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EDITORIAL

Cardiac innervation electrifies!

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Cardiovascular disease remains a major risk factor for death in the western world and accounts for example for 1 of every 3 deaths in the United States, remaining higher than any other major cause of death [1].

Patients with heart failure (HF) are a well-known subgroup with associated increasing prevalence and costs. In 2012, total cost for HF was estimated to be $30.7 million. Of this total, 68 % was attributable to direct medical costs. Projections show that by 2030, the total cost of HF will increase almost 127 % to $69.7 billion from 2012 [2]. For Europe, these numbers are equally disturbing.

These projections of increasing numbers and thereby increasing associated costs with declining healthcare budgets give urge to the need for the development and implementation of tools able to better risk stratify patients. This will lead to an optimization of the allocation of the available resources (i.e., better identification of possible therapy responders from non-responders).

This need to better discriminate therapy responders from non-responders coincides with a slowly changing view toward diagnostic tests. In recent years, evaluation of diagnostic tests (e.g., myocardial perfusion scintigraphy) has shifted from diagnostic accuracy alone to an assessment of their effect on clinical outcomes in relation to treatment and in particular cost-effectiveness.

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In the nuclear cardiology diagnostic arsenal, apart from assessing myocardial perfusion, there are other important possible targets to optimize risk-stratification, for example the autonomic system. The autonomic system plays a major role in maintaining cardiovascular hemodynamic and electrophysiological stability at rest and in response to changing demands. The autonomic nervous system consists of sympathetic innervation mediated by norepinephrine (NE) and parasympathetic innervation mediated by acetylcholine. In the pathophysiology of HF, the autonomic system plays a key role, both through circulating mediators such as NE and by direct myocardial innervation, which can be imaged with radiotracers.

However, before implementation of any (imaging) technique a good understanding of the pathophysiology behind the disease process is essential for an adequate interpretation of the outcome measures. This means that for HF patients it is pivotal to understand how the outcome parameters of the different imaging modalities relate to the pathophysiological HF processes.

For the readily available and easily clinically implementable imaging with ^{123}I-*meta*-iodobenzylguanidine (^{123}I-*m*IBG) this perquisite has been fulfilled. Recent data have shown that ^{123}I-*m*IBG myocardial scintigraphy has the potential to become part of routine HF imaging. The so-called late heart-to-mediastinum ratio is a well-validated independent prognostic predictor in patients with HF. The technique has also the potential to assist in identifying the most adequate candidates for implantable defibrillators and resynchronization therapy. However, it is important to realize that the latter is for now only based on some initial promising results and that convincing data to support this claim are currently lacking. Ongoing prospective trials will most likely further validate the role of ^{123}I-*m*IBG myocardial scintigraphy in identifying the most appropriate candidates for cardiac implantable devices.

In addition to a good understanding of the outcome parameters of ^{123}I-*m*IBG myocardial scintigraphy, standardization of the technique is essential. The technique is highly reproducible and has a small inter- and intra-observer variation. However, the lack of standardization between different institutions is one of the factors that have hampered the wide-scale clinical implementation of ^{123}I-*m*IBG myocardial scintigraphy. Some initial efforts have been made to harmonize and standardize myocardial ^{123}I-*m*IBG scintigraphy. These recommendations include proposals for patient preparation, administered amounts of ^{123}I-*m*IBG activity, scanning parameters (e.g., choice of collimators), and analysis of the acquired data to obtain the most used semi-quantitative parameters (i.e., early and late heart-to-mediastinum ratio and myocardial washout). To further the role of ^{123}I-*m*IBG scintigraphy a strict use of these recommendations is essential.

^{123}I-*m*IBG has been validated mainly in HF patients, both ischemic and non-ischemic. However, the technique is also often used to better understand smaller patient populations like, for example, patients with Tako-Tsubo cardiomyopathy or hypertrophic cardiomyopathy. This aspect of the technique is very valuable and helps in gaining knowledge but most likely ^{123}I-*m*IBG will not be used in these specific populations on a larger scale.

Although the obtained parameters of ^{123}I-*m*IBG myocardial scintigraphy seem to be helpful in HF patients, they are primarily limited by the lack of true quantification and restricted spatial resolution. PET may overcome these limitations and has been shown to be of added value in HF patients. Especially since the enormous growth in clinical available PET (-CT) scanners this would seem a valuable option. However, the relative short half-life of the current clinically available PET tracers for the assessment of the sympathetic nervous system is a major limitation. This makes that the imaging with PET-tracers is for now limited only to centers with on-site cyclotrons in combination with an adequate radiochemistry department. However, interesting developments might give way to a ^{18}F-labeled tracer for the clinical assessment of the cardiac autonomic system.

In conclusion, we feel that imaging of the cardiac autonomic innervation offer unique benefits over other options. In addition, we believe that imaging of the cardiac autonomic innervation will provide essential information for a better allocation of expensive treatment options in a still growing HF patient population in an area of declining budgets. Therefore imaging of the cardiac autonomic innervation may help to improve individual patient care and reduce the socioeconomical burden.

Compliance with ethical standards

Disclosure and potential conflict of interest Alberto Cuocolo and Hein J. Verberne both declare no conflict of interest. No funding was received for this article.

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