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Anatomy and function: PET-CT

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Abstract

CT coronary angiography and perfusion PET form an attractive combination to study coronary artery lesions and their consequences in patients with coronary artery disease. Whereas CT provides non-invasive assessment of coronary lumen and wall, PET perfusion is a reliable method for the evaluation of myocardial flow. CT, although very capable of ruling out significant coronary artery disease, is less than satisfactory in assessing the actual significance of the detected lesions. PET imaging, despite its excellent sensitivity, fails to describe the exact anatomy of the epicardial vessels. By fusing image data from these two modalities, lesions can be accurately correlated with their physiological or anatomical counterparts. Hybrid PET-CT devices, now in wide clinical use, allow such fusion in a one-stop-shop study. Although still seeking its place in clinical scenarios, growing evidence suggests that hybrid PET-CT imaging of coronary anatomy and myocardial perfusion can accurately – and non-invasively – assess the existence and degree of coronary artery disease.

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Introduction

CT coronary angiography with multidetector scanners has proven to be a valuable non-invasive alternative to diagnostic invasive coronary angiography for the evaluation of known or suspected coronary artery disease. While the negative predictive value of CT is extremely good, it is not possible to accurately assess the functional significance of the detected morphological lesions. On the other hand, positron emission tomography (PET) offers a non-invasive means to reliably estimate the myocardial blood flow and its possible impairment due to stenoses detected at CT. Thus, with the advent of hybrid PET-CT scanners, it has become appealing to combine these two techniques into one to achieve a comprehensive single-session study of both coronary anatomy and function.

Anatomy: CT

Coronary artery disease (CAD) remains highly prevalent and represents a healthcare burden: symptomatic atherosclerosis is the second leading cause of death by the age of 65. To enhance earlier diagnosis, an expansion and refinement of non-invasive armamentarium has occurred, and an intense debate regarding the strengths and weaknesses of competing imaging technologies and their appropriate clinical use is still on-going. The introduction and dissemination of new technology provides the potential for enhancing and expanding our understanding of disease processes and hopefully extend our treatment options while providing a tool for monitoring therapeutic responses.

Traditionally, evaluation of patients with suspected CAD has been based on non-invasive methods of detecting myocardial ischaemia followed by invasive coronary angiography to visualise the presence of luminal stenosis. This paradigm, however, has recently been challenged by the development of coronary multidetector CT (MDCT), which has emerged as a widely utilised alternative for a non-invasive diagnostic test of CAD. As an evolving method, its appropriate usage is still discussed and the indications are not indisputable. Despite this, the number of coronary CT studies has increased rapidly as improvements in technology have occurred. The ability to non-invasively image coronary arteries and obtain important clinical information on the presence, severity, and characteristics of CAD including the visualisation of luminal obstruction and atherosclerotic plaque, constitutes an attractive addition to previously available diagnostic tools.

Modern CT offers the tools for successful imaging of fast moving small structures such as coronary arteries. Images are ECG gated or triggered for freezing the motion, acquisition is fast enough for covering the heart during a few heart beats; new technologies allow for fast gantry rotation with narrow collimation and good image quality.

As its main implication for cardiac imaging, CT enables direct visualisation of coronary stenoses through the use of intravenous iodinated contrast. At present, a large number of studies with industry standard 64-section MDCT technology have been published. The meta-analyses have shown that the negative predictive value is excellent, close to 100%, suggesting that MDCT can reliably rule out the presence of haemodynamically significant CAD. Positive predictive values, however, have been less impressive[1,2]. Of the two multicentre trials published, one was consistent with the results of meta-analyses[3], but the other showed only moderate negative predictive value for CAD[4].

The accuracy for detecting stenoses depends highly on image artefacts. False-positive and false-negative interpretations are attributed to image artefacts in 90% to 100% of cases, where the major cause is usually the presence of calcifications. They often cause a blooming artefact that exaggerates the extent of the calcifications, thus resulting in overestimation of the stenosis.

Unlike invasive angiography, CT has the valuable ability to visualise not only vessel lumen, but also its walls to characterise plaques. Potentially, such assessment may help to identify plaques at risk of rupture, and direct treatment. Thus far, however, plaque assessment has had minor clinical impact on patient care – one may readily distinguish calcified from non-calcified plaques but separation of the different components of the soft lesion is more difficult.

Anatomy vs. function

One needs to keep in mind that it is ischaemia, not the epicardial disease as such, that determines the need for treatment. When revascularisation is performed in patients with documented ischaemia, the total mortality is reduced after procedure[5,6] because the ischaemic burden is reduced[7]. Although CT gives an estimate of the burden, and may even reveal some plaques at rupture risk, it fails to assess endothelial health, vascular reactivity or the possible other flow limiting consequences of the luminal changes detected. Hence, there is often discrepancy between anatomy of lesions and their effects on myocardial blood supply. This phenomenon, of course, is independent of modality and is evident when comparing the findings at invasive angiography (ICA) and fractional flow reserve (FFR)[8]. Only about half of the anatomically significant lesions detected with CTA are actually flow-limiting: Meijboom and colleagues[9] reported 49% accuracy of CTA predicting reduced FFR during ICA.

Considering the above, functional assessment is needed particularly in the evaluation of intermediate lesions, and the therapy of stenoses without functional effects may be deferred. The measurement of FFR during ICA has been suggested as a gate keeper for angioplasty, but in practice most therapy decisions are still based on anatomy[8].

Assessment of myocardial perfusion with PET

Positron emission tomography is (PET) is a nuclear imaging method based on the use of short-lived radioactive isotopes such as ^{18}F, ^{11}C and ^{15}O. A range of either natural substrates, substrate analogues or pharmaceuticals can be labelled with these radionuclides, enabling quantitative, non-invasive measurements of physiological and biochemical processes in living tissue.

Many studies have since the 1980s demonstrated that myocardial perfusion may be evaluated using PET[10]. As compared to PECT, PET has several advantages: First, image quality is superior due to the higher energy level of PET radio-pharmaceuticals leading to higher spatial resolution and less scatter. Attenuation correction is routinely used in PET thus reducing attenuation artefact. Second, the diagnostic accuracy of PET is high. A recent meta-analysis demonstrated good overall (92% sensitivity, 85% specificity) and coronary territory-based (81% sensitivity, 87% specificity) accuracy in PET[11]. A similar study, but using solely PET-CT instrumentation, showed sensitivity of 93% and specificity of 83%[12]. In direct comparisons between SPECT and PET, the ability of the latter to identify multivessel ischaemia has repeatedly proven better.

One of the reasons for PET`s superior performance is that, unlike in SPECT, quantification of tissue blood flow is a feature inherent in and typical to PET. ^{15}O-water and ^{13}N-ammonia are the tracers most widely used for the quantification of myocardial perfusion, with both tracer kinetic models well validated in animals against the radio-labelled microsphere method over a wide flow range[13,14] and equivalent in quantifying the perfusion[15].

The most widely clinically used cardiac PET perfusion tracer is, however, ^{82}Rb, which may be produced with a generator, and thus at sites without a cyclotron, provides an important clinical advantage. Although still limited in number due to non-linear kinetics of the tracer, studies performed with ^{82}Rb indicate that measurements of the myocardial perfusion are feasible and reasonably accurate at least with low MBF's[16].

Anatomy and function: PET-CT

The principal argument for hybrid imaging originates from the spatial correlation of morphological and functional information on the fused images, which facilitates a comprehensive interpretation of coronary lesions and their pathophysiologic relevance. An essential prerequisite of hybrid imaging is accurate image co-registration, because misalignment may result in erroneous allocation of perfusion defects to corresponding coronary arteries. From a technical point of view, image co-registration can be achieved by either a software-based or hardware-based approach. Hardware-based image co-registration permits the acquisition of fused anatomical and functional images using hybrid scanners (such as PET-CT devices) with the capability to perform nuclear and CT acquisition almost simultaneously with the patient in fixed position. Implicitly, image fusion is achieved fully or semi-automatically by superposition of image data sets. Such use of hardware-based image co-registration for cardiac applications requires certain quality measures. The variations in the position of the heart need to be controlled. The potential effects of gating differences need to taken into account and well was respiratory motion of heart.

In addition to localising and assessing coronary lesions and their effects, there are at least two other reasons to fuse PET and CT into a hybrid PET-CT. First, CT images can be used for attenuation correction of the nuclear scan, thus speeding up the study. Second, a very important benefit for the patient, a comprehensive study can be performed in a one-stop-shop fashion in a short time. The potential disadvantage is that the sequential procedure requires careful planning of logistics to enable fast patient turnaround. When performed successfully, however, these protocols are short and efficient, providing comprehensive information on cardiac anatomy and function in a 30-minute one-stop-shop study.

How-to: PET-CT step-by-step

The patient preparation for a hybrid PET/CT study is basically the same as for the individual scans. It is of vital importance that the patient's heart rate is controlled for CT, and that caffeine-containing drinks are avoided during the preceding 12 hours, because pharmacological stressors are commonly used in hybrid imaging. There are several protocols for hybrid imaging – each with certain advantages and disadvantages. In the options where the need of a perfusion study is individually decided upon after the findings in CT angiography, the protocol naturally starts with CT. This approach is powerful, because it utilises the high negative predictive value of CT, and only those patients with suspicious or indeterminate findings in CT will continue with perfusion imaging. Depending on the patient population, this fraction is usually between 25% and 50%; thus, on the average one perfusion session is needed for every three patients. The potential limitation is that the beta blockers often administered prior to CT angiography may also affect perfusion, although this is probably less significant with pharmacological stressors such as adenosine and dipyridamole.

If PET perfusion is performed first, this problem is avoided. On the other hand, the analysis of perfusion images is usually not fast enough to be available for an immediate decision on whether to leave CT angiography out in the case of a completely normal perfusion result. In addition, information on coronary plaques – even if they do not cause significant luminal narrowing – may be important for diagnosis and to direct appropriate medication. Thus, in the PET-first protocols, both studies are usually performed in all patients.

The positioning of the patient to the scanner bed is crucial. The patient should be relaxed and comfortable with the arms supported upright and out of the field of view. The CT protocol depends on the system used; it often includes a calcium score study that is performed first followed by a contrast enhanced CT angiography study. Thereafter, a low-dose CT scan for attenuation correction is performed (in some systems, the calcium score study can be used for this). The PET perfusion protocol depends on the tracer. In hybrid imaging, the stress study is performed using pharmacologic stressors such as adenosine, dipyridamole, or dobutamine. With short-lived PET tracers such as ^{82}Rb and ^{15}O-water (half-life 76 seconds and 112 seconds), the stress study can be performed almost immediately after the baseline (rest) study. With ^{13}N-ammonia, stress imaging is delayed for about 30 minutes to allow tracer decay. If a method to correct patient motion between stress and rest studies is not available, a second low-dose CT scan for attenuation correction is needed. In all protocols, however, quality control is needed to ensure proper alignment of the CT attenuation and PET emission scans, after which possible misalignment needs to be corrected. If the system is able to perform list mode acquisition, the data can be collected as ECG-gated mode that allows the simultaneous assessment of regional and global left ventricular wall motion from the same scan data, which is particularly practical in ^{82}Rb studies. The total time required for whole study session depends on the tracer used. With ^{15}O-water and ^{82}Rb, the whole session may be completed in 30 minutes, while the duration with ^{13}N-ammonia is 80 minutes. It is even feasible to shorten these protocols considerably if only a single stress perfusion scan is performed – which is possible with the assessment of the quantification of the myocardial blood flow.

The analysis of CT angiography includes standard processes and techniques such as visual assessment of original transaxial slices, multiplanar reconstructions (MPR), and utilisation of quantitative tools available. The analysis of the PET studies also follows standard procedures that have been explained in detailed guidelines[17]. However, to utilise the true power of hybrid imaging, an analysis system that is able to handle fused images and data should be used. By doing so, the individual coronary anatomy can be visualised together with functional information enabling accurate association between coronary anatomy and, e.g., perfusion. The most advanced analysis includes visualisation of perfusion in diagnostic quality multiplanar reconstructions of CT. If quantitative measurement of flow has been performed, the absolute stress flow values should be included in the analysis.

The added value of hybrid imaging – clinical perspectives

As mentioned before, comprehensive assessment of CAD requires not only morphologic information about coronary artery stenosis location and degree but also functional information on lesion severity. The evaluation of functional consequences of coronary stenoses is difficult with CT, and that is where perfusion imaging provides useful complementary information. Hybrid images offer superior diagnostic information with regard to identification of the culprit vessel and therefore increase diagnostic confidence. The initial experience from combined SPECT perfusion imaging and CT coronary angiography studies indicates that in almost one-third of patients the fused SPECT-CT analysis provided added diagnostic information on pathophysiologic lesion severity that was not obtained on side-by-side[18]. Similar results have been obtained using hybrid PET-CT imaging[12]. Because of the variations in the coronary anatomy in each individual as well as the complex disease pattern in these patients, correct allocation of perfusion defect and the subtending coronary artery was only achieved by the hybrid images. In addition, the diagnostic confidence for categorising intermediate lesions and equivocal perfusion defects was improved. Interestingly, most of the lesions that were originally found to be equivocal with regards to pathophysiologic severity on side-by-side analysis (due to the fact they could not be firmly assigned to a perfusion defect) were classified with high confidence by hybrid image evaluation.

From these preliminary results one can conclude that the greatest added value appears to be in the firm exclusion of haemodynamically significant coronary abnormalities seen on CT coronary angiography, which might be useful to avoid unnecessary interventional procedure. Other patients in whom hybrid imaging is likely to be clinically useful are those with multivessel CAD. Usually, myocardial perfusion analysis is based on the relative assessment of perfusion distribution. This technique, however, often uncovers only the coronary territory supplied by the most severe lesions. In multivessel disease, coronary flow may be abnormal in all territories, thereby reducing the heterogeneity of flow between “normal” and “abnormal” zones. This is obviously limiting the ability of relative perfusion analysis to detect multivessel CAD. An elegant solution to the problem is using quantification of myocardial perfusion[13-15] which provides independent information about all myocardial territories. In addition, integrated PET-CT offers an opportunity to assess the presence and magnitude of subclinical atherosclerotic disease burden and to measure absolute myocardial blood flow as a marker of endothelial health and atherosclerotic disease activity. Last, but not least, anatomical information from CT is able to identify the patients with severe balanced multivessel disease despite globally reduced but relatively homogeneous myocardial perfusion.

Figures 1-4 demonstrate clinical cases in which hybrid imaging proved beneficial. In Figure 1, quantification of perfusion reveals 3-vessel disease. Figure 2 demonstrates a case with a non-assessable coronary segment in CT with accompanying hybrid images. Figure 3 presents a patient with probable microvascular disease, whereas Figure 4 shows the power of hybrid imaging in the assessment of a culprit lesion.

Although the role of hybrid imaging still remains to be determined, it appears that this approach may have the potential to become an important decision-making element in the diagnostic and therapeutic strategy for patients with coronary artery disease. In addition to imaging myocardial perfusion and viability, vulnerable coronary atherosclerotic lesions may be studied. The ruptures of such plaques account for one-third of all deaths worldwide and constitute a major source of disability and cost. Non-invasive techniques such as MDCT can characterise morphologic criteria while the extremely sensitive nuclear imaging methods PET and SPECT utilise radio-labelled molecules designed to specifically target individual inflammatory activities in the plaques. This approach is possible only with high-resolution morphological imaging of the coronary arteries using hybrid imaging. Thus, with the newest generation of the hybrid imaging, it is likely that use of hybrid imaging shall extend from the detection of coronary artery disease using CT coronary angiography and nuclear perfusion imaging to other molecular imaging applications that are entering clinical cardiology.

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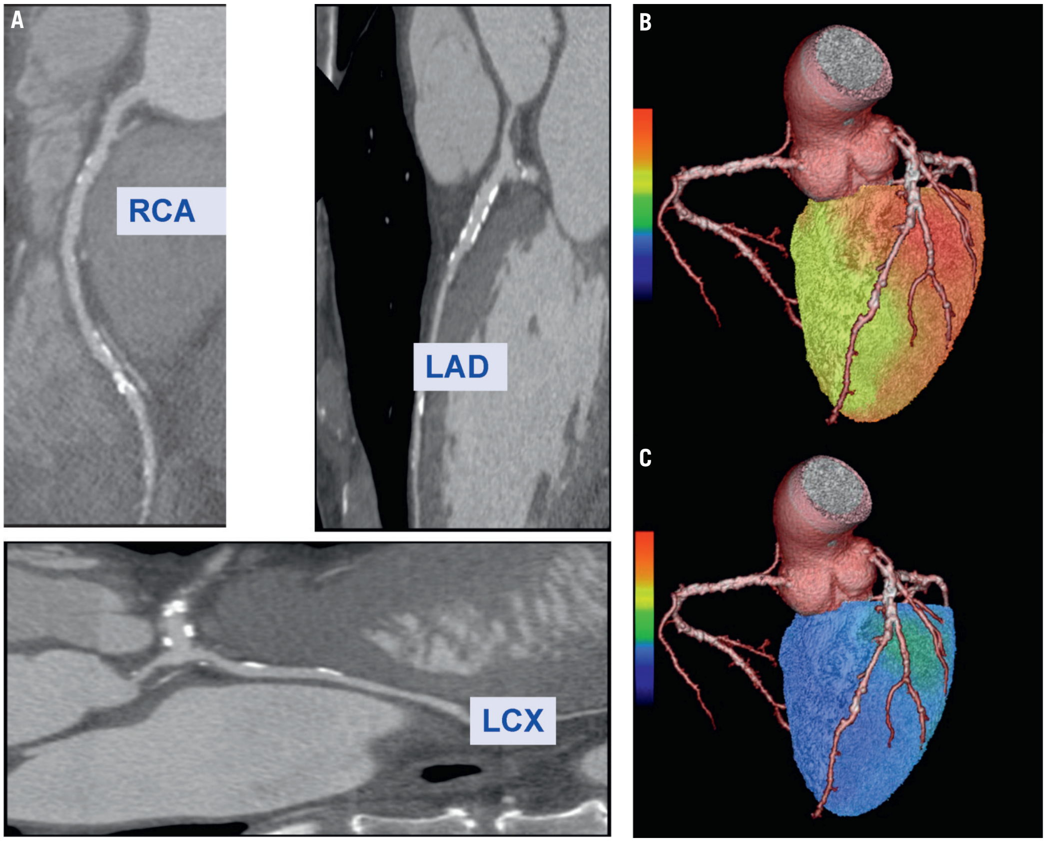

Figure 1. Images of a 67-year old male with 3 months` exercise associated angina that gradually got more severe. In exercise test, he had normal capacity and ECG. After the test, however, chest pain and ST-depressions appeared. The images show the potential of the absolute quantification of flow: 3-vessel disease is masked by relatively small regional differences between the vascular territories when only relative differences in flow are assessed. The diffusely reduced perfusion is, however, easily distinguished in the images portraying absolute values of blood flow. Panel A. CT angiography curved multiplanar reconstructions of the main coronary vessels. LM: left main, LAD: left anterior descending, LCX: left circumflex, RCA: right coronary artery. LM had >70% stenosis in CTA and invasive angiography (not shown). There was a long 50% stenosis in distal RCA was 50% in both modalities. Changes in LCX were non-significant. Panel B. Hybrid PET-CT volume rendered images of the heart. The images are displayed with stress PET perfusion colouring the surface of the left ventricular wall. Relative perfusion images. Panel C. Hybrid PET-CT volume rendered images of the heart. The images are displayed with stress PET perfusion colouring the surface of the left ventricular wall (absolute scale 0-3.5 ml/g/min). Normal perfusion is >2.5 ml/g/min (red to yellow colour). Blue colour denotes to significantly reduced perfusion in all vascular territories.

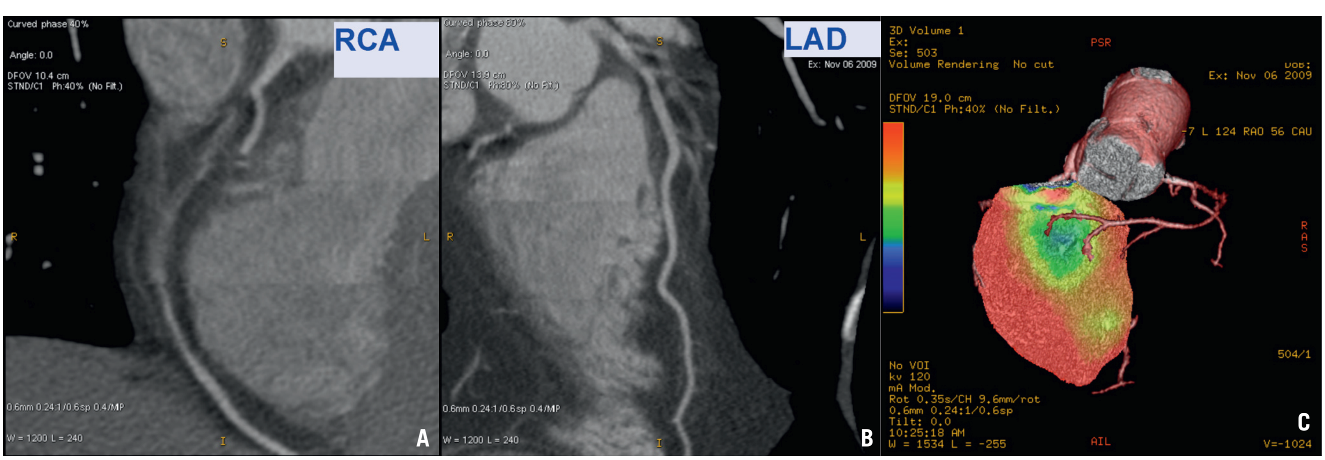

Figure 2. CT hybrid PET-CT images of a 47-year old male with chest pain. These images show the ability of hybrid imaging to assess segments not evaluable by CT because of artefacts. In RCA, image quality is severely degraded by motion but PET-CT is able to accurately detect a localised perfusion defect attributable to a significant stenosis in RCA. Panel A. CT angiography curved multiplanar reconstructions of the right and left coronary arteries. LCA: left coronary artery. RCA: right coronary artery. Panel B. Hybrid PET-CT volume rendered image of the heart. The images are displayed with stress PET perfusion colouring the surface of the left ventricular wall (absolute scale 0 – 3.5 ml/g/min). Normal perfusion is >2.5 ml/g/min (red to yellow colour). The area supplied by RCA has clearly diminished blood flow. Panel C. Video file of PET-CT.

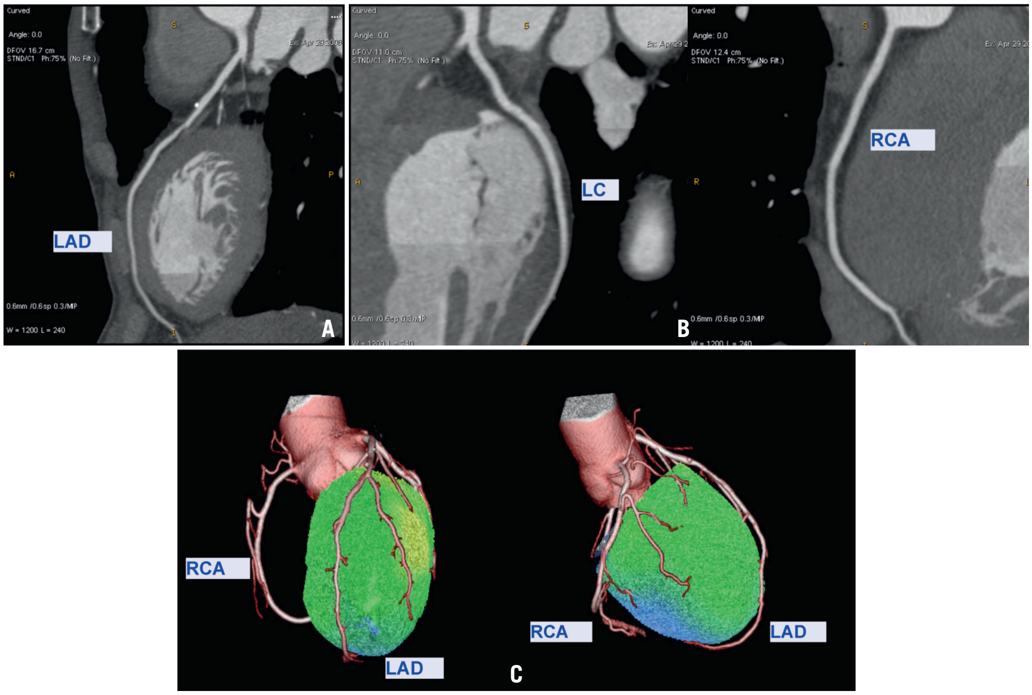

Figure 3. A 64-year old male with diffusely but inhomogenously reduced myocardial blood flow with no significant stenoses in epicardial vessels. This is an example of a case with suspected microcirculatory disease – invasive angiography confirmed the non-significant findings of the CTA. Panel A. CT angiography curved multiplanar reconstructions of the main coronary vessels. No significant stenoses in any of the vessels, only slight wall changes. Panel B. Hybrid PET-CT volume rendered images of the heart. Reduced and inhomogenous perfusion in all vessel territories. Panel C. Video file of PET-CT.

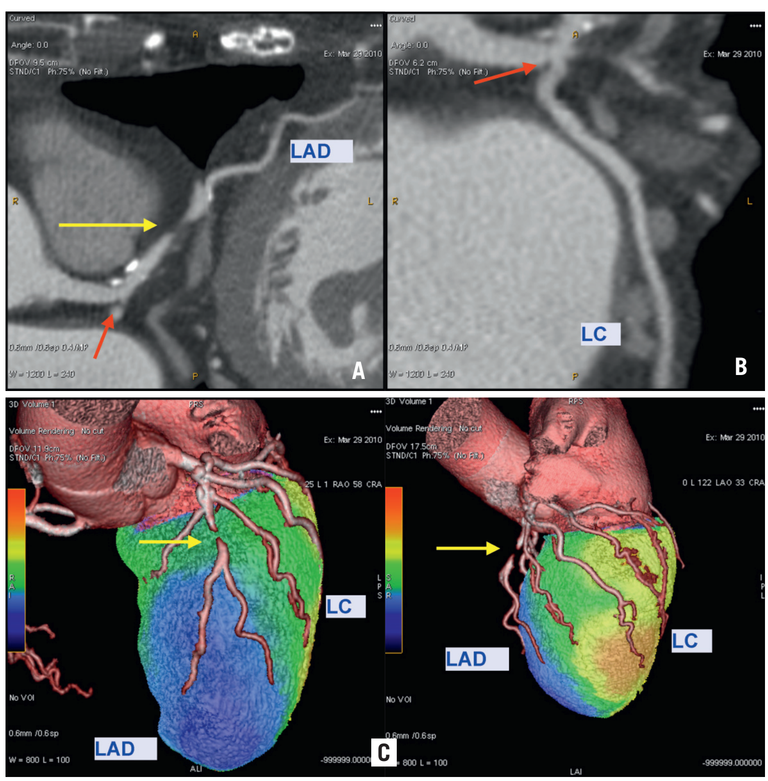

Figure 4. Images of a 76-year-old female with COPD and chest pain. RCA is normal. CT shows borderline calcified plaque at trifurcation (LAD, LCX, IM). Hybrid study confirms that it is not hemodynamically significant. In mid LAD, however, occluded segment causes markedly reduced perfusion distal to lesion. This is an example of how hybrid imaging can detect the culprit lesion. Panel A. CT angiography curved multiplanar reconstructions of the left coronary artery. Yellow arrlow: occluded LAD. Red arrow: calcified plaque at trifurcation Panel B. Hybrid PET-CT volume rendered images of the heart. Only the areas supplied by the LAD exhibit reduced perfusion. The myocardial blood flow in LCX territory is intact. Yellow arrow: occluded LAD. Panel C. Video file of PET-CT.

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Online data supplement

Video 1 (Case 1). 3-vessel disease: diffusely reduced perfusion is easily distinguished in the images portraying absolute values of blood flow.

Video 2 (Case 2). In RCA, CT image quality is severely degraded by motion but PET-CT is able to accurately detect a localised perfusion defect.

Video 3 (Case 4). The culprit lesion: several anatomically suspicious stenoses of which only the lesion in mid LAD is haemodynamically significant.