sympathetic innervation. But as underlined also by a recent report, the heterogeneity of innervation may be more prognostically relevant than the assessment of the degree of sympathetic denervation [5]. As such, an imaging modality able to allow for a regional assessment of myocardial sympathetic innervation would be highly desirable. In this regard, new heart dedicated camera systems equipped with cadmium-zinc-telluride (CZT) solid-state detectors may constitute a valid alternative. Owing to improved image quality and temporal and spatial resolution over standard SPECT, a regional assessment of sympathetic innervation activity is feasible and accurate [6, 7]. Unfortunately, despite its great advantages, this novel, recently available SPECT technology is not widely deployed yet.

Hence, PET may be a preferred technique for the assessment of the cardiac sympathetic nervous system, able to yield a significantly higher impact on clinical practice. PET provides superior sensitivity and resolution over conventional nuclear imaging, thus allowing for a precise localization of innervation defects. To date, the main limitation of PET relates in the need of an on-site cyclotron, which is required to produce ^{11}C–labeled radiotracers such as ^{11}C- hydroxyephedrine (HED) for the study of the sympathetic innervation activity. Implementing ^{18}F–labeled tracers would, therefore, be essential for a wider dissemination of PET imaging in clinical practice.

In this issue of the *Journal*, Kobayashi and co-workers report on new promising ^{18}F–labeled PET radiopharmaceuticals targeting the sympathetic nervous system [8]. Similarly to what was already established for ^{18}F–FDG, the improved cost-effectiveness of the dispatch of fluorinated tracers from central cyclotron facilities is expected to enhance the diffusion of PET-based sympathetic innervation imaging.

Of the new tracers, a phase-1 trial on 12 healthy subjects reported a favorable biodistribution for ^{18}F–LMI1195, similar to that of metaiodobenzylguanidine (MIBG), as well as an acceptable radiation dose. These characteristics are conceivably expected to make this radiocompound the first choice for an easy implementation in clinical practice.

Even more interestingly, another two radiopharmaceuticals, i.e., ^{18}F–4F-MHPG and ^{18}F–3F-PHPG, were proven in animal models to yield accurate quantitative measures of regional nerve density along with a favorable heart-to-liver ratio.

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Although only one first-in-human study has been performed to date [9], it seems that these radiopharmaceuticals have the potential for a robust absolute quantification of the tracer uptake.

A full quantitative analysis of many biological mechanisms, including myocardial denervation, bears great importance for the development and the diffusion of PET imaging. As a matter of fact, the quantitation is the main diagnostic goal of nuclear medicine, since the possibility of measuring a process or quantifying a disease reflects the ability of a diagnostic tool to provide a detailed understanding of the mechanism of a physiological process. On the other hand, the visual interpretation is a completely different process, representing the difference between modern evidence-based medicine and the medicine of past years based on physicians' subjectivity rather than objective interpretation of the data. A truly quantitation of the myocardial sympathetic innervation imaging would also represent a reliable tool to overcome limitations due to global downregulation of myocardial catecholamine storage, which is frequently reported in patients with heart failure [10].

As such, a quantitative approach should be routinely implemented, capitalizing on the experience with myocardial perfusion PET imaging, wherein the lack of well-established clinical software for quantification prevented for a long time many larger-scale clinical trials to focus on the absolute quantification of myocardial blood flow. However, due to recent advantages in the use of hardware and software, many studies demonstrated a significant incremental value of absolute flow quantification [11]. By extension, we might speculate that a similar experience can be encountered for myocardial sympathetic innervation imaging with PET. Specifically, a full quantitative approach would allow for performing larger-scale trials able to expand on the important findings of the renowned PAREPET study [4], wherein a truly quantitative analysis of HED uptake and retention in the myocardium was not performed. A re-analysis of the PAREPET data with a quantitative approach may lead to clinical implementation of absolute quantification for catecholamine retention [12] and it is conceivable that the introduction of these novel fluorinated tracers will be of invaluable help to reach this target.

Another intriguing opportunity offered by molecular imaging is to evaluate the myocardial sympathetic innervation activity along with other molecular-targeted agents to provide useful prognostic information in patients with heart failure. For example, simultaneously investigating myocardial sympathetic innervation and perfusion/viability may help in the identification of the pro-arrhythmic, denervated but viable infarct borderzone [13, 14]. Alternatively, very specific insights may be provided by combining information on myocardial sympathetic activity and various agents identifying, for example apoptosis, extracellular matrix activation, or angiogenesis [15].

The improved energy resolution of CZT cameras permits a simultaneous detection of multiple isotopes in a single acquisition, thus allowing for a targeted molecular and cellular nuclear cardiology [16, 17].

But a multi-isotope approach can be effectively pursued also on PET imaging, capitalizing on different half-lives of various beta-emitters. For example, the above-mentioned PAREPET study simultaneously investigated the sympathetic innervation activity (with ^{11}C–HED), the perfusion status (with ^{13}N–ammonia) and the myocardial viability (with ^{18}F–FDG) in a large group of patients, demonstrating a higher rate of sudden cardiac death in patients with mismatch ^{13}N–ammonia/^{11}C–HED, consistent with the presence of viable but denervated myocardium [4]. As such, it does not seem unrealistic to foresee a growing interest in the near future for PET imaging with a multi-isotope approach, boosted by the implementation of novel fluorinated tracers targeting the sympathetic nervous system.

A multi-tracer approach, by combining information from different pathophysiologic mechanisms, bears great importance for the prognostic assessment of patients with heart failure. The ability to predict the occurrence or the progression of a disease remains one of the most intriguing areas of cardiac molecular imaging and represents a unique feature, able to differentiate functional imaging from conventional radiologic imaging. The more these novel developments in tracers and instrumentation will be targeted to a comprehensive and quantitative assessment of the pathophysiologic mechanisms leading to heart failure, the greater the possibility that nuclear cardiology will survive the test of time and will be in the near future an invaluable tool in clinical care.

Compliance with ethical standards

Conflict of interest The author has no disclosure of any personal or financial support or author involvement with organization(s) with financial interest in the subject matter – or any actual or potential conflict of interest.

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