The integrative value of myocardial perfusion-function imaging with 13N-ammonia positron emission tomography
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Summary, Discussion, Future Trends in non-invasive imaging of coronary artery disease and Conclusions
DISCUSSION OF SUMMARIZED FINDINGS

The present thesis has attempted to provide arguments about the methods and clinical utility of the absolute quantification myocardial perfusion with the state-of-the-art technique known as PET (Chapter 1) in myocardial ischemia due to coronary artery disease (CAD). Furthermore, it addressed the complex associations between measurements of myocardial perfusion (such as rest and stress myocardial blood flow [MBF] and myocardial perfusion reserve [MPR]) and functional components of left ventricular motion (left ventricular ejection fraction [LVEF] and entropy).

Section II

The methodological feasibility of the simultaneous assessment of cardiac and renal perfusion was studied in Chapter 2 by means of a rat model for myocardial infarction (MI). Although the sample size in the study was limited, we were able to document and effect of the decreased cardiac perfusion and systolic function on the medullar and cortical perfusion of the kidney. Additionally, effect size calculation was performed and reported. Effect sizes served us as means to objectify differences independently from statistical testing. Moreover, they allow for future comparisons with alternative results in the area.

There is no simple relationship between cardiac perfusion and function. Therefore, measurements acquired through different techniques should seek to be complementary rather than overlapping. Figure 1 depicts the profile of findings concerning perfusion, function and (coronary) anatomy, which varies according to the clinical risk profile of the population studied.

Further, it is clear that previous cardiovascular events such as an MI strongly modify the relationship between perfusion and ventricular function. There are two main measures of coronary vasodilatory capacity namely, stress MBF and MPR. In Chapter 3 we described how stress MBF is better correlated with resulting systolic function than MPR (both in patients with and without a previous MI). We believe that this partially contributes to explain the previously reported better performance of stress MBF in the detection of significant CAD or residual ischemia.

It is true that there is a range of perfusion abnormalities that may not translate into functional abnormalities. However, it is likely that reversible
### The Spectrum of CVS Risk and Non-invasive Evaluation Findings

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<tr>
<th>Normal</th>
<th>Subclinical Disease</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
<th>Post-CVS Event</th>
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**Figure 1.** Profile of findings in cardiac perfusion, function and coronary anatomopathological findings according to traditional risk stratification. Checkmark, preserved; ̃, variable; X, affected.
perfusion abnormalities translate in subtle decreases in ventricular function. We documented that quantitative perfusion abnormalities and overt functional deterioration are better coupled phenomena when the functional reserve of the myocardium has been compromised, for example, when there is evidence of a previous MI (residual scar tissue evidenced by fixed perfusion defects). It is in this clinical scenario when quantitative myocardial perfusion may constitute the best surrogate to evaluate the effectiveness of therapeutic management, as it correlates with residual ventricular function independently from the extension of the non-viable myocardial area (Chapter 4).

The clear influence of residual scar tissue after an infraction on perfusion quantification incited us to try a modified method that would be able to exclude areas of fixed perfusion defects. We generated an “in-house” algorithm that delivered perfusion measures which were better correlation with left ventricular ejection fraction independently from the area of scarring (example polar maps were shown in Chapter 4). However, this method of MBF estimation did not prove to be time-efficient and it is likely that future software can aim to facilitate this process in a valid and reliable fashion.

Section III

By means of retrospective clinical study, we evaluated how comorbidities like type 2 diabetes mellitus (DM2) are deleterious for the ventricular functional performance of the myocardium through coronary vascular function -dependent and -independent mechanisms (Chapter 6). In this sense, we documented a possible direct effect of DM2 on systolic function is a population of patients with no previous scarring or major adverse cardiac events. We believe that the value of the perfusion-function evaluation is modified by the additive effect of these co-morbidities and we suspect that adjusted prognostic thresholds may be of interest in the future. A comprehensive scheme is presented in Figure 2.

In the last original chapter, a systematic review and meta-analysis, the prognostic value of myocardial perfusion reserve for the occurrence of major adverse cardiovascular events was demonstrated. A number of relevant concerns that arise from the current protocols for quantification of myocardial perfusion were also highlighted (Chapter 7).

Scientific methodological research has strived in the last years to pursue
standardization. Implementation of technically demanding techniques, such as cardiac PET, has been further complicated by the constant modernization of equipment and protocols. This has resulted in a non-negligible amount of methodological heterogeneity in PET application. Still, the repercussion of this heterogeneity on the clinical outcomes of patients or even in the daily diagnostic determinations has no yet been fully described, and this represents a challenge for comparability.

Large common databases to conduct the needed large scale studies on
PET are still lacking (1). Technique standardization and optimal selection of the most appropriate patient population that will likely benefit from this evaluation, constitute important objectives to be addressed. The same applies for the integration of the complementary ventricular function evaluation.

A lot of discussion has taken place around the optimal application of cardiac PET imaging due to its elevated cost. This argument is growing in the verge of newer integrative techniques such as PET/MR. This is because the existence of powerful imaging techniques cannot automatically justify broad clinical application if they do not translate into clear-cut diagnostic or prognostic benefits in a patient-to-patient basis.

This thesis contributes with the body of knowledge around the utility of the integration of measures of cardiac perfusion and function derived from PET imaging. A next step would be the construction of an algorithm to address parameter combination as this could provide more sensitive estimates for diagnosis and risk stratification in cardiovascular disease. A crucial issue that remains is whether results of an improved risk stratification may be modified by adaptation of current management policies (2).

A very relevant area deserving attention is hybrid imaging. As diagnostic performance can improve when performing hybrid imaging (either side-to-side or true fusion) (see “Intermedio” related to PET/CT) the same should be expected in the area of prognostic evaluation (SPECT/CT, PET/CT and PET/MR).

I present the following integrative Figure 3. This image offers a comprehensive view of the progression of coronary artery disease, its pathologic findings, related manifestations, areas of non-invasive evaluation benefit and current uncertainties.

**FUTURE TRENDS**

It is evident, especially for clinicians, that a significant and growing proportion of patients fall outside the scope of traditional risk estimation (having survived major adverse cardiovascular events and/or interventions). Therefore, an updated view should extend the traditional depiction of atherosclerosis progression into the “post-event” (MI) realm (see Figure 3).

Although an increasing number of specialized centers around the world have implemented hybrid equipment in the form of PET/CT (and now
The Ischemic Cascade and Non-invasive Evaluation

**Figure 3.** The extended model of the progression of CAD. This depiction shows how broad the application of current non-invasive imaging techniques can be. Therefore, insights into the diagnostic and prognostic value of PET will have to be further outlined starting from the location of the patients within the spectrum of coronary artery disease.
also PET/MR), numerous imaging departments may still be operating using PET-only or older PET/CT cameras. Future studies will have to find creative solutions to this heterogeneity in order to generate robust statements about their clinical utility.

Imaging studies have been and will certainly remain an important part of the approach to the patient with cardiovascular disease. SPECT, PET and hybrid imaging trends will be described next, as well as what is expected from the choice for a utilizing an imaging technique.

**SPECT**

SPECT is the most widely spread nuclear technique and a great body of evidence has been generated around it. However, conventional SPECT has some limitations, such as a relatively long acquisition time, limited image resolution, frequent artifacts due to patient movement, extra-cardiac tracer uptake and patient radiation exposure. There is a search for improvement through implementation of attenuation correction (a standard component of PET imaging) through hybrid SPECT/CT, which will reduce the attenuation artifacts created by surrounding tissue.

Two other recent developments have driven innovation in SPECT imaging. One is the recent implementation of IQ-SPECT, a technology that may achieve improved resolution and focused zoom in cardiac acquisition through the use of a directed centripetal structure of its collimators with lower radiation doses and shorter acquisition time (3–5). The other one is the development of the highly sensitive cadmium-zinc-telluride (CZT) crystals, which have opened the door for dynamic SPECT and the potential to quantify myocardial blood flow and perfusion reserve in the near future (6).

**PET**

Apart from the characterization of myocardial perfusion and function, PET imaging has developed in the evaluation of inflammation of the atherosclerotic plaque. Inflammation plays a critical role in the formation, progression and rupture of atherosclerotic plaques. Parallel to this, there is a clear need to monitor the effects of atheroma-modifying therapies and $^{18}$FDG ($^{18}$F-fluorodeoxyglucose) PET has already demonstrated to play an important role (7). Unfortunately, imaging of the coronary vasculature with FDG is limited by resolution as well as motion artifacts (8,9). In consequence,
further characterization of plaque status has been proposed using a different tracer, \(^{18}\text{F}-\text{sodium fluoride}\) (\(^{18}\text{F}-\text{NaF}\)). \(^{18}\text{F}-\text{NaF}\) is able to identify active microcalcification associated with high-risk plaques (10–12), and hopefully, it will further contribute with the comprehensive evaluation of risk of hard events in cardiovascular patients.

There is a clear need to bypass the need for an on-site cyclotron, and upcoming results from the trials involving \(^{18}\text{F}-\text{fluripirdaz}\) (as well as other novel tracers in earlier phases of development) may offer a new dimension in the reach of clinical myocardial perfusion imaging with PET.

Finally, there is increased attention being directed to protocol optimization in discrete subgroups of patients who may benefit from stress-only acquisitions in order to rule-out significant CAD, and measures such as stress MBF and stress LVEF may play a fundamental role.

**Hybrid Imaging**

The combination of multiple imaging techniques, when appropriately indicated, could integrate the strengths, and address several limitations particular to each modality. For instance, the combination of PET with computed tomography (CT) or magnetic resonance (MR) and SPECT with CT may allow for a reduction in radiation dose and scan time while enhancing image quality.

Integrated PET/CT has shown value by adding anatomic evaluation of the coronary vessels providing detection of calcified and non-calcified atherosclerotic plaques as well as associated coronary artery calcium score (13,14). The standard cardiac PET/CT protocol includes the attenuation correction computed tomography image acquisition, followed by the rest/stress PET stage, and if clinically indicated, either a coronary artery calcification score or CT angiography (CCTA). CCTA provides complementary anatomical information. In this sense, a completely normal CCTA can rule out epicardial atherosclerotic disease with a sensitivity of 96% and negative predictive value of 94%. However, due to its moderate specificity of 76% and positive predictive value of 84%, it requires confirmation of normal peak-stress MBF and MPR to rule out coronary microvascular dysfunction.

The concept of hybrid imaging should also be understood as the possibility to characterize pathological processes (such as CAD) with the utilization of protocols involving double radiotracers (in the case of
PET, perfusion and micro-calcification may be of interest) in addition to the simultaneous CT or MR assessment. In this way, complementary pathophysiological information can be obtained while anatomy is accurately characterized. A handful of centers are now equipped with PET/MR cameras, and their benefits in terms of patient safety (due to less radiation exposure) and advanced tissue characterization will likely represent the next leap in integrative non-invasive cardiovascular imaging. Currently, studies on technique cross validation and protocol optimization are being undertaken.

Choice of Imaging Study

Evidently, the different features of each imaging modality may enhance a broader comprehension of distinct aspects of CAD. However, it would be inadequate to undertake a liberal approach of performing multiple unjustified studies. There is no single imaging study with impeccable accuracy and universally indicated for cardiovascular diseases; the physician must always take into consideration the study’s availability, cost, advantages and limitations, inherent risks (as the still not completely solved incompatibility of MR scanners and metal-containing devices, or the variable radiation doses of CT and nuclear imaging according to the utilized protocol and hardware), expected benefits, as well as the patient’s preferences, health status and healthcare costs.

CONCLUSION

Non-invasive cardiovascular imaging has developed at a tremendous pace. PET myocardial imaging play an important role in current non-invasive evaluation of coronary artery disease. It offers unique advantages such as perfusion quantification in absolute terms and the complementary evaluation of ventricular function. The data provided by PET perfusion imaging is bound to improve the integrative evaluation of patients at risk of cardiovascular events, especially if optimal combinations of pathological cut-off are established.

This growth in the modality repertoire is visibly leading to the implementation of non-invasive multi-modality approaches which harvest individual techniques’ strengths and particular indications, the expected “one-stop-shop” for cardiovascular evaluation. In the near future, a clinical
reality in which a single comprehensive study may be swiftly selected and performed in order to correctly diagnose and evaluate prognosis, is desired. We believe that PET imaging will represent a key player in this area.

Futures research must still account for standardization through guideline implementation and protocol optimization as we advance into an era of multiple and newer radiotracers as well as hybrid equipment.
REFERENCES


