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Cardiac PET-CT for Monitoring Medical and Interventional Therapy in Patients with CAD: PET Alone Versus Hybrid PET-CT?

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Abstract

This review focuses on optimal use of PET and PET-CT in monitoring medical and interventional therapy in patients with CAD. PET provides quantitative measurement of absolute myocardial blood flow and thus permits comprehensive physiological assessment of the coronary circulation. Hybrid PET-CT, in particular CCTA, adds anatomical information to maximal MBF measurement and so facilitates distinction of triple vessel focal epicardial disease from coronary microvascular disease or diffuse coronary atherosclerosis without focal stenoses. Hybrid PET-CT also may be of value in determining appropriateness and feasibility of percutaneous interventional therapy for chronic total coronary occlusion. PET alone, however, is the preferred modality to address functional status of the coronary circulation and response over time, if required, to medical or interventional therapy. CT at a minimum provides attenuation correction. More detailed CCTA should be added only when a well-defined need for anatomical information is required to answer the clinical question posed.

Keywords

Cardiac PET; Hybrid PET-CT; Myocardial blood flow; Coronary artery disease; Treatment of CAD; Coronary flow reserve; Medical and interventional therapy

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Any discussion either of positron emission tomography (PET) alone or in combination with computed tomography (CT) for monitoring medical or interventional therapy in coronary artery disease (CAD) should start with consideration of the circumstances under which the monitoring is to occur. Two broad categories immediately suggest themselves and are fundamentally different in nature. Thus, in the experimental setting, monitoring, however it is to be done, will be driven by a variety of considerations not least is the hypothesized outcome and the time over which changes from baseline are expected to occur. The type of changes which are to be measured is a key factor in determining the need for PET alone versus hybrid PET-CT. Any study for instance in which both coronary anatomy and physiology are the focus of interest will clearly require the hybrid approach unless anatomical information (e.g., invasive coronary angiography) is already available. Physiological changes in response to an intervention in subjects with known chronic CAD on the other hand would be best studied with PET alone [1, 2] and in the majority of cases would not require hybrid PET-CT (save for CT based attenuation correction). PET-CT, however, will be required for research in which ^{18}F FDG is used, for instance, to study vascular inflammation [3–5]. Further, hybrid PET-CT is likely to be increasingly employed with a variety of either ^{18}F or ^{11}C labeled molecular probes for experiments directed at elucidating pathophysiology of processes such as cardiac remodeling in heart failure [6, 7•] most commonly due to chronic CAD, activity of the autonomic nervous system in the setting of cardiac transplantation [8] as well as chronic CAD [9], risk for ventricular arrhythmia and sudden cardiac death in the setting of chronic myocardial infarction [9] as well as monitoring gene transfer expression [10] and stem cell therapy [11–14] for CAD.

In contrast, patients who are studied exclusively for clinical reasons present a very different set of considerations regarding the choice of PET versus hybrid PET-CT. First, it should be recalled current appropriateness criteria and American College of Cardiology/American Society of Nuclear Cardiology (ACC/ASNC) “Choose Wisely” program strongly discourage serial imaging with ionizing radiation (i.e., single photon emission CT [SPECT], PET, CT) in asymptomatic patients and those who are doing well clinically with unchanged, stable symptoms even if they have had prior percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) [15•, 16, 17]. Those in whom there is concern regarding incomplete revascularization or have onset of new symptoms consistent with myocardial ischemia either 2–5 years post prior PCI or CABG or more than 3 months post recent PCI are considered appropriate candidates for repeat myocardial perfusion imaging [17]. The choice of PET alone versus hybrid PET-CT in large measure will depend on individual clinical circumstances. In the majority of cases PET alone to assess for functional abnormality (e.g., impaired maximal myocardial blood flow in one or more vascular distributions) is likely to suffice [18•, 19, 20, 21•]. Subsequently, depending on outcome, the clinician is in an excellent position to determine if cardiac catheterization with an eye to coronary revascularization either by PCI or CABG is the appropriate next step. More detailed clinical scenarios and discussion of PET alone versus hybrid PET-CT follow.

CT Technical Considerations

The choice between stand-alone PET and hybrid PET-CT exam will depend at least in part upon a number of technical considerations related to the capabilities of the scanner itself and the precise nature of the information required. While hybrid PET-CT scanners allow for attenuation correction, they may also be utilized for coronary artery calcium (CAC) score or coronary CT angiography (CCTA). Specifically to patients with known CAD, the addition of CCTA may provide incremental anatomical information to maximal myocardial blood flow (MBF) measurement by delineating triple vessel epicardial disease from coronary microvascular disease or diffuse coronary atherosclerosis without focal stenoses. However, the risk-benefit ratio of extra radiation exposure and requirement for iodinated contrast needs to be weighed with respect to the complementary CCTA data.

Special consideration is needed with respect to the CT portion of the hybrid system. Current hybrid PET-CT scanners remain single-source CT scanners, with the number of slice detectors ranging between 4- to 128-slice and require specialized cardiac CT software. The standard cardiac PET-CT protocol include the attenuation-correction CT image acquisition, followed by the rest/stress PET portion, and if clinically indicated either a CAC score or CCTA. Myocardial scar imaging with CT delayed enhancement imaging is yet another scan acquisition that would be performed 10 minutes post iodinated contrast administration [22]. CT protocols for attenuation correction alone differ from requirements for obtaining formal CAC score scan which in turn differ from that required for CCTA [23]. Thus, the decision to include either a dedicated CAC score or CCTA with or without delayed enhancement following the PET acquisition needs to be determined prior to the patient's exam. Particularly with CCTA, there are additional requirements including the need for patient preparation with beta-blockers, sublingual nitroglycerin administration, intravenous contrast, and proper instruction for optimal breath-hold.

The attenuation-correction CT scan is a non-contrast, not electrocardiographically (ECG)-gated, free breathing acquisition performed to best match the PET scan and has excellent though not perfect agreement for detection of coronary calcium as compared to a dedicated CAC scan, which is ECG-gated [24]. CAC score scanning, whether obtained from the attenuation-correction CT scan or separately after the PET study, provides little risk with no requirement for intravenous iodinated contrast and may be performed with low radiation dose (typically <2 mSv). While the utility of a calcium score has been well-established for asymptomatic patients without known CAD [25, 26], this benefit is negated for those with symptoms and known CAD especially since absence of calcium does not equate to absence of obstructive CAD [27••]. As such, the dedicated ECG-gated CAC scan after the attenuation-correction CT-PET scan is probably not warranted in most patients with known CAD, and can be eliminated from the protocol to reduce scan time and unnecessary radiation to the patient.

With regards to CCTA, the field of imaging the coronary arteries has rapidly advanced since the late 1990s due to the development of multi-detector CT technology. Initially with the 4-slice CT scanner, full volumetric coverage of the heart was possible over multiple heartbeats and a single breath-hold of approximately 30 seconds. As CT scanner technology improved,

wider detector array increased to 64-slice detectors, now most commonly employed up to as many as 320-slice scanners. The greater number of detectors allows more of the heart to be imaged within one cardiac cycle, which in turn means the entire heart can be scanned in just a few heartbeats. Accordingly, radiation exposure is reduced and breath hold time of <10 seconds made possible. Additionally, dual-source CT scanners where there are two X-ray sources aligned with opposing 128-slice detectors are now available. These technological improvements in CT scanners (with the 256-slice or 320-slice single source CT or the dual-source 128-slice CT scanners) allow for single-beat image acquisitions providing full coverage of the heart in one cardiac cycle, thereby further reducing radiation exposure to <1 mSv [28, 29•, 30•].

Several CT acquisition techniques may be utilized including retrospective-gating without tube modulation as well as dose-saving algorithms of retrospectively-gating with tube modulation or prospectively-triggered algorithm (Fig. 1). While the selection of acquisition mode affects radiation dose, it is driven by the patient's body habitus, heart rate and rhythm [31]. With retrospective or helical scanning, the typical median radiation dose from a CCTA is 12 mSv [31]. While there remains controversy on the increase of cancer risk from one medical imaging scan [32•], the theoretical concerns that there were non-negligible cancer risk (which were estimated from simulation models [33]) have led to the successful implementation of newer CT scanner technology as well as dose-saving algorithms, such as prospectively-triggered scanning and lower kVp to yield radiation doses on the order of 3–6 mSv, though typically at the cost of inability to obtain cardiac contractile function [34•, 35•].

However, current hybrid PET-CT scanners do not have the newer, dedicated CT scanner capabilities since the CT portion of the hybrid PET-CT remains single-source. The number of detectors range from as few as 4-slice, to the current standard of 64-slice, up to a maximum of 128-slice detectors with some newer hybrid PET-CT models. Performance of CCTA in accordance with current practice guidelines requires minimal technical capabilities of CT equipment with 64 or more slices, submillimeter spatial resolution, and gantry rotation time less than 420 ms [36]. For single-source CT scanners, the temporal resolution is half the speed of the gantry rotation time. At the temporal resolution of 150–210 ms, depending on the scanner, beta-blocker use is needed for heart rate reduction of <65 beats per minute to obtain motion-free images of the coronary arteries. Additionally, intravenous iodinated contrast and sublingual nitroglycerin are required to opacify and maximally dilate the coronary vasculature. Thus, for hybrid PET-CT scanners with less than 64-slice CT technology or slow gantry rotation time on the order of 500 ms, it is not advisable to perform coronary artery assessment due to the poor image quality related to slab and motion artifacts as well as unwarranted higher radiation exposure, and prolonged breath-hold. Moreover, for patients whose heart rate is >65 bpm and cannot tolerate beta blockers (or calcium channels blocker) or those with cardiac rhythm disturbances including sinus arrhythmia, frequent atrial or ventricular premature contractions, or atrial fibrillation, CCTA is best avoided on the hybrid PET-CT scanner since the single-source detector would require retrospectively-gated acquisition without tube-current modulation, and so result in an unnecessarily high radiation dose (median 14–18 mSv) [35•].

Cardiac CT has the ability to assess for the presence of myocardial scar. Late enhancement imaging, 10 minutes post iodine contrast administration correlates well with results of cardiac magnetic resonance imaging, since the kinetics of iodine are similar to that of gadolinium [22, 37, 38]. While it does not require additional contrast administration beyond that of the CCTA, the non-contrast delayed scan exposes the patient to further radiation, similar to that of the CCTA itself and prolongs the examination by another 10 minutes. The extra radiation exposure from the CT portions of the exam needs to be added onto the radiation dose from the 20 mCi injection of ^{13}N of 1.48 mSv for the PET portion [39].

Perhaps in the future, as CT hardware and software technology continues to improve, radiation dose will continue to decline and information on hemodynamically significant coronary stenosis may be determined with just a single CCTA scan. Physiological assessment of coronary stenosis severity using computational fluid dynamic modeling to determine fractional flow reserve (CT-FFR) in conjunction with CCTA has been compared to standard invasive measurements [40•]. While accuracy (73 %), sensitivity (90 %), and negative predictive value (84 %) of CT-FFR versus invasively measured FFR (0.80 for hemodynamically significant stenosis) were good to excellent, sample size was small (80–252 patients depending on parameter assessed) and both specificity (54 %) and positive predictive value (67 %) either poor or only fair at best. In comparison with CCTA alone the study demonstrated improvement in ROC AUC in accuracy for detection of hemodynamically significant stenosis (0.68 v 0.81, respectively, $P<0.001$) even though it failed to attain its pre-specified goal of increasing the lower bound of per patient diagnostic accuracy above 70 % by addition of CT-FFR to CT alone (observed 95 % confidence interval 0.67–0.78). Accordingly, considerable additional research is required before the methodology is applicable for routine, widespread clinical use. Presently, in fact, the methodology remains proprietary (HeartFlow Inc, Redwood City, CA) and is available for research only through the company's web site to which patient data must be uploaded for analysis by HeartFlow [40•].

It is apparent, therefore, that a number of technical factors must be taken into consideration in choosing between stand-alone PET and hybrid PET-CT. In some cases, detailed CT information may be difficult or impossible to obtain and even when possible will increase the radiation exposure of the exam. Clearly, the added time, contrast load and radiation exposure must be considered against the clinical importance and impact on patient management the PET-CT exam will provide.

Diagnostic Evaluation

Perhaps the most common clinical scenario encountered in patients with known CAD relates to the need to assess the functional status of the coronary circulation in one or more specific vascular territories. Such patients often have had prior intervention, CABG or PCI or both, and present with recurrent symptoms indicative of myocardial ischemia. Stand-alone PET quantitative measurement of myocardial blood flow under conditions of maximal vasodilation, typically with adenosine, though regadenoson or dipyridamole may be employed, has been shown to be an accurate method for detection of hemodynamically significant coronary stenoses [18•, 19, 20, 21•]. Since absolute myocardial blood flow is

measured (ml/min/g), it is possible to independently evaluate all three major coronary vascular distributions and compare flow response in each to an absolute standard in order to determine if any or all are compromised. While the absolute value of maximal MBF which best predicts the presence of an hemodynamically significant stenosis may vary depending on technical factors such as tracer employed, scanner, acquisition and reconstruction parameters, published values from several laboratories using a variety of methods and tracers have been fairly consistent. Thus, maximal MBF in the range of 1.85 to 2.20 ml/min/g have been reported as optimal cut points and have been associated with high predictive accuracy for presence (or absence) of hemodynamically significant stenosis [18•, 19, 20, 21•]. In the great majority of clinically encountered cases anatomical information offered by addition of CCTA will not be required [18•]. Thus, PET alone has the advantage of reduced cost and radiation dose compared to that of a PET-CTexam. A more detailed CCTA study, as discussed below, should be considered, if for instance, information pertinent to determination of myocardial viability or the status of coronary collaterals is essential to clinical decision making. Similarly, addition of anatomical data (i.e., CCTA) will help distinguish diffuse coronary atherosclerosis (without focal stenoses) or microvascular disease which could be mistaken for severe triple vessel epicardial coronary disease based on physiological information alone [21•, 41, 42•, 43•].

Selection of Patients for Complex Coronary Intervention

Recent advances in interventional cardiology have made it possible to better approach and intervene upon chronic total coronary artery occlusions [44, 45]. There are at least two important factors which come into play in determining if such intervention 1) is warranted and 2) is technically feasible. Evidence of myocardial viability, typically associated with prominent collateral supply to the distal vessel, is one factor since there obviously is little value in attempting reperfusion of scar. Moreover, the presence of well-developed collateral circulation opens the option of retrograde approach to the occlusion [45], which depending on the precise anatomy, may be the optimal or even only way to approach it. The viability issue is addressed by assessment of the transmural extent of delayed hyper enhancement just as it is in MRI [46–49, 50•]. In an initial preliminary small study using the newer CT technology of dual-source CT scanner, the accuracy of CT assessment of myocardial viability has been shown to be similar to that of MRI, though with lower contrast-to-noise ratio and higher noise [50•]. Additional radiation is required for the exam in comparison with that for simple CCTA but permits an assessment of extent of transmural scar, if any, and adequacy of the collateral circulation distal to the occlusion. Accordingly, PCI for revascularization of chronic total coronary occlusion represents a clear example in which hybrid PET-CT (with at least 64-slice CT technology) may be more useful than PET alone.

Evaluation of Patients with Heart Failure

Another scenario in which hybrid PET-CT may prove more useful than stand-alone PET assessment of maximal myocardial blood flow will be in circumstances in which maximal MBF is globally reduced and the differential must be made between severe, epicardial triple vessel disease and either diffuse coronary atherosclerosis without focal stenosis or diffuse microvascular disease [19, 20, 41, 42•]. The latter is commonly encountered in patients with

heart failure, generally with LV dilation and reduced LVEF [41, 42•], who often have associated diabetes or hypertension or obesity or some combination of each [51–55]. In cases such as these it may be best from a logistics standpoint to plan on a hybrid exam rather than attempt real time image reconstruction, processing and analysis of the MBF data before determining if CCTA will be required. However, in patients in whom contrast load may be an issue (e.g., diabetes, renal insufficiency) analysis of the MBF data first is the best approach prior to making a decision on CCTA. The hybrid PET-CT study is best suited to heart failure patients with low to intermediate prior probability of CAD in whom the primary purpose of the procedure is to exclude extensive CAD as the etiology of heart failure and thereby avoid the risks and expense of invasive coronary angiography. It also should be noted the functional information gained regarding maximal dilator capacity of the coronary circulation carries important prognostic information which may be more predictive of cardiac death than either left ventricular ejection fraction [56] or extent of epicardial CAD [57]. Once the coronary anatomy has been defined follow up examination(s) for assessment of the functional status of the coronary circulation, should they be required, may be accomplished by PET measurement of maximal MBF alone.

Conclusions

In the clinical realm, monitoring medical or interventional therapy or both in patients with known or even suspected CAD is done on an as needed basis to address a specific clinical issue. Routine follow up exams in patients who are doing well and have no new issues, in general, are strongly discouraged with few, if any exceptions. Clinical or basic research is another matter entirely and generally will require multiple studies over time. The choice between PET alone and PET-CT will be determined by the hypothesis being tested and the nature of the intervention employed. Clinically, the decision to employ PET quantitative measurement of myocardial blood flow versus hybrid PET-CT to obtain both physiological and anatomical data should be based on the issue requiring attention. In the majority of cases physiological data, particularly maximal myocardial blood flow in response to vasodilator stimulation will provide the needed information with which to formulate an appropriate clinical plan. PET measurement of rest MBF also may be necessary in selected patients especially if coronary “steal” is an important clinical issue (e.g., LIMA graft distal to subclavian stenosis or collateral dependent myocardium supplied by jeopardized collaterals).

Certain scenarios, however, will require anatomical data to satisfactorily answer the clinical question in which case hybrid PET-CT becomes the modality of choice. Complex coronary intervention of chronic total occlusion and associated assessment of extent of transmural myocardial scar is a notable example. Likewise, in the heart failure patient with LV dilation and impaired contractile function the differential between severe triple vessel CAD and the microvascular disease associated with diabetes, hypertension and obesity is best made by PET hybrid CT exam, particularly in patients with low to intermediate risk of CAD and normal renal function. As noted above, the physiological information obtained concerning maximal dilator capacity of the coronary circulation has considerable prognostic value over and above traditional indicators such as left ventricular ejection fraction and extent of epicardial CAD [56, 57] and so provides further justification for a combined physiological anatomical exam as opposed to a purely anatomical one (i.e., invasive coronary

arteriography). The point, therefore, is to “choose wisely” [15•, 16, 17]. If physiological data alone will provide the answer to the clinical question, then PET quantitative measurement of maximal MBF is the most appropriate exam. Addition of anatomical data is appropriate when the clinical question cannot be answered without it.

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Fig. 1.

Schematic of the CT portion of the hybrid PET-CT system. **a.** Single-source computed tomography with a gantry that houses the X-ray tube and multi-detector array on the opposing side. The patient lies in the center of the table that moves through the rotating gantry. ECG-gating allows for image reconstruction at a fixed interval of the cardiac cycle to freeze cardiac motion. **b.** In retrospectively ECG-gated scan, the X-ray tube remains continuously on and image acquisitions are acquired in a “spiral” or “helical” mode with maximum tube current (middle) or with tube current modulation (bottom) where the X-ray tube current is decreased during portions of the cardiac cycle that are not of interest (e.g., systole) to reduce radiation exposure. Image reconstruction is performed afterwards. **c.** In prospectively ECG-triggered (“sequential” or “step-and-shoot”) scan, the X-ray tube is turned on only during image acquisition at a pre-defined set duration after the QRS complex. The table is then advanced and the next series of images are acquired prospectively, typically every other heartbeat. (Modified with permission from: Truong QA, Joshi SB, Hoffmann U: Cardiac Computed Tomography: Description of Technology and Protocols. In Cardiac Imaging in Electrophysiology. Edited by Auricchio A, Singh J, Rademakers F. London: Springer; 2012:47–62) [58]