MPI in the era of CZT cameras: Absolute numbers are still better than relative figures

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In the last decades, the clinical characteristics of the patients that have been investigated by myocardial perfusion imaging (MPI) have changed dramatically, with a progressive reduction of the average cardiovascular risk and of the pre-test probability of coronary artery disease (CAD).¹ These data have been recently confirmed by the results of some accurate retrospective analyses coming from leading institutions in the field of cardiac imaging, showing that in the current clinical practice the majority of patients undergoing nuclear cardiac imaging with single-photon emission computed tomography (SPECT) mainly report atypical symptoms and show a strikingly lower evidence of positive test results than in the past.² Interestingly, those data were independent of the patients' clinical profile, with a disturbingly high prevalence of negative test results both in subjects with suspected and known CAD.^{2,3} Considering the strict interconnection between the accuracy of any ischemia test and the underlying prevalence of the disease, it is not surprising that the diagnostic capability of "standard" cardiac imaging methodologies has been decreasing substantially as compared to classical data. Those findings have been further confirmed by a comparative prospective cardiac imaging study for the diagnosis of patients with suspected CAD that demonstrated clearly that the accuracy of the major non-invasive functional imaging tests is, at best, in the range of 70%, a rather modest result that can barely influence

patients' management.⁴ Among the major non-invasive myocardial imaging strategies, conventional SPECT seems to suffer relatively more from the changing of the patients' population, with relatively lower values of diagnostic accuracy than some other "competitors."^{5,6} As an example, as reported in the recent "Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC)" trial, the sensitivity of MPI performed with traditional SPECT cameras in detecting obstructive CAD is significantly lower than that of cardiac magnetic resonance,⁵ although the clinical impact of such a difference is still disputed.⁷ Accordingly, an evolution of SPECT technology was urgently needed to maintain its long-standing status as an accurate and trusted strategy for the evaluation of CAD patients. The introduction of dedicated cardiac SPECT cameras equipped with cadmium-zinc-telluride (CZT) detectors has revolutionized nuclear cardiac imaging, as a technology that could allow a more accurate and faster evaluation of regional myocardial perfusion than standard Anger cameras.⁸ As a matter of fact, an increasing number of reports has demonstrated repeatedly that the increased photon sensitivity and spatial resolution of CZT pixelated crystals might overcome most of the technical limitation sodium-iodine (Na-I)-based devices, with superior diagnostic performances even in the most complex patients' categories, such as those with multi-vessel CAD.^{9,10} Moreover, CZT technology might allow investigating what is commonly regarded as the "holy Grail" of coronary pathophysiology, namely absolute myocardial blood flow (MBF) and myocardial perfusion reserve (MPR).^{11,12} In fact, absolute assessment of MBF is difficult with standard SPECT cameras, mainly because of the inadequate properties of the currently available flow tracers that show a non-linear extraction fraction at higher flow rates, coupled with the unfavorable physical properties of the Na-I crystals that typically saturate at higher count rates. CZT cameras

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allow image acquisition in a non-rotating mode and therefore acquisition of time-activity curves, which entail the computation of absolute myocardial perfusion parameters.^{12,13} As shown by a wide number of reports, the computation of myocardial perfusion parameters allows obtaining some of the most accurate predictors of CAD, possibly individuating even subtle alterations of myocardial perfusion heterogeneity—as a possible result of sub-clinical and/or diffuse CAD, endothelial/microvascular dysfunction—that would be unapparent with a qualitative evaluation.^{13,14}

Nevertheless, initial studies that have reported on the feasibility of absolute MBF with CZT technology have shown a systematic underestimation of flow values if compared with the available non-invasive and invasive gold standards, showing some of the possible limitations of this approach.¹² Moreover, a direct comparison of the diagnostic capabilities of qualitative vs quantitative myocardial perfusion analysis at CZT is still lacking.

In their study, Nudi et al tried to compare the different capabilities of qualitative and quantitative myocardial perfusion assessment in patients with suspected or known CAD submitted to CZT imaging, with a particular reference on patient characteristics, imaging diagnostic yield, and short-term patients' outcome.¹⁵

To this purpose, a retrospective single-center evaluation of MPI data obtained with a dedicated cardiac CZT camera in 66 patients was performed. Patients underwent a single-day stress-rest CZT scan with sequential dynamic and static acquisitions and myocardial perfusion heterogeneity was evaluated both semi-quantitatively and in absolute terms. Interestingly, a non-conventional semi-quantitative evaluation of regional myocardial perfusion was performed, using an alternative 7-region LV segmentation model previously reported by the same group of authors instead of the standardized 17-segment LV model. On the contrary, absolute MBF quantification was performed more traditionally and the average values of MBF and MPR for the 3 main coronary vascular territories were computed. According to the methodology, patients were followed up for major cardiovascular events for ≥ 1 year, although no information on the event rate is provided.

The study mainly demonstrated the existence of a significant diagnostic discordance between the semi-quantitative estimates of myocardial perfusion heterogeneity and absolute MBF and MPR values. In particular, only in 38 of the 66 enrolled patients (58%) absolute and semi-quantitative perfusion analysis actually agreed, while in the remainders a discordant output was observed. This difference was mainly explained by the presence of a consistent number of patients with abnormal MPR values despite the absence of regional

myocardial perfusion abnormalities on visual assessment. Interestingly, only limited impact of major demographical and clinical variables on myocardial perfusion variables was observed, with almost all the major cardiovascular risk factors having limited or insignificant association with any perfusion data.

Surprisingly, an abnormal LV perfusion on visual analysis appeared to be more strongly associated with the presence of obstructive CAD than absolute MBF, although no accuracy analysis was actually performed.

The authors should have commended for the CZT imaging protocol that tries to exploit all the advantages that this new technology offers in terms of superior architecture, photon sensitivity, and image resolution, which ultimately allow effective dynamic myocardial perfusion imaging.

Nevertheless, while the overall results of the study might be still of interest, a number of key limitations should also be considered for a comprehensive interpretation of the findings. First of all, it is not clear how the non-conventional LV segmentation model that was used actually takes into account the presence of myocardial scar, a parameter that, considering the clinical characteristics of the overall population (20% with previous myocardial infarction), could have influenced the results.

Moreover, it is strange that the 12 supposedly normal patients showed significant burden of inducible myocardial ischemia and scar, as demonstrated by elevated summed rest and difference scores (2.6 ± 1.5 and 10.1 ± 3.9 , respectively). Moreover, the curious finding that out of the total of 66 patients, no one presented anterior LV ischemia, and that only few (12%) showed more than mild myocardial perfusion abnormalities poses doubts on the generalizability of the results.

In addition, saying that visual analysis was more accurate than absolute MBF quantification in detecting significant CAD is a countersense, since the presence of a significant reduction of stress MBF is what actually defines a hemodynamically significant stenosis. It is likely that only patients with significant regional myocardial perfusion abnormalities were submitted to ICA, resulting in a referral bias that could have affected the diagnostic accuracy of myocardial perfusion variables in detecting angiographically significant CAD.

Nevertheless, the study by Nudi et al alluded to one of the most clinically relevant questions in modern nuclear cardiology: is there a difference in terms of CAD diagnosis and patient prognostication between absolute and relative measures of myocardial perfusion heterogeneity?

Regarding the diagnosis of significant CAD, solid evidence has shown the inconsistent relationship between stenosis anatomic severity and downstream MBF abnormalities, demonstrating that a combined

assessment of CAD anatomic burden and regional myocardial perfusion is needed to evaluate patients with ischemic heart disease (IHD).^{14,16} In this context, absolute MBF quantification with positron emission tomography (PET) has been shown as the most accurate technique for the evaluation of the hemodynamic relevance of CAD, and when combined with computed tomography coronary angiography (CTCA) through hybrid imaging it may entail a completely non-invasive coronary anatomic-functional analysis.¹⁷ In addition, the prognostic value of absolute MBF analysis in patients with IHD has been also accumulating, and recent reports have demonstrated how a relatively preserved coronary flow capacity associates with a favorable prognosis even in the presence of extensive CAD, while the presence of a more compromised absolute myocardial perfusion confers a dismal outcome, individuating patients that would benefit from aggressive therapeutic approaches (i.e., surgical coronary revascularization).¹⁸

Finally, the absolute quantification of myocardial perfusion has a capital role in the evaluation of patients with non-obstructed coronary arteries, in whom only MBF assessment may unmask the presence of functional alterations of coronary circulation (i.e., endothelial or microvascular dysfunction due to cardiovascular risk factors).¹⁹ However, the limited availability of cardiac PET scanners and the intrinsic technical complexity of the methodology have prevented the diffusion of absolute MBF evaluation in daily clinical practice.

The introduction of dedicated cardiac CZT camera has represented a technological breakthrough in the field, giving also the chance to perform dynamic cardiac acquisitions in the context of a clinically indicated myocardial perfusion scan.^{11–13} Accordingly, initial evidence has confirmed the feasibility of MBF quantification on CZT cameras, allowing mirroring the results obtained by PET imaging and predicting the presence of flow-limiting CAD as evaluated by invasive fractional flow reserve (FFR).¹² In particular, while the evaluation of relative myocardial perfusion may still remain the cornerstone for the diagnosis of CAD in the majority of patients, absolute MBF analysis may prove particularly beneficial in patients with extensive CAD burden, in whom semi-quantitative measures may fail to unmask coronary involvement and possibly predict appropriately the risk of future cardiac events.²⁰ At the opposite extreme, patients with subtle myocardial perfusion abnormalities on semi-quantitative CZT analysis but preserved regional MBF and MPR could be reasonably spared from any further diagnostic test and invasive therapy, because of the superior prognostic impact of optimal medical therapy in this setting.

CZT devices may thus represent the long-awaited innovation in the field of MPI, regenerating the interest for

a methodology that had recently suffered the competition with some other competing imaging modalities. The evaluation of absolute MBF and MPR can be seen as the “ace in the hole” of CZT MPI, allowing investigating the most intimate aspects of coronary pathophysiology in an entirely non-invasive manner at the cost of an extremely contained radiation burden.^{11–13} In this context, while global MBF and MPR are among the most powerful prognosticators in cardiac patients,¹⁴ the assessment of patients with IHD requires the computation of regional myocardial perfusion data, in order to individuate more subtle alterations of MBF distribution that might indicate the presence of intermediate coronary lesions that might benefit from coronary revascularization.²⁰

Disclosure

Drs. Liga and Gimelli have nothing to disclose.

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