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EDITORIAL COMMENT

The Relativity of Reference Values for Myocardial Perfusion Imaging*

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Myocardial perfusion imaging (MPI) has acquired a crucial role in the diagnosis and management of chronic coronary syndrome, as acknowledged by the latest European Society of Cardiology Guidelines (1). An estimated 15 to 20 million procedures are performed annually worldwide, and diffusion of technology and expertise has led to its progressive adoption in developing countries as well (2). The downside is that MPI accounts for a substantial proportion of the radiation exposures every person gets per year from all medical sources (3). For example, nuclear cardiology accounts for more than one half of all nuclear medicine procedures and 26% of the overall medical exposure of patients in the United States (4). Cardiologists and nuclear medicine specialists, then, have the responsibility to avoid unjustified and nonoptimized use of radiation.

The risk of cancer attributable to radiation exposure has been estimated as 1 in 100 subjects (and ranging from 1 in 30 to 1 in 300) following exposure to 100 mSv, which roughly corresponds to 20 single-photon emission computed tomography (SPECT) scans with ^{99m}technetium (Tc)-labeled tracers (2,3). Although these estimates are extremely imprecise, it is indisputable that the risk of radiation-related cancer increases with the radiation dose and, therefore, can be reduced by limiting radiation exposure. Following the "as low as reasonably achievable" principle, MPI needs to be performed with a radiation dose as low as possible (2). Additionally, the activity of a radiopharmaceutical to be administered must be determined in agreement with national legislation and the European Council Directive Euratom 2013/59. Diagnostic reference levels (DRLs) for radiopharmaceuticals are a crucial element of this legislation. DRLs correspond to levels of activity for broadly defined types of equipment and groups of standard-sized patients, not to be exceeded for standard procedures, and derive from distributions of actual patient examinations (5). DRLs are reference values that are useful for identifying outliers, whose instruments and protocols can then be re-evaluated (5). Their implementation as a dose-reduction strategy is widely endorsed by professional societies and national agencies for radiological protection and is required by the International Safety Standards (5). The achievable administered activity (AAA), another measure proposed more recently, is calculated as the median of a dose distribution, and it provides a goal that laboratories should strive to achieve even when they fall below DRLs.

Tracer activity is, in general, a compromise between image quality and radiation exposure. The higher the activity administered, the better the image quality and the higher the radiation exposure to the patient and staff (6). The activity to administer depends on the type of equipment (a single-head or multiple-head scintillation camera or a camera based on a cadmium-zinc-telluride detector), patient characteristics (body weight), acquisition protocol (1-day or 2-day protocols, imaging time, pixel size, and gated acquisition), and the radiopharmaceutical (^{99m}Tc compounds or ^{201}thallium [Tl] chloride) (6). The reconstruction method may also be of importance, that is, filtered back-projection versus iterative reconstruction. When a 1-day ^{99m}Tc protocol is used (i.e., 2 administrations of activity on 1 day), the activity for the second examination has to be 3 times

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higher than the first administered activity. Furthermore, if the stress examination is performed first and the findings are reported as normal, the rest examination can be omitted (6).

Technological advances in scanner, hardware, and software equipment for image acquisition and reconstruction have led to a dramatic improvement in the efficiency and quality of MPI, allowing a progressive reduction of radiation doses (2). In parallel, a variety of best practices have been developed to decrease radiation exposure. These have been summarized as follows: avoid Tl stress, avoid dual isotope, avoid too much Tc or Tl, perform stress-only imaging when possible, use camera-based dose-reduction strategies, and use weight-based doses of Tc (7). The International Atomic Energy Agency Nuclear Cardiology Protocols Cross-Sectional Study (INCAPS) has represented the first attempt to evaluate technologies, best practices, and the resulting radiation exposure on a worldwide scale (7). A total of 308 nuclear cardiology laboratories from 65 countries were asked to provide data regarding consecutive MPI studies performed during a single week in 2013. The worldwide median laboratory radiation dose from MPI was 10.9 mSv, ranging over an order of magnitude (2.2 to 24.4 mSv) depending on the laboratory, and fewer than a third of laboratories achieved the median effective dose of ≤9 mSv recommended in professional society guidelines (8). Radiation exposure differed between world regions, being lowest in Europe and highest in Latin America. Adherence to best practices was higher in Europe, and adherence to the best practices listed here was associated with a significantly lower ED (7).

So far, DRL and AAA values have been established at the local or national level. In this issue the *iJACC*, the INCAPS investigators propose DRLs and AAA values for SPECT imaging, calculated on a worldwide scale and for geographic regions (Africa, Asia, Europe, Latin America, North America, and Oceania) (9). For example, the investigators report that worldwide DRLs for rest/stress or stress/rest studies using ^{99m}Tc-labeled tracers were 11.2 mCi (first dose) and 32.0 mCi (second dose) for 1-day protocols and 23.0 mCi (first dose) and 24.0 mCi (second dose) for multiday protocols. The corresponding AAAs were 10.1 mCi (first dose) and 28.0 mCi (second dose) for 1-day protocols and 17.8 mCi (first dose) and 18.7 mCi (second dose) for multiday protocols. DRL and AAA values were clearly lower for stress-only protocols. The investigators also considered examinations using ^{201}Tl or dual isotopes, which were still used in a non-negligible proportion of studies in Europe, Asia, Oceania, and Latin America. DRL and AAA values for each protocol displayed wide variations (up to 14 mCi for DRLs and 15 mCi for AAAs) across regions, which was evidently explained by different technologies and an uneven adoption of best practices, as previously demonstrated in the same INCAPS cohort (7).

It is unfortunate that these results, based on MPI examinations dating back to 2013, were published just before the start of INCAPS 2. Nonetheless, Hirschfeld et al. (9) should be congratulated even just for introducing the notion that DRLs and AAAs should be established for the entire world and single continents. The availability of these reference values may represent a major step toward the standardization of MPI practices and a general decrease of the activity administered. On the other hand, targeting uniform DRLs and AAAs is still not the best we can do to reduce global radiation exposure. Indeed, DRLs and AAAs are calculated from real-world data and are necessarily higher than values achievable through state-of-the-art technology and rigorous adoption of best practices. Therefore, the next step will be to pursue the minimal activity needed to have an interpretable examination in standard conditions. This activity should be defined for each tracer, examination protocol, and technology by an independent regulatory board, and it would represent the real optimal target to pursue. Defining minimal activities for each technology would also stimulate competition among the producers of SPECT cameras, who would try to progressively reduce the doses needed.

In summary, Hirschfeld et al. (9) has the great merit of proposing, for the first time, international DRLs and AAAs. Although these are useful targets for SPECT laboratories, they are suboptimal compared to "ideal" minimal doses, which are yet to be established. Understanding the relativity of reference values could represent important progress toward the reduction of radiation exposure from MPI.

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