The fascinating study by Rispler et al. (1) in this issue of the Journal represents another validation milestone in the search for a noninvasive imaging strategy that will eventually provide integrated evaluation of anatomy and physiology in patients with coronary artery disease. At last, it has now become possible to access coronary anatomy noninvasively with the emergence of multidetector computed tomography (CT). As a consequence, currently applied diagnostic strategies and noninvasive imaging paradigms are being challenged. It used to be that patients with suspected or probable coronary artery disease would undergo noninvasive evaluation for diagnostic and prognostic stratification purposes, thereby preventing access to the invasive coronary angiography to many patients who nevertheless have the disease but whose prognosis is deemed favorable. With the explosive growth of interventional revascularization procedures and now, even more so, with the advent of CT angiography, the gatekeeper function of stepwise functional testing is likely to disappear. This raises increasing concerns about appropriateness of the use of diagnostic CT, also considering that the simple documentation of the presence of plaque will be deemed sufficient to trigger coronary stenting, irrespective of symptomatic status, functional significance of the stenosis, or any form of prognostic evaluation. Currently up to 71% of percutaneous revascularization procedures are being performed in the absence of any sort of functional evaluation (2), and it is feared that this worrisome trend will amplify with the generalization of the previously described scenario. As stated by Rispler et al. (1), "luminology might determine patient management with the so-called oculostenotic reflex resulting in a large number of therapeutic interventions." Thus, although CT angiography is universally acclaimed as a unique opportunity to extend our capability to diagnose coronary artery disease with the potential to impact on sudden ischemic cardiac death and unheralded acute myocardial infarction, we are faced with the unmet need to redesign diagnostic work-up paradigms. Most importantly, the critical question relates to the specific role and appropriate use of CT in the various populations and patient subgroups with suspected or probable coronary artery disease (3).

A Glimpse Into the (Near) Future?

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A Visionary Approach

The contribution by Rispler et al. (1) addresses that very issue in a population of 44 patients with a high prevalence of coronary artery disease (70%). They have used an integrated single-photon emission computed tomography (SPECT)/CT device to identify the presence of coronary stenoses, and in the same go, they have determined their functional significance by myocardial perfusion imaging. Both results are presented in an extremely attractive fused display mode (Fig. 3 in Rispler et al. [1]) that immediately conveys the relevant information even to lay eyes. As expected, many stenoses identified by anatomy did not cause perfusion defects: of 32 patients with stenoses at angiography, SPECT was abnormal in 24 patients. Compared with the combined invasive angiogram and the SPECT results as the standard of reference, diagnostic performance indexes, in particular specificity and positive predictive value, were superior for the combined SPECT/CT approach, as opposed to CT alone. The potential implications of such findings are far reaching. If indeed only hemodynamically significant lesions should be revascularized (4), then targeted mechanical revascularization can be planned on the basis of the available information, whereby stenting shall be restricted to significant stenoses. Although not stated in their manuscript, the invasive therapeutic procedure should be avoidable in a number of patients in whom plaque is present by anatomy (CT) but ischemia is absent by functional testing (SPECT). As a result, unnecessary stent implantations and a number of unnecessary revascularization procedures could be deferred. Considering the escalating costs of interventional procedures with drug-eluting stents and the concerns regarding their long-term safety, the proposed approach seems to make a lot of sense.

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From the Cardiovascular Center Aalst, Aalst, Belgium, Dr. Wijns has been principle investigator or coprinciple investigator for trials investigating drug-eluting stents (nearly all companies). Any honoraria on behalf of Dr. Wijns go to the Cardiovascular Center Research Foundation (nonprofit organization), which is the cofounder of Cardio 3, a biotechnology start-up company focusing on cell therapy.
A Constructive Critique

The authors themselves are offering a critical discussion of some of the limitations of their work. Appropriate concerns about the radiation burden of hybrid imaging technology are discussed. However, one should not forget that the proposed strategy could contribute to reducing the radiation exposure during subsequent invasive interventional procedures if indeed their duration can be shortened or some can even be deferred. As mentioned earlier, it would have been of interest to include a "per patient" analysis, even though the study group is small. It is regrettable that Table 2 (1) does not provide the reader with the detailed figures (numerator and denominator). As expected, a significant number of coronary segments could not be analyzed by CT angiography, and as a result, 12 patients had to be excluded from the analysis. Most likely, this is owing to the use of a 16-slice CT machine. From a broader perspective, it is obvious that the currently available hybrid machine must be an early-generation prototype that does not yet allow for each technology to be applied at its optimum. As mentioned, the performance of more recent CT machines surpasses the 16-slice technology that was used (5). Somewhat surprisingly, the authors do not provide a detailed description of the correlation between their findings at invasive angiography versus CT angiography. Likewise, SPECT could not be applied at its best. As acknowledged, SPECT imaging did not yet incorporate attenuation correction. Dealing with misalignment artefacts between SPECT (acquired while breathing) and CT (acquired during breath holding) will require further software improvement. From a clinical perspective, it would have been of interest to know whether actual treatment decisions regarding revascularization were indeed respectful of the combined anatomic-functional data, as reported here.

But the main criticism to the author's approach is that the study design incorporates a strong component of self-fulfilling prophecy. Indeed, the SPECT functional data were analyzed in combination with both the invasive angiography (reference dataset) and the CT angiography (dataset to be tested). In this way, the authors are correlating apples with apple mousse, and the comparisons are necessarily flawed by internal consistency. Proper validation of the hybrid SPECT/CT approach would require an independent functional evaluation with either noninvasive or invasive functional testing. In addition, one is entitled to raise concerns about the accuracy of myocardial perfusion imaging in identifying the significance of individual stenoses, in particular in the context of multivessel disease. Lima et al. (6) have shown in 143 patients with severe triple-vessel disease by angiography that a scintigraphic pattern of triple-vessel disease was seen in only 10%, 2 vessels were declared abnormal in 36%, only 1 territory showed abnormal perfusion in 36%, and none in the remainder. Although the performance of myocardial perfusion imaging is excellent for the detection of significant disease on a "per patient" basis, its performance with individual lesions is limited. If indeed combined noninvasive anatomic-functional imaging will be used to decide whether individual stenoses should or should not be revascularized, the entire process—including choice of tracer, type of stress, imaging protocol, instrumentation, data analysis, and reporting—will need to be reengineered as to improve the accuracy and discriminative power of SPECT imaging on a "per vessel" basis. This leads us to the next important question.

Which Hybrid Imaging Technology to Choose: SPECT/CT or Positron Emission Tomography (PET)/CT?

As we have just alluded to, simply transferring the best of contemporary, state of the art, SPECT myocardial perfusion imaging to the hybrid SPECT/CT device might not be sufficient to establish the technology as the cornerstone on which to build the new diagnostic and therapeutic paradigm in patients with known coronary artery disease. Interventional cardiologists and surgeons will not endorse a recommendation to defer therapy, unless the gatekeeper is proven robust and sensitive. Yoshinaga et al. (7) have demonstrated why relative perfusion imaging with SPECT has important inherent limitations for the determination of hemodynamic significance of individual lesions when compared with quantitative oxygen 15-labeled water and PET. Segments with coronary stenosis but normal SPECT still showed reduced coronary flow reserve at 2.22 ± 0.87 (significantly lower than 3.86 ± 1.24 for normal segments, p < 0.001). Thus, so as not to underestimate the extent of inducible ischemia, it might be desirable to invest in hybrid PET/CT instrumentation, even though tracer availability and quantification of blood flow in absolute terms remain challenging (8).

Future Steps

The world of cardiac imaging is proposing to the clinician an ever-increasing spectrum of options and tools, with the disadvantage that patients are submitted to multiple, sequential, time-consumimg, and costly diagnostic procedures and tests, sometimes contradicting each other. The concept of obtaining combined anatomic and functional tridimensional noninvasive imaging of the coronary circulation in a single session through hybrid SPECT/CT instrumentation is particularly appealing. As discussed earlier, this approach has the potential to become the central decision-making element in the future diagnostic and therapeutic strategy for patients with coronary artery disease. However, there is a long road ahead to achieve this endeavor. Validation studies like the present one (1) will be essential but not sufficient. The technology requires further improvement, and the strategy itself will have to be tested prospectively. Until now, diagnostic imaging techniques have been implemented largely on the basis of observational studies, with only few prospective randomized trials. A change in paradigm like the one proposed by Rispler et al. (1) will not
be adopted unless appropriate evidence becomes available from patient-outcome–based randomized trials with clinical efficacy and cost-effectiveness end points.

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REFERENCES