ESC textbook of imaging: Chapter 1D

Hybrid imaging: PET-CT and SPECT-CT

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1d.1 Introduction

Hybrid scanners combining PET or SPECT with high resolution multidetector CT are becoming the standard for almost all commercially available systems. Hybrid scanners offer the ability to assess the anatomy of the heart and coronary arteries, and the functional evaluation either at stress (for assessment of induced ischemia), or at rest (for viability) in association with the left ventricular systolic function. Therefore, combining functional information from PET or SPECT is appealing (1).

1d.2. Definition of cardiac hybrid imaging

The term cardiac hybrid imaging has been proposed if images are fused combining two data sets, whereby both modalities are equally important in contributing to image information. Mostly this refers to combining CT with a nuclear myocardial perfusion imaging technique. Some reports have referred to X-ray based attenuation correction of perfusion imaging as hybrid imaging, raising confusion about its exact meaning because in such setting the CT data do not provide added anatomical information, but are simply used to improve image quality of the PET or SPECT modality. Similarly, the parametric maps obtained from low-dose CT do not provide image information beyond that needed for attenuation correction, although it could be used to obtain calcium scoring (2,3).

Others have used the term hybrid imaging for the mere side-by-side analysis of perfusion and CT images. To avoid confusion we suggest using the term hybrid imaging to describe any combination of structural and functional information beyond that offered by attenuation correction or side-by-side analysis, by fusion of the separate data sets for example from CT coronary angiography and from SPECT or PET into one image. Similarly, separate acquisition of structural information as well as functional data such as for example perfusion on two separate scanners or on one hybrid device would allow mental integration of side-by-side evaluation but only fusion of both pieces of information would result in what should be considered a hybrid image (**Figure 1**).

1d.3 Rationale for cardiac hybrid imaging

The field of cardiac imaging has witnessed an enormous development in the past years and is now offering an ever-increasing spectrum of tools and options to the clinicians. The potential disadvantage is that the patients may now be exposed to multiple, sequential, time-consuming, and costly diagnostic test and procedures, which may deliver occasionally even contradicting results. This may have contributed to the fact that the majority of patients are referred to diagnostic invasive coronary angiography and consequently to percutaneous coronary interventions (PCI) in the absent of any sort of functional evaluation (4,5) although professional guidelines call for objective documentation of ischemia prior to elective PCI (6,7,8). It is this background which has paved the way for the conceptual search of a non-invasive technique to assess coronary artery disease in which the detected perfusion abnormalities can be immediately and accurately associated with the individual's coronary anatomy.

Although CT coronary angiography with multidetector scanners has proven to be a valuable alternative to diagnostic invasive coronary angiography for the evaluation of many subgroups of patient with known or suspected coronary artery disease it only allows assessing coronary luminology, thus providing purely morphological information. The limitations of morphologic measures for delineating the physiologic implications of stenoses are well-described (9). The vasomotor tone and coronary collateral flow, both of which are known to affect myocardial perfusion cannot be estimated by measures of stenosis severity. The percent diameter stenosis is only a weak descriptor of coronary resistance as it does not take into account the length and shape or stenoses. Lastly, CTA is limited in its ability to accurately define the severity of stenosis.

Accordingly, the major drawback of the CT has been found to be the relatively low positive predictive value and that the estimation of the hemodynamic significance of the detected stenosis is difficult (9-11). In contrast, myocardial perfusion imaging provides a simple and accurate integrated measure of the effect of all of these parameters on coronary resistance and tissue perfusion, thereby optimizing selection of patients who may ultimately benefit from revascularization. This has triggered the idea of obtaining combined anatomic and functional noninvasive imaging of the coronary circulation in a single session through hybrid instrumentation.

Early studies conducted with image fusion of invasive coronary angiography and myocardial perfusion imaging from SPECT showed limited success due to the disadvantages inherent in warping planar 2D angiogram into a fusion with a 3D perfusion data set. Furthermore, the fusion process was time consuming and, therefore, not helpful for rapid decision making during an ongoing intervention. Alternatively, combined information can be gained by mental integration of the information e.g. from invasive of CT angiography and SPECT. However, the planar projections of coronary angiograms and axial slice-by-slice display of cardiac perfusion studies make a subjective integration difficult. This may lead to inaccurate allocation of the coronary lesion to its subtended myocardial territory, particularly in patients with multivessel disease and intermediate severity lesions. In addition, standard distribution of myocardial territories corresponds with the real anatomic coronary tree in only 50-60% of cases which may cause misleading interpretation.

Therefore, the concept of hybrid imaging to deliver comprehensive integrated morphological and functional information is particularly appealing. In addition to being intuitively convincing, these images provide a panoramic view of the myocardium, the regional myocardial perfusion or viability and the coronary artery tree, thus eliminating uncertainties in the relationship of perfusion defects, scar regions and diseased coronary arteries in watershed regions (**Figure 2**). This may be particularly helpful in patients with multiple perfusion abnormalities (**Figure 3**) and complex CAD including situations after bypass surgery (**Figure 4**). Combining anatomical information with perfusion also helps to identify and correctly register the subtle irregularities in myocardial perfusion (**Figure 5**).

1d.4. Integrated scanners versus software fusion

The potential added value of hybrid imaging originates from the spatial correlation of structural and functional information on the fused images which facilitates a comprehensive interpretation of coronary lesions and their pathophysiologic relevance. An important prerequisite of hybrid imaging is accurate image coregistration as misalignement may result in erroneous allocation of perfusion defects to coronary artery territories. From a technical perspective, image coregistration can be achieved by a software-based or hardware-based approach.

Hardware-based image coregistration permits the acquisition of fused anatomical and functional images using hybrid scanners (such as PET/CT or SPECT/CT devices) with the capability to perform nuclear and CT image acquisition almost simultaneously with the patient's position fixed. Inherently, image fusion is performed fully or semi-automatically by superposition of image data sets. The real benefit of fusing different imaging modalities is also in the ability of using the anatomical information acquired *in situ* to improve the scan efficiency and to use the CT images for attenuation correction of the nuclear scan. Last but not least, the very important benefit for the patient is that comprehensive study can be performed in short single session of scans. The drawback is that the sequential procedure requires careful planning of logistics to enable efficient patient throughput.

Alternatively, with software-based coregistration, image data sets can be obtained on standalone scanners and fused manually through the use of landmark-based coregistration techniques. Intuitively, the hardware-based approach appears preferable since manual coregistration may be hampered by issues of accuracy and user interaction. While hybrid PET/CT devices are the preferred tool for whole-body

PET/CT imaging predominantly used in oncology, the routine use of fully automated hardware-based image coregistration for cardiac hybrid applications is challenged by certain organ-specific characteristics. First, minor beat-to-beat variations in the heart's position may interfere with accurate image coregistation despite fixation of the patient's position and orientation. Second, CT image acquisition and analysis requires electrocardiographical gating and images are generally reconstructed in mid- to end-diastolic phases and acquired during breath hold. In contrast, with SPECT and PET nongated data sets are used resulting in a slight mismatch of ventricular size between the image sets. Furthermore, the position of the heart is susceptible to respiratory motion, SPECT and PET images are typically acquired during normal breathing. These facts can result in misalignment of the heart between PET/SPECT and superimposed CT and can also lead to diagnostic errors (12). Therefore, nowadays software realignment of cardiac image sets is performed even if the scans were acquired in a single session using hybrid device.

Despite the integration of high-end CT devices with nuclear scanners to form dedicated cardiac hybrid scanners, software-based image coregistration may still remain a common form of hybrid imaging. Dedicated cardiac fusion software packages are now commercially available allowing hybrid imaging with an excellent interobserver reproducibility and short processing durations. Image transfer processes to workstations performing coregistration is currently simple and fast. A recent validation study has documented that 3D SPECT/CT image fusion (**Figure 6**) from image sets obtained on stand-alone scanners with such software package is feasible and reliable, allowing correct superposition of PET/SPECT segments onto cardiac CT anatomy. Such software is used irrespective of whether the images are acquired on a hybrid device or on two different standalone scanners.

Indeed, with SPECT the standalone scanner setting may appear favourable in view of the fact that with latest generation multidetector CT scanners coronary angiography is acquired within seconds while emission scans for stress plus rest gated SPECT with ^{99m}Tc-based radiotracers at standard doses take at least 45 minutes (13). Thus, in a hybrid cardiac device the high-end CT facilities will be blocked during long emission scan periods and therefore operate at low capacity. Advances in nuclear medicine such as newly-developed dedicated cardiac detectors systems (14) and novel image reconstruction algorithms (15) may contribute to reduce emission scan times considerably and may eventually help shifting the balance in favor of hybrid scanners in the future.

With PET there are several advantages of hybrid imaging using hardware-based image fusion. The efficiency of imaging is enhanced. The PET imaging protocols are short allowing both CT angiography and perfusion imaging to be performed in a single session below 30 minutes of total scan duration. It is expected that PET/CT is increasingly used in traditionally difficult patient populations such as obese and diabetic subjects. There are also other promising future applications that involve molecular imaging of cardiac targets and these may further enhance the clinical utility of hybrid imaging using PET/CT.

As explained in earlier chapters PET imaging offer unique possibility to measure myocardial perfusion quantitatively in absolute terms. This is useful in patients with diffuse CAD or balanced disease where relative assessment of myocardial perfusion cannot uncover global reduction in perfusion (**Figure 7**). Typically, in relative analysis of perfusion only the regions supplied with the most severe stenosis are detected.

Quantification of myocardial perfusion using dynamic PET provides a high performance level for the detection and localization of CAD (16). The incremental value of quantitative analysis was also recently studied and it was found that the accuracy of PET was further improved by quantitative analysis (17, 18, 19).

1d.5. Imaging protocols for hybrid imaging

The patient preparation for hybrid study is mostly the same than for the individual scans. It is important that the patients heart rate is controlled for CT and that caffeine containing drinks are avoided during the preceding 12 hours since pharmacological stressors are commonly used in hybrid imaging. There are several options for hybrid imaging which each have certain advantages and disadvantages.

In the protocols where the need of perfusion study is individually decided upon the findings in CT angiography, the protocol naturally starts with CT. This procedure is powerful since it utilises the high negative predictive value of CT and only that fraction of the patients that had suspicious findings in CT will continue with perfusion imaging. Depending on the selected patient population this fraction is about 25-50% and, thus, on the average one perfusion session is needed for each three patients. The potential limitation is that the premedication needed for CT angiography may also affect the perfusion results although this is likely less significant with pharmacological stressors such as adenosine and dipyridamole.

If perfusion study is performed first, the above mentioned potential problem is avoided but currently the analysis of perfusion images is not fast enough to be used immediate decision whether to leave out CT angiography in the case of completely normal perfusion result. Thus, in this protocol both studies are performed in all patients.

The positioning of the patient to the scanner bed is critical to prevent any motion artefacts. It is strongly recommended that hands are supported upright and not within the field of view. The calcium score study can be performed first followed by CT angiography study. The detailed protocol of CT angiography depends on the system used. Thereafter low-dose CT for attenuation correction scan is performed if needed (in some systems calcium score study can be used for this).

The perfusion imaging protocol depends on whether PET or SPECT or which tracer is used. In hybrid imaging the stress study is performed using pharmacologic stressors such as adenosine, dipyridamole or dobutamine. With PET tracers such as ^{82}Rb and ^{15}O-water studies (half-lives 76 s and 112 s) the stress study can be performed practically without delay after the rest study. With ^{13}N-ammonia stress testing is delayed for about 30 min to allow tracer decay. If method to correct patient motion between stress and rest studies is not available, second low-dose CT scan for attenuation correction is needed. In all studies quality control process is needed to ensure optimal alignment of the CT attenuation and PET emission scans and, if necessary, misalignment needs to be corrected (**Figure 6**).

If the system is capable to 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. This is particularly practical in Rb-82 studies. The total time required for whole study session depends on the tracer used.

With ^{15}O-water and ^{82}Rb the whole session can be finished in 30 minutes and with ^{13}N-ammonia in 80 minutes. The protocols may further shorten significantly since in hybrid approaches only single stress perfusion imaging may be needed especially when using quantification (19).

If hybrid imaging is used to assess myocardial viability the standard patient preparations and procedures are used as in stand alone imaging.

1d.6. Image analysis and interpretation of hybrid imaging

The analysis of CT angiography includes the standard processes and techniques such as visual assessment of original transaxial slices, multiplanar reconstructions and utilisation of quantitative tools available. The analysis of PET/SPECT studies follows also the standard procedures that have been explained in detail in guidelines (20-22). However, to utilise the true power of hybrid imaging, analysis system that is able to handle fused images and data should be also used. By this way 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 also 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 also included in the analysis (**Figure 7**).

1d.7. Radiation safety aspects

Utilising hybrid imaging, the patient radiation dose will further increase since the 'additional' imaging techniques utilise also ionising radiation. The dose for patient from CT angiography has been reported to be in the range of 6 to 20 mSv depending on the system and protocol used. Recently, techniques that reduce patient dose have been developed and the doses have been reduced as low as 1-7 mSv (23). The radiation doses from single SPECT perfusion imaging range from 5 to 8 mSv (^{99m}Tc-based tracers). The radiation dose from PET perfusion studies is small e.g. radiation dose from single PET perfusion study is 0.8 mSv ^{15}O-water and 1 mSv for ^{13}N-ammonia. Therefore, although the use of hybrid imaging obviously causes increased radiation dose for the patient, the recent technical development has improved the radiation safety tremendously and a complete hybrid imaging can now be performed with radiation dose below 10 mSv (24-26).

1d.8. Clinical impact of cardiac hybrid imaging

As metioned above, it is well established that a comprehensive assessment of CAD requires not only morphologic information about coronary artery stenosis location and degree but also functional information on pathophysiologic lesion severity. Eventually, many factors that cannot fully be assessed with coronary luminology determine whether a given lesion really induces a myocardial perfusion defect (**Figure 8)** (see also **Figures 3, 5** and **7**). It has been repeatedly shown that only about half of the lesions classified as significant in CT are linked with abnormal perfusion (9-11, 27).

In a study by Namdar et al (28), the concept was evaluated in patients with suspected CAD yielding a sensitivity and specificity of 90% and 98% respectively, to detect hemodynamically important coronary lesions (as compared to the combination of stress-rest PET perfusion imaging and invasive coronary angiography). In a recent study using PET/CT systems with 64-slice CT scanner it was found that the positive predictive value of stenosis in CT was low (around 50%) in predicting stress-inducible perfusion abnormalities in PET but the negative predictive value was over 90% (29). This indicates that the assessment of functional consequences of coronary stenoses is difficult with CT, and that perfusion imaging provides useful complementary information.

Although these studies provide important clinical information about the performance of different imaging modalities, they do not directly show the incremental value of the hybrid imaging. Hybrid images may offer superior diagnostic information with regard to identification of the culprit vessel and therefore increase diagnostic confidence (19, 27). The initial experience combined SPECT perfusion imaging and CT coronary angiography studies indicate that in almost one third of patients the fused SPECT/CT analysis provided added diagnostic information on pathophysiologic lesion severity not obtained on side-by-side analysis (29). The incremental value was most pronounced for functionally relevant lesions in distal segments and diagonal branches and in vessels with extensive CAD or substantial calcification on CT. Similar results have been also obtained using hybrid PET/CT imaging (27, 30). Due to the variant coronary anatomy in each individual and the complex disease pattern in these patients correct allocation of perfusion defect and subtending coronary artery was only achieved by the hybrid images. As hybrid images offered superior information with regard to identification of the culprit vessel the diagnostic confidence for categorizing intermediate lesions and equivocal perfusion defects was significantly 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 the firm exclusion of hemodynamic significance of coronary abnormalities seen on CT coronary angiography, which might be useful to avoid unneccessary interventional procedure.

Another group of patients in whom hybrid imaging is likely clinically useful are those with multivessel CAD. Typically myocardial perfusion analysis is based on relative assessment of perfusion distribution. This technique, however, often uncovers only the coronary territory supplied by the most severe stenoses. In multivessel disease coronary flow reserve may be abnormal in all territories thereby reducing the heterogeneity of flow between ‘‘normal’’ and ‘‘abnormal’’ zones (**Figure 7**). This is obviously limiting the ability of relative perfusion analysis to delineate the presence of multivessel CAD.

There are several alternatives to solve this problem. The response of left ventricular ejection fraction to stress can be measured from perfusion data and decrease in peak stress indicates multivessel disease (31). PET has here some benefit since the acquisition is done during stress, unlike with SPECT where post stress imaging is performed. Another solution would be using quantification of myocardial perfusion in absolute terms (in mL/g/min) which is readily possible with PET (17-19) and 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 homogenous myocardial perfusion.

Although assessment of myocardial viability using stand-alone systems is well established, the hybrid imaging provides clear benefits. The detected dysfunctional but viable or scar regions can be directly linked with the individual's coronary anatomy and linked with coronary stenoses. The limitation of hybrid approach in this patient group is that substantial fraction of the patients has other diseases that prevent to use iodinated contrast agents.

1d.9. Future perspectives

Although the role of hybrid imaging in daily clinical routine remains to be determined, it appears that this approach may have the potential to become the central decision-making element in the future diagnostic and therapeutic strategy for patients with coronary artery disease. Studies assessing the prognostic value and cost-effectiveness of hybrid imaging are warranted.

Currently, the position of nuclear imaging in cardiovascular research and patient care is primarily based on its capacity to image perfusion and glucose metabolism. However, the methods allow for imaging and quantification of molecular interactions and pathways with picomolar sensitivity. Thus, number of cellular processes can be studied, e.g. receptor density, enzyme activity, inflammatory processes and gene expression.

Rupture of vulnerable coronary atherosclerotic lesions account for one third of all deaths worldwide and constitute a major source of disability and health care costs. Non-invasive techniques such as multislice CT can characterise morphologic criteria associated with high risk of atherosclerotic plaque rupture. In contrast, PET and SPECT utilise radiolabeled molecules designed to specifically target individual inflammatory activities in atherosclerotic plaques. This approach is possible only with high-resolution morphological imaging of the coronary arteries using hybrid imaging.

1d.10. Conclusion

The newest generation of the hybrid imaging devices have matured to the level that they can be successfully used for clinical cardiovascular imaging. In addition, software based image fusion has became readily available allowing robust and fast image merging. It is likely that in the near future the primary clinical use of hybrid imaging is in the detection of coronary artery disease using CT coronary angiography and nuclear perfusion imaging but in long term also other molecular imaging applications are entering into clinical cardiology.

FIGURE LEGENDS

Figure 1

Three-dimensional cardiac hybrid PET-CT image providing a panoramic view of stress perfusion MPI (red and yellow colours indicate normal perfusion) in relation to the coronary territories. Despite several calcifications in the proximal segments of the left and right coronary arteries there is no relevant ischemia.

Figure 2

Three-dimensional cardiac hybrid SPECT-CT image: a volume rendered CT coronary angiography image is fused with the stress perfusion SPECT. The left panel shows a basal inferior ischemic area (blue area, black arrow heads). The middle panel reveals a lesion in the right coronary artery (white arrow), with otherwise unremarkable coronaries and normal perfusion. Invasive coronary angiography confirmes a significant lesion in the RCA (white arrow).

Figure 3

CT coronary angiography images (curved multiplanar reconstructions) of a male patient with effort angina. The images of RCA (a), LAD (b) and LCX (c) show several calcified and noncalcified plaques, which suggest significant multi vessel disease. Three-dimensional cardiac hybrid PET-CT images of anterior (d) and right lateral view (e) shows very different stress perfusion patterns in each vessel region. The perfusion in region supplied by LCX was normal (red and yellow color), slightly reduced in region supplied by LAD (green color) and severely compromised in region supplied by RCA (blue color).

Figure 4

In situations of complex coronary CAD and after bypass surgery hybrid cardiac imaging provides added value. CT coronary angiography may allow visualization of patent bypass grafts but the evaluation of the anastomoses remains difficult. A conclusion about hemodynamic relevant lesions can only be reached in conjunction with perfusion. The image documents residual ischemia in the distal left anterior descending artery territory.

Figure 5

Examples of two clinically similar symptomatic patients who had also similar findings in LAD and the first diagonal branch (D1) in CT angiography (left panels). The patient 1 (upper row) showed in hybrid PET/CT imaging (right panel) only subtle reduction in territory supplied by D1. The patient 2 (lower row) showed large poorly perfused region covering whole anterior wall supplied by both LAD and D1.

Figure 6

Illustration of the main steps for creating a cardiac hybrid SPECT-CT image from stand alone systems. The main steps include a) image coregistration, b) epicardial contour detection, c) coronary artery segmentation, and d) MPI and CT image superposition (with permission from Gaemperli et al. Eur J Nucl Med Mol Imaging 2007;34:1097–1106. DOI 10.1007/s00259-006-0342-9). The same steps are also performed even if hardware based hybrid imaging (PET/CT or SPECT/CT) device were used.

Figure 7

Hybrid images from stress PET/CT with extensive coronary artery disease. The images (a and b) scaled to relative scale where the best perfused region is set to maximum and has the brightest color (in rainbow scale lowest=blue and highest=red). The hybrid images of anterior (a) and posterior (b) views suggested only minor perfusion abnormalities in the anterior wall. The images scaled according to absolute scale (c and d) (0 ml/g/min=blue and 3.5 ml/g/min=red) uncovered global reduction of perfusion. The hybrid images of anterior (c) and posterior (d) views showed severely reduced stress perfusion in the anterior wall but also abnormally low perfusion in other myocardial territories (green color).

Figure 8

A) Hybrid images from stress SPECT MPI fused with the CT coronary angiography indicating that the territory subtended by the ectatic lef anteriof descending (LAD) is ischemic (blue area). B) CT coronary angiography shows the extent of the ectatic coronary disease involving also the right (RCA) and the circumflex (CX) coronary arteries. (with permission from Husmann L. et al. Eur J Nucl Med Mol Imaging 2008 Nov;35(11):2142. DOI 10.1007/s00259-008-0895-x)

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