Myocardial perfusion imaging with cadmium–zinc–telluride cameras: Harry Potter and the Radiation Hallows?

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Of course it is happening inside your head, Harry, but why on earth should that mean that it is not real?
J.K. Rowling

Ongoing developments in the diagnosis and management of ischemic heart disease require a global reappraisal of practitioners, approach to non-invasive imaging tools, ranging from myocardial perfusion imaging (MPI) to computed tomography angiography (CTA) and cardiac magnetic resonance (CMR).[1–3] Notwithstanding the need to focus on an integrative approach based on hybrid imaging, capitalizing on the synergy between functional and anatomic imaging tests, it is important to reconsider a time-tested yet elusive concept, which has many important direct and indirect implications for cardiovascular imaging specialists and practitioners: hormesis.[4]

This term, deriving from the Ancient Greek ''to set in motion,'' refers to a biological process characterized by an altogether different pathophysiologic dose–response effect, such as low-dose exposure is associated with benefits in comparison to no exposure, whereas high-dose effects are clearly detrimental, notwithstanding the fact that there is no exposure threshold associated with absence of risk.[5] Visually, hormesis is easily picture as a U-shaped or J-shaped curve, and indeed, this is rather common phenomenon in biology and medicine. Radiation hormesis has been analyzed in great detail, yet several uncertainties persist and is confounded by the established distinction between stochastic and determinist effects of radiation. The typical pathophysiologic framework is that low-dose radiation exposure activates beneficial cellular reparative mechanisms (e.g., autophagy) yielding improved cell function and viability, with corresponding benefits at the tissue, organ, system, and organism level.[6] Thanks to the study by Baumgarten et al. hereby reported, which highlights the beneficial impact on radiation exposure of myocardial perfusion imaging (MPI) of cadmium–zinc–

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Patient A **56-year-old man** with **multiple cardiovascular risk factors** (HTN, NIDDM, smoking) symptomatic for stable angina (CCS III), with **normal excercise stress test** (normal ST, RRP 27200, maximum workload 10 METS)	Patient B **68-year-old woman** with dyslipidemia, symptomatic for dyspnea, with **abnormal exercise stress test** (2 mm downsloping ST-segment depression at peak, RRP 24320, maximum workload 8.5 METs)
Patient C **49-year-old woman** with family history of coronary artery disease, asymptomatic, with **high calcium score at coronary computed tomography** (Agatson scores: 559 on RCA, 358 on LAD, 288 on LCX, total 1205)	Patient D **71-year-old man** with paroxysmal atrial fibrillation, asymptomatic, with **80% diameter stenosis in the proximal LAD** involving the first diagonal branch at computed tomography coronary angiography

Figure 1. Baseline features for 4 prototypical patients undergoing stress-only myocardial perfusion imaging with single photon emission computed tomography, highlighting the usefulness of cadmium–zinc–telluride technology given its very high negative predictive value (in terms of both diagnosis and prognosis): patient A—a symptomatic subject with normal stress ECG; patient B—an asymptomatic subject with positive stress ECG; patient C—an asymptomatic subject with elevated coronary calcium score at computed tomography; patient D—an asymptomatic subject with angiographically significant stenosis on the left anterior descending at computed tomography coronary angiography. *CCS*, Canadian Cardiovascular Society; *HTN*, hypertension; *LAD*, left anterior descending; *LCX*, left circumflex; *MET*, metabolic equivalent of task; *NIDDM*, non-insulin-dependent diabetes mellitus; *RCA*, right coronary artery; *RRP*, rate pressure product..

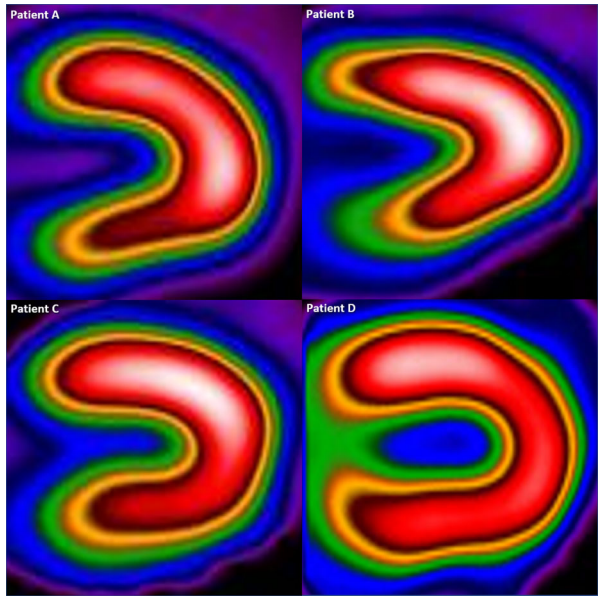

Figure 2. Stress-only myocardial perfusion imaging with single photon emission computed tomography using cadmium–zinc–telluride technology for the same patients described in Figure 1, all showing normal perfusion..

Figure 3. Warranty periods based on the integration of clinical, diagnostic, and imaging results described in Figures 1 and 2, for the same patients thereby described..

telluride (CZT) cameras, we are happy to introduce provocatively a new concept: clinical hormesis. With clinical hormesis, we envision a framework to analyze the risk/benefit profile of a cardiovascular test (e.g., MPI) or procedure, not as a function of its specific and absolute effect, but rather highlighting its complex dose–response relationship with overall outcomes, considered in a comprehensive framework.[7]

In keeping with radiation hormesis theory and practice, we are all aware that high-dose radiation has clear cytotoxic effects, and thus moderate or severe exposure leads to higher risk of failure or adverse outcomes. Yet, low-dose radiation has beneficial effects, such as mild exposure, and is associated with lower risk, when compared to no exposure at all.[8] Similarly, in the context of a complex pathophysiologic condition such as coronary artery disease (CAD) leading to ischemic heart disease (IHD), aggressive testing, including multiple and repeat tests with overlapping features, and a low threshold for invasive coronary angiography, is likely associated with overindication to revascularization, poor resource use, and iatrogenic risk, thus amounting to an overall increase in the rate of adverse outcomes in comparison to baseline rate.[9] Similarly, no testing whatsoever and reliance simply on behavioral and

pharmacologic therapy likely miss the opportunity for optimal selection of patients for revascularization, thus leaving many with adverse clinical and angiographic features (e.g., unprotected left main, severe multivessel disease) at substantial risk of adverse events.[10] Accordingly, appropriately selective use of non-invasive imaging tests (e.g., CTA, CMR, and/or MPI), including their smart integration in a logic of hybrid imaging, may improve patient outlook and reduce risk in comparison to the baseline, thanks to favorable diagnostic and prognostic accuracy, as well as improved decision-making and elucidation of warranty period.[1,11] Indeed, nuclear medicine in general and nuclear cardiology in particular capitalizes more on the hormesis concept as radiation exposure is not concentrated in a few seconds or minutes, and thus, cellular repairing mechanisms are more capable of adapting appropriately to the corresponding radiologic risk.[6] This framework is also reinforced by an intuitive application of population attributable risk: as IHD is much more prevalent than radiation-induced cancer, the benefits of clinically appropriate imaging testing with limited radiation exposure clearly outweigh the drawbacks.

This diagnostic hormesis concept is all too relevant in the current era dominated by the late-breaking results of the International Study of Comparative Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial, which randomized more than 5000 patients with moderate or severe ischemia, albeit not universally using an imaging test, to an initial invasive strategy based on invasive coronary angiography vs best medical therapy with invasive assessment reserved to those failing medical therapy or presenting with clinical instability.[3] After a median of more than 3 years, event rates were similar in the two groups, despite a trend toward lower risk in the invasive management group, and a significant increase in the rate of spontaneous myocardial infarction in the conservative group.[3,12] While results of this trial are already subject of intense and hot debate, and their implications will be far reaching, it is clear that putting these two strategies one against the other misses the point of capitalizing on each approach strengths. Indeed, appropriately moderate (i.e., selective) use of invasive testing, following thorough diagnostic and prognostic assessment with a hybrid anatomic and functional cardiac assessment, is evidently posed to minimize the risk of invasive assessment and unnecessary revascularization, while simultaneously improving patient outlook in comparison to a nihilistic and completely conservative clinical management, which reminds us of historical and obsolete clinical practice.[12] Moreover, even admitting that precise characterization of ischemia severity and extent does not improve decision-making for revascularization purposes, it is clear that such assessment would still benefit patients by means of accurate risk prognostication and definition of warranty period.

Furthermore, even disregarding or refusing altogether the hormesis concept, it is well established that lifetime risk associated with medical radiation exposure is minimal in comparison to many other common risk factors, which range from trauma due to motor vehicles or bicycling, arsenic in drinking water, or home radon exposure.[8] Yet, all these exposures are socially acceptable despite lacking any beneficial input for medical decision-making. Instead, nuclear cardiology offers detailed data on diagnosis, prognosis, warranty period, and management guidance, often avoiding or minimizing unnecessary radiation exposure due to other downstream tests.[13] Accordingly, selective application of non-invasive imaging to patients at moderate or high risk of adverse events minimizes any risk and is not only clinically reasonable but ethically mandated, given the necessity to accurately proceed with diagnosis.

Within this broader context, and the renewed perspective of hormesis, we applaud Baumgarten et al. for their comparative diagnostic and clinical study comparing MPI with Anger vs CZT cameras in patients with suspected CAD in a large-volume Brazilian center.[7] They indeed found that CZT MPI was associated with less radiation exposure acutely, and also when considering all subsequent procedures (thus amounting to indirect radiation exposure as well). Obese patients seemed to benefit less from CZT MPI, with higher exposure acutely and more downstream invasive procedures, but whether this depends on actual drawbacks of CZT technology or on the limitations of Baumgarten and colleagues' non-randomized trial remains to be confirmed, as obesity in itself represents a diagnostic and clinical challenge.[14]

In any case, the push toward CZT is supported also by hormesis premises, as this imaging technologies enable physicians to administer much lower doses of radionuclides (even 1/3 of the dose used with Anger cameras).[11] Several other advantages of CZT should also be kept in mind, which include the refined imaging quality with ensuing lower risks of false positives and false negatives, the combined appraisal of myocardial perfusion reserve, and the possibility to perform stress-only imaging, thus drastically reducing eventual radiation exposure while yielding high prognostic accuracy, as for instance a negative test is associated with an extremely low rate of adverse cardiovascular events.[15,16] In these patients, a negative/normal result (in terms of both diagnosis and prognosis) excludes the indication to myocardial revascularization. Accordingly, the association between a non-invasive imaging test result with other clinical and diagnostic features enables the exact definition of a warranty period individualized and

tailored for each patient (Figures 1, 2, and 3). Furthermore, CZT fosters a new age for time-tested thallium, given its optimal kinetics and total flow dependency in comparison to technetium.[17] In addition, thallium remains the gold standard for viability appraisal, for instance, to guide choice between percutaneous and surgical revascularization aimed at viable regions and discarding non-viable ones. Finally, simultaneous imaging with thallium and metaiodobenzylguanidine (MIBG) by means of CZT cameras can identify in patients with recent or prior myocardial infarction the presence of match vs. mismatch of viability (either present or absent) and denervation (either present or absent), and thus optimally guide clinical decision-making in favor or against the use of implantable cardioverter-defibrillators (ICD).[18]

In conclusion, in the current ISCHEMIA-dominated era, the role of non-invasive diagnostic testing remains crucial in the diagnostic and prognostic work-up of patients with CAD. Indeed, clinical hormesis postulates that no invasive testing and excessive (i.e., universal) invasive assessment is clearly detrimental to patients and wastes resources, whereas selective invasive assessment based on non-invasive testing (e.g., hybrid imaging compiling MPI with CZT and CTA) is going to substantially reduce short- and long-term risk of adverse outcomes.

Conflict of interest

Drs. Francesco Nudi, Alessando Nudi and Orazio Schillaci report no conflict of interest. Prof. Giuseppe Biondi-Zoccai has consulted for Replycare.

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