Promises and pitfalls of relying on angiography-derived indexes to identify myocardial ischemia: A tale of Romulus and Remus

Alessandro Nudi, MD,^a Giuseppe Biondi-Zoccai, MD, MStat,^{b,c}
Francesco Versaci, MD,^d and Francesco Nudi, MD^{a,e,f}

^a Service of Hybrid Cardiac Imaging, Madonna Della Fiducia Clinic, Rome, Italy

^b Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy

^c Mediterranea Cardiocentro, Naples, Italy

^d Unità Operativa Complessa di UTIC Emodinamica e Cardiologia, Ospedale Santa Maria Goretti, Latina, Italy

^e Ostia Radiologica, Rome, Italy

^f Replycare, Rome, Italy

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Rome wasn't built in a day.

John Heywood

Ischemic heart disease (IHD) still represents a clinical challenge despite many decades of intense efforts aimed at optimizing prevention, diagnosis, risk stratification, treatment, and rehabilitation.¹ While IHD recognizes several causes and pathophysiologic mechanisms, coronary artery disease (CAD) due to atherothrombosis maintains a pivotal role in determining IHD, especially in its most clinically impactful manifestations.² Historically, efforts at elucidating the diagnosis and prognosis of CAD have focused on two independent and actually opposing perspective: a functional one, based on the characterization of myocardial viability, perfusion, or function, and an anatomical one, based on the definition of actual anatomic extent of CAD, either from a solely luminological perspective, or also including plaque and vessel wall characterization.³

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Reprint requests: Francesco Nudi, MD, Service of Hybrid Cardiac Imaging, Madonna Della Fiducia Clinic, Rome, Italy; francesco.nudi@gmail.com

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This contrast between function and anatomy reminds of the struggle between Romulus and Remus.⁴ Indeed, just as any alliance is better than actual fight, modern cardiovascular imaging should arguably be founded on the optimal integration (i.e., fusion or hybrid imaging) between functional and anatomic detail, in order to better elucidate in an multidimensional yet integrative fashion all patient features, which may range from diagnosis, subgroup, risk, prognosis, warranty period, and therapeutic choice.^{5,6}

Despite this rosy prophecy, the road to optimal integration of functional and anatomic cardiac data remains a challenging one, reminding indeed of the long time required to build from scratch a city, especially a complex and monumental one.⁴ Several hurdles must indeed be overcome to effectively and efficiently use hybrid imaging, but the main one rests in the eye of the beholder: to discard prior paradigms based on the test control comparison, in which a new test is appraised against to an established one (often considered a “gold standard”).⁷ Indeed, considering a functional test as a valid comparator of an anatomic one, or vice versa, misses the whole point of patient-centered integration of multimodality imaging.⁸ This logical step is, however, challenging for many, including ourselves. Yet we need to recognize that, for instance, using invasive coronary angiography as a diagnostic benchmark for myocardial perfusion imaging (MPI) was a crude comparative approach, in as much as it is using MPI to validate non-invasive angiography-derived indexes.⁹ Indeed, the only true benchmark would be long-term outcomes, ranging

Figure 1. Multifaceted benefits of single photon emission computed tomography (SPECT) to assess myocardial ischemia, myocardial necrosis, dyssynchrony, dysinnervation/denervation, and also enable the integration of angiography-derived parameters (including but not limited to % diameter or area stenosis) with functionally relevant parameters in a logic of hybrid imaging with computed tomography coronary angiography.

from mortality to morbidity, quality of life, and resource use.

This issue of the Journal offers a very interesting example of the promises and challenges offered by state-of-the-art imaging technologies in patients with or at risk of IHD, and also highlighting the difficulties faced by modern cardiovascular imaging experts wishing to advance this field of clinical practice.¹⁰ In particular, von Felten et al. report an interesting observational study of 87 patients undergoing coronary computed tomography angiography (CCTA) imaging with a 256-slice scanner and MPI based on ^{99m}Tc-tetrofosmin with a cadmium-zinc-telluride camera in a leading academic center in Switzerland. On top of standard reporting of luminal narrowings and perfusion details, CCTA data were processed offline to compute two angiography-derived indices of perfusion: transluminal attenuation gradient (TAG), which is an established one, and

transluminal cross-sectional area gradient (TCG), which is a novel one.¹¹ Notably, while less extensively studied than CCTA-derived fractional flow reserve (FFR), TAG and TCG have the advantage of requiring less computing time and resources, being conceptually based on the premise that a functionally more significant stenosis will lead to greater contrast intensity decrease over the length of a diseased coronary lesions.¹²

Briefly, von Felten et al. found that, considering MPI as the gold diagnostic standard for per-vessel diagnostic yield, CCTA had 100% sensitivity and 70% specificity (for an area under the curve of the receiver operating characteristic of 0.85), CCTA plus TAG 100% and 75% (0.88), and CCTA plus TCG 100% and 71% (0.87). Furthermore, neither TAG nor TCG seem capable of identifying coronary vessels associated with ischemia at MPI (both $P > 0.05$). The authors appear clearly disappointed of these findings, which indeed hint

Table 1. Compilation of tools for non-invasive anatomic and functional assessment of ischemic heart disease, focusing on single photon emission computed tomography (SPECT) and computed tomography (CT)

Technology	Scope	Detail	Feature
SPECT	Functional	Myocardial perfusion imaging	Myocardial perfusion during clinical stress and rest
CT	Anatomic	Myocardial perfusion reserve	Dynamic myocardial perfusion during stress and rest
		Calcium quantification	Calcium localization and quantification
		Plaque characterization	Plaque size and feature analysis
		Stenosis	Stenosis localization and quantification (as diameter, area and percentage)
	Functional	Transluminal attenuation gradient	Regression modeling
		Transluminal cross-sectional area gradient	Regression modeling
		Fractional flow reserve	Computation fluid dynamics
		Perfusion	Myocardial perfusion at rest

at the persistent focus of CCTA data, even after post-processing, mainly (if not only) on anatomy. It is true that limitations of this work are several. For instance, sample size is relatively small, as low is the overall risk profile of included patients. In addition, CCTA-derived FFR was not appraised in anyone. Furthermore, only 6 subjects underwent treadmill exercise testing, which is often considered much more valid than adenosine, dipyridamole, dobutamine, or regadenoson, as stress agent. Finally, 6 major vessels out of 261 could not be adequately analyzed at CCTA, and thus also at TAG and TCG.

Despite these disappointing results, this work should best be viewed as a useful adjunct to the expanding evidence base on established and novel non-invasive indexes of anatomic and functional significance of CAD (Table 1).^{13,14} In addition, strong content knowledge of pathophysiology should always guide decision making in clinical practice as well as in research. Indeed, the whole concept of TAG could be viewed as groundless just by reflecting on the fact that necrotic myocardium fed by an angiographically moderate lesion would most likely (and wrongly) yield an abnormal TAG results, given the reduced flow throughout in the vessel, unless a very close reference is chosen. This argument, which may apply similarly to TCG as well as CT-FFR, is not aimed at debasing CCTA-derived indexes of functional significance of CAD, but rather at highlighting the importance to see

each index and parameter as complementary to another.^{15,16}

Indeed, we firmly believe that modern cardiovascular practice should aim for default hybrid imaging with CCTA and stress only MPI with CZT cameras (Figure 1). Such imaging strategy would yield a veritable mine of anatomic and functional details, overall and at the subvessel and myocardial regional level, ranging from calcium score to plaque characterization, stenosis area and percentage, stress and rest perfusion, necrosis, stunning, hibernation, and functional assessment (including dyssynchrony but possibly also, by means of dual-isotope or repeat imaging, dysinnervation and denervation).^{17,18}

In conclusion, in keeping with Thomas A. Edison (the actual founder of General Electric together with John Pierpont Morgan) who stated “I have not failed. I’ve just found 10,000 ways that won’t work”, we compliment von Felten et al. effort at refining diagnostic yield of CCTA-derived indices of functional significance of CAD for showing us that TAG and TCG cannot be considered ready for prime clinical time.^{19,20} While we are not surprised that MPI with state-of-the-art CZT cameras proved repeatedly the gold standard in their work, we should pursue a more integrative approach capitalizing on the pros of both anatomic and functional imaging modalities, capable of better informing patient diagnosis, prognosis, and management strategy in a safe and efficient, yet precise, manner.

Disclosure

Prof. Biondi-Zoccai has consulted for Replycare, Rome, Italy.

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