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Additional diagnostic value of integrated analysis of cardiac CTA and SPECT-MPI using the SMARTVis system in patients with suspected coronary artery disease

This chapter was adapted from:

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Abstract

Introduction CT angiography (CTA) and SPECT myocardial perfusion imaging (SPECT-MPI) are complementary imaging techniques to assess coronary artery disease (CAD). Spatial integration and combined visualization of SPECT-MPI and CTA data may facilitate correlation of myocardial perfusion defects and subtending coronary arteries, and thus offer additional diagnostic value over either stand-alone or side-by-side interpretation of the respective data sets from the two modalities. In this study, we investigate the additional diagnostic value of a software-based CTA/SPECT-MPI image fusion system, over conventional side-by-side analysis, in patients with suspected CAD.
Methods Seventeen symptomatic patients who underwent both CTA and SPECT-MPI examination within a 90-day period were included in our study; seven of them also underwent an invasive coronary angiography (ICA). The potential benefits of the **S**ynchronized **M**ultimodal he**ART Vis**ualization (SMARTVis) system in assessing CAD were investigated through a case-study, involving four experts from two medical centers, where 1) a side-by-side analysis using structured CTA and SPECT reports, and 2) an integrated analysis using the SMARTVis system in addition to the reports, were performed.
Results The fused interpretation led to 1) a more accurate diagnosis, reflected in an increase of the individual observers' sensitivity and specificity to correctly refer for invasive angiography eventually followed by revascularization, and 2) a better inter-observer diagnosis agreement (increase from 74% to 84%). The improvement was primarily found in patients presenting CAD in more vessels than the number of reported perfusion defects.
Conclusions Integrated analysis of cardiac CTA and SPECT-MPI using the SMARTVis system results in an improved diagnostic performance.

Coronary artery disease (CAD) is a major cause of death worldwide [187]. Invasive coronary angiography (ICA) is regarded as the reference standard imaging technique for diagnosing CAD [137]; it enables determining the location, the extent, and the severity of the vessel obstructions. Computed tomography coronary angiography (CTA) imaging is gaining popularity [257]; it non-invasively provides high-resolution images of the cardiac and coronary artery anatomy and allows assessment of the presence, extent and type of coronary stenoses. Still, neither CTA nor ICA provides information on the functional implications of detected stenoses; a stress test may therefore be required to evaluate presence and extent of myocardial ischemia. Single photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) is one of the possible ischemic tests. In the conventionally used side-by-side analysis, integration of CTA and SPECT-MPI findings are mentally performed by using a standardized myocardial segmentation model that allocates each segment to one of the three main coronary arteries [47]. However, this myocardial perfusion territories distribution does not always correspond with the actual coronary anatomy [177]. Spatial integration and combined visualization of CTA and SPECT-MPI data may facilitate correlation of myocardial perfusion defects and subtending coronary arteries, and thus offer additional diagnostic value over either stand-alone or side-by-side interpretation of the respective data sets [22, 81–83, 115, 163, 197, 199, 221].

Hybrid cardiac imaging systems, and software allowing fusion of images obtained separately, are promising non-invasive techniques to assess CAD. It is expected that such systems will gain in popularity in the future, to reduce the number of patients unnecessarily referred for ICA examination. Here, we present the software-based **S**ynchronized **M**ultimodal he**ART Vis**ualization (SMARTVis) fusion system, which allows comprehensive analysis of cardiac multimodal imaging data for assessment of CAD. The aim of the present study is to investigate to what extent integrated analysis of cardiac CTA and SPECT-MPI with the SMARTVis system result in an additional diagnostic value, by performing a comparative study (side-by-side versus fused using SMARTVis).

6.1 Materials and Methods

6.1.1 Study population

Seventy-one patients who underwent cardiac CTA and SPECT-MPI at the Leiden University Medical Center (Leiden, The Netherlands) were randomly selected. After applying exclusion criteria (Figure 6.1), seventeen patients were included in our study; images from an invasive coronary angiography (ICA) procedure performed within a 90-day period were available for seven of them. Patient characteristics are presented in Table 6.1. For retrospective anonymized studies, institutional review board approval is not required by our institutes.

6.1.2 SPECT-MPI

SPECT-MPI image acquisitions were performed using a two-day protocol with stress-test imaging on the first day and rest-imaging on the second day. The patients underwent bicycle ergometry or, when contraindications were present, adenosine or dobutamine infusion to induce stress. The radioisotope (500 MBq Tc-99m tetrofosmin) was injected either at peak exercise, three minutes after starting adenosine perfusion or at peak heart rate during dobutamine infusion. For both stress and rest scans, the image was acquired one hour after the radioisotope was injected. A triple-headed camera system (Toshiba CGA 9300, Tokyo, Japan) and a low-energy-high-resolution collimator were used. ECG gating was performed at 16 frames per cardiac cycle, with a tolerance window of 50%. No attenuation or scatter correction was applied.

An experienced nuclear physicist, blinded to both CTA and ICA results, analyzed the scans using the Corridor4DM software package (Version 6.1, INVIA Solutions, Ann Arbor, MI, USA) [74]. SPECT-MPI images were interpreted using oblique slices, polar maps and quantitative/functional values. The SPECT-MPI interpretation was summarized into a report, following guidelines presented in [78]: the observer graded each of the 19 myocardial segments as being normal (no perfusion defect) or abnormal (reversible or fixed defects), and indicated the extent of myocardial infarction or ischemia.

6.1.3 Computed Tomography based Angiography

Five patients were scanned using a 64-slice CT scanner (Aquilion 64, Toshiba Medical Systems Corporation, Otawara, Japan) and the remaining twelve patients were scanned using a 320-slice CT scanner (Aquilion ONE, Toshiba Medical Systems Corporation, Otawara, Japan). In case the heart rate was higher than 65 beats/min, additional oral β-blockers (metoprolol 50 mg, single dose, one hour before scan) were provided when tolerated. A prospectively triggered coronary calcium scan (non-contrast CT scan) was performed before acquiring CTA images. Images were acquired with a collimation of 64 x 0.5 mm (resp. 320 x 0.5 mm), a tube rotation time of 400 ms, and tube current of 300 mA at 120 kV for patients with normal posture (BMI < 30 kg/m2).

If a patient had a higher body mass index, tube current was increased to 350 or 400 mA at 135 kV. For electrocardiographically triggered prospective reconstruction, the temporal window was set to 75% after the R-wave. Between 80 and 110 ml non-ionic contrast material (Iomeron 400H, Bracco Atlanta Pharma, Konstanz, Germany) was administered with a flow rate of 5 ml/sec depending on the total scan time. The timing of the scan was determined using automated detection of peak enhancement in the aortic root. Acquisition of all images was conducted during an inspiratory breath hold of approximately 10 s, with simultaneous registration of the patient's electrocardiogram.

Table 6.1: Patient characteristics (N=17)

Characteristics	
Age (y)	61 ± 9
Males (N)	15 (90%)
Body Mass Index (BMI) (kg x m-2)	22.8 ± 4.4
Calcium score (Agatston)	1164 ± 1336
Medical history based on CTA	**N (%)**
No significant disease	3 (17)
1-vessel disease	2 (12)
2-vessel disease	5 (29)
3-vessel disease	7 (42)
Cardiovascular risk factors	**N (%)**
Current smoker	7 (42)
Hypertension	11 (65)
Diabetes mellitus	14 (82)
Hypercholesterolemia	12 (70)
Family history of CVD	4 (24)
Imaging	**Mean ± std [min,max]**
Day-period between CTA and SPECT-MPI (N=17)	31 ± 31 [1,79]
Day-period between CTA and ICA (N=7)	45 ± 30 [8,85]

Table 6.2: Findings from CTA, SPECT-MPI and ICA for the 17 patients

Pat.	Sex	Age	CTA findings		SPECT-MPI findings		QCA findings	CTA	SPECT-MPI
		(y)	Agatston score	≥ 50% stenosis in	Reversible	Fixed	≥ 20% stenosis in	suspected	suspected
1	M	61	819.6	11	Anterior basal-mid Inferior mid-apical		5 (38%), 6 (46%),11(63%)	single	double
2	M	73	2840.5	1,2,3,7,8,9,10,11,12		Inferior mid-apical	NA	triple	single
3	M	55	9.9	-	Anterior-Anteroseptal mid	Inferior-Inferolateral mid-apical	-	no	double
4	M	56	4797.4	3,4,8,9,11,12,13	Anterolateral basal	Inferior	3 (53%), 12(51%), 13 (70%)	triple	double
5	M	65	315.4	6,13,16	Anterior basal-mid Antero/Infero-lateral apical Antero/Infero-septal basal	Inferior	NA	double	triple
6	F	49	109.3	4,7,8,9,13	Anterior apical		NA	triple	single
7	M	60	493.8	4,12,13,16	Antero/Infero-lateral apical		NA	double	single
8	F	81	NA	2,4,16,17		Anterior + Anteroseptal	NA	double	single
9	M	46	60.6	-		inferior	NA	no	single
10	M	68	962.3	1,6,8,9	Anterolateral mid		NA	double	single
11	M	53	0	6,14	Anteroseptal mid Inferolateral basal-mid		NA	double	double
12	M	58	727.8	4,7,8,9,11,13,16	Antero/Infero-lateral basal-mid	Inferior + Inferoseptal	1 (40%), 2 (76%), 7(46%), 13 (70%), 16 (58%)	triple	double
13	M	60	373.8	1,2,6,7,14		Inferior	1 (52%), 5 (26%), 7 (41%), 12 (38%), 14 (58%)	triple	single
14	M	59	NA	1,2,6,7,9,12,16		Inferior + Inferoseptal Anterior + Anteroseptal	1 (100%), 6 (50%)	triple	double
15	M	63	15.6	-		Anterior + Anterolateral + Apex Inferior + Inferoseptal	-	no	double
16	M	70	1932.5	8		Inferior + Inferolateral apical	8 (100%)	single	single
17	M	59	1676.9	3,10,12,13,14	Anterior Antero/Infero-lateral	Inferior + Inferoseptal	NA	triple	triple

An experienced radiologist/cardiologist, blinded to both SPECT-MPI and ICA results, analyzed the scans using the Syngo.Via workstation (Siemens Healthcare, Erlangen, Germany). CTA images were interpreted using trans-axial image stacks and (curved) multi-planar reformatted images (MPR/cMPR), which are especially recommended to delineate the lumen morphology. The CTA interpretation was then summarized into a report, following guidelines presented in [184]: for each coronary artery lesion present in one of the modified 17-AHA-segments (American Heart Association), the observer reported the stenosis location (origin, proximal, mid, distal, end), the stenosis severity (mild, moderate, severe, occluded), the stenosis plaque type (non-calcified, mixed, calcified), the overall image quality / artifacts, and the confidence in the interpretation.

Table 6.3: Diagnostic performance for the side-by-side and fused CTA/SPECT-MPI analysis.

	Total	Side-by-Side				Fused CTA/SPECT-MPI			
Patients with ICA	7								
Agreement with QCA/SPECT-MPI		0.81				0.91			
Inter-observer agreement		0.66				0.82			
All observers		AD	AS	IAY	RJvG	AD	AS	IAY	RJvG
Sensitivity		80%	50%	60%	80%	100%	70%	80%	90%
Specificity		83%	100%	94%	83%	94%	100%	100%	83%
All patients	17								
Inter-observer agreement		0.74				0.84			

6.1.4 Quantitative Coronary Angiography

ICA was performed in accordance with standard medical practice in our institute. One experienced cardiologist, unaware of the CTA and SPECT-MPI scoring results, performed quantitative coronary angiography (QCA) on the seven available angiograms. All coronary segments were identified and analyzed using the modified 17-segment AHA classification. Segments were visually classified as normal (smooth parallel or tapering borders, visually ≤20% narrowing) or as having coronary obstruction (visually ≥20% narrowing); the stenoses in these last segments were quantified by a validated QCA algorithm [186] (CAAS, Pie Medical, Maastricht, The Netherlands). Stenoses were evaluated in the worst angiographic view and classified as significant if the lumen diameter reduction exceeded 50%.

6.1.5 SMARTVis : a software-based CTA/SPECT-MPI fusion system

In this work, we extend the Synchronized Multimodal heART Visualization (SMARTVis) software-based system introduced in [122] to fuse CTA with SPECT-MPI data. An overview of the CTA and SPECT-MPI processing and fusion is given in Figure 6.2. The SMARTVis system provides comprehensive 2D and 3D fused visualizations of the anatomical and functional information for relating coronary stenoses and perfusion defect regions (Figure 6.3). The coronary artery tree extracted from CTA can be projected onto the 2D stress/rest polar map (PMAP), and, similarly, the perfusion information visualized on a 3D stress/rest PMAP can be fused with a 3D model of the heart and its coronary artery tree. Furthermore, the SMARTVis system provides a list of automatically detected and quantified coronary artery stenoses [219]. To further assist the user in assigning a culprit lesion to a specific perfusion defect, a (distance-based) estimation of the patient-specific coronary perfusion territories is provided. Last, the 2D and 3D PMAP viewers are synchronized with the CTA

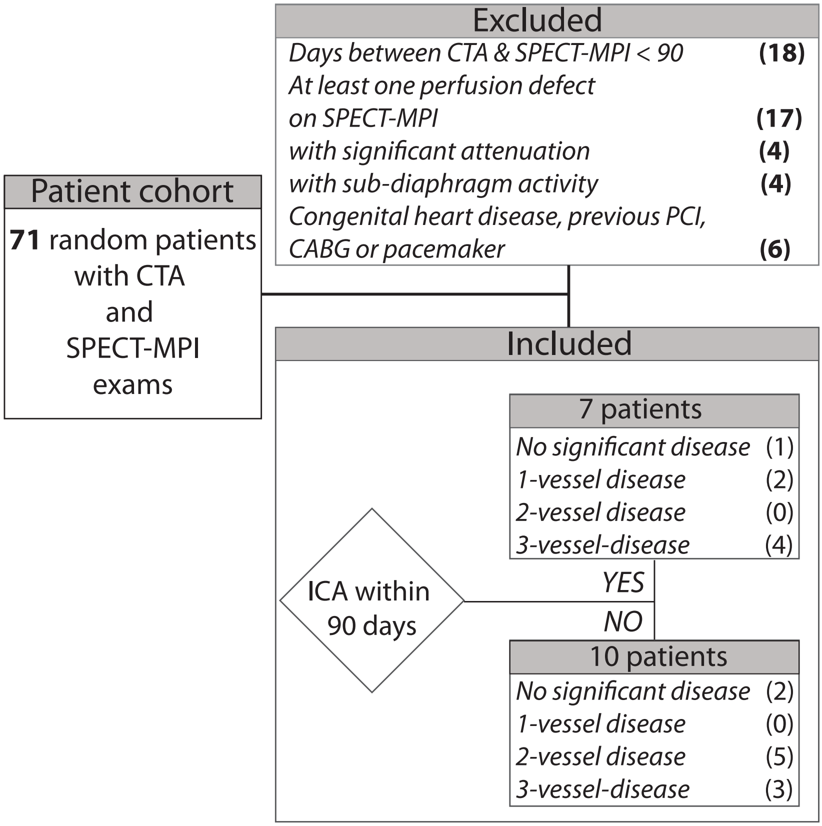

Figure 6.1: Patient's selection and exclusion criteria

stenosis findings and images.

6.1.6 Study design

The additional diagnostic value of the SMARTVis system to assess CAD was investigated through a case-study evaluation, involving four experts from two medical centers (Erasmus Medical Center, Rotterdam, The Netherlands; Leiden University Medical Center, Leiden, The Netherlands). An overview of the study design is presented in Figure 6.4.

During the analyses, for each of the 17 coronary artery segments that presented at least one ≥20% stenosis on CTA, the observer had first to either relate the stenosis to a myocardial region presenting a perfusion defect on SPECT-MPI, or indicate that the coronary artery segment did not induce a perfusion defect. Second, the observer had to indicate the most appropriate therapeutic decision: medical therapy or revascularization of specific coronary segment(s).

6.1.7 Analysis

The revascularization decision strategy and target vessel selection of each observer were compared with both the other observers' decisions and the reference decision, derived

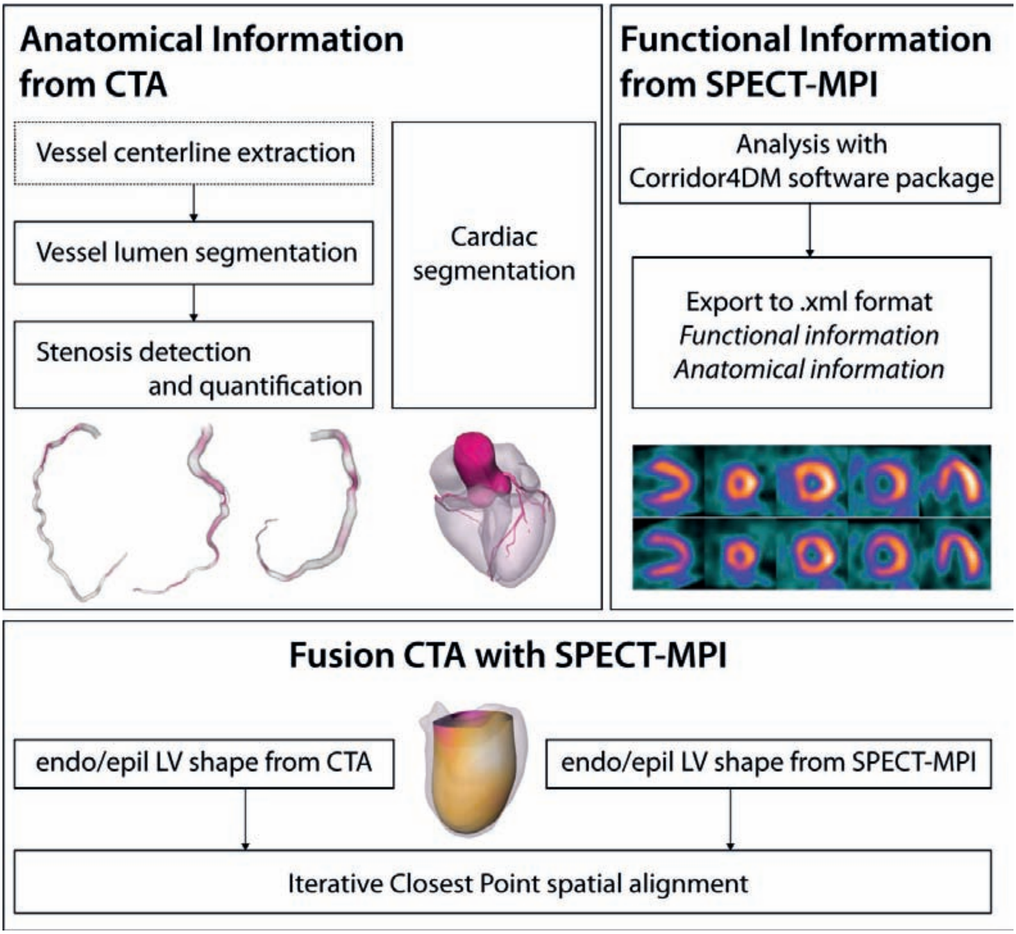

Figure 6.2: Overview of image processing performed on CTA and fusion of CTA/SPECT-MPI. The dashed box corresponds to semi-automatic process, while the solid boxes correspond to fully automatic processes. Coronary artery stenoses were detected and quantified on CTA using the method presented in [219]; coronary calcium was quantified using [220]; cardiac chamber shapes were obtained from CTA by applying method presented in [120]. The SPECT-MPI left ventricle shape was automatically provided by the Corridor4DM software, as well as landmark points indicating the septal and apical positions. LV shapes and landmark points were subsequently used to align CTA and SPECT-MPI data by applying iterative closest point algorithm.

from interpretation of QCA and SPECT-MPI. The diagnostic performance of CTA, SPECT-MPI and their fusion were compared on a per-vessel basis to determine the therapeutic decision agreements, as well as the sensitivity and specificity. For all seventeen patients, an inter-observer therapeutic decision agreement percentage was computed per patient as follows:

$$Agreement^{P}_{Inter-Obs} = \frac{1}{4} \times \sum_{v=1}^{4} w_v, \text{where } w_v = \begin{cases} 100 \text{ if all observers agree} \\ 50 \text{ if 3 observers agree} \\ 0 \text{ otherwise} \end{cases} \tag{6.1}$$

with v and w_v representing the main arteries (RCA, LAD, LCX, IMB) and the corresponding observer therapeutic agreement, respectively. For the subset of seven patients who underwent ICA, a therapeutic decision agreement percentage with respect to the QCA/SPECT-MPI decision was computed per patient, P as follows:

$$Agreement^{P}_{QCA} = \frac{1}{4} \times \sum_{v=1}^{4} w_v, \text{where } w_v = \begin{cases} 100 \text{ if all observers agree} \\ 50 \text{ if 3 observers agree} \\ 0 \text{ otherwise} \end{cases} \tag{6.2}$$

Also, the sensitivity and specificity for revascularization of a coronary artery were computed.

6.2 Results

First, the results of the mono-modality analyses are reported. Subsequently, we report on inter-observer agreement and agreement with the reference standard (combined QCA/SPECT-MPI) for the conventional side-by-side analysis, and the integrated analysis, respectively. Finally, we compare the performance of integrated analysis of fused CTA/SPECT-MPI with the side-by-side analysis.

6.2.1 SPECT-MPI findings

Ten of the patients showed a reversible perfusion defect (58%), twelve had a fixed perfusion defect (70%), and five patients (30%) revealed a mixed perfusion defect. Eight patients (47%) showed a perfusion defect in a single coronary territory, seven (41%) in two of them, and two (12%) in all three of territories. The exact locations of the perfusion defects are listed in Table 6.2.

6.2.2 CTA findings

Image quality was excellent in twelve patients (70%) and moderate in five patients (30%). Percentiles 0%, 25%, 50%, 75%, 100% yield Agatston scores 0, 85, 494, 1319, 4797; four patients (24%) had a calcium score above 1000. In total, 263 segments were evaluated and significant stenoses were present in 66 of them (25%). The remaining 197 segments (75%) were normal or contained only non-significant stenoses (<50%). Among all segments, eighteen coronary segments (7%) were qualified as blurred and six segments (2%) were heavily calcified. Three patients did not show any signs of CAD. In two patients single-vessel disease was suspected, in five double-vessel disease and in seven triple-vessel disease. The calcium scores and significant stenosis locations are listed in Table 2.

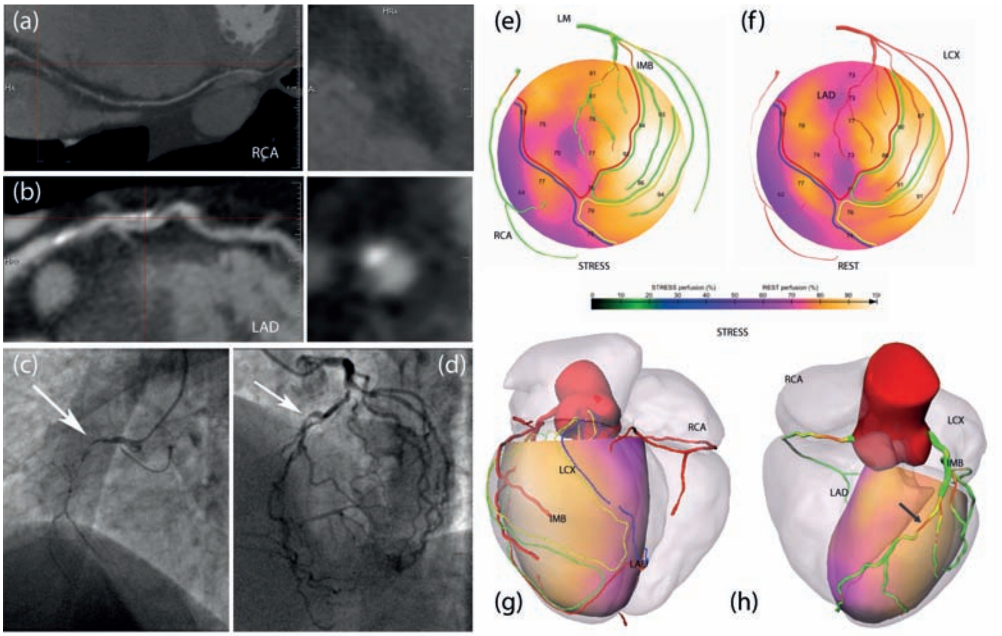

Figure 6.3: Example of patient14 (male, 59 y.o.), who presents fixed perfusion defects in the inferior and anterior wall on SPECT-MPI and suspected triple-vessel disease on CTA. A complete occlusion was detected in the proximal RCA (a) and a moderate mixed plaque was detected in the middle LAD (b). The QCA reveals a complete occlusion in proximal RCA (c) and a 50% stenosis in the middle LAD (d). Comprehensive visualizations proposed in the SMARTVis system: (e)(f) 2D stress and rest polar maps (PMAP) fused with projection of the coronary tree extracted from CTA. On the stress PMAP (e), coronary arteries are color coded with the degree of stenosis; on the rest PMAP (f), coronary arteries are coded with the distance to the epicardium: the more transparent the artery, the further it is from the epicardium. Patient-specific perfusion territories are also projected: LAD in red, LCX in yellow, MO in green and RCA in blue. (g)(h) 3D model of the heart and coronary artery tree extracted from CTA fused with 3D stress PMAP.

6.2.3 QCA findings

In seven of the seventeen patients (41%), a conventional ICA was performed within 45 ± 30 days after the CTA study. In these seven patients, 15 (resp. 26) of the 100 vessel segments had a stenosis of more than 50% (resp. 20%) on ICA. One patient did not show any CAD, one patient had single-vessel disease, three double-vessel disease and two triple-vessel disease. The artery segment presenting ≥20% stenosis and the QCA values are listed in Table 6.2. Based on the QCA and SPECT-MPI findings, revascularization was advised in segment(s) of ten coronary arteries.

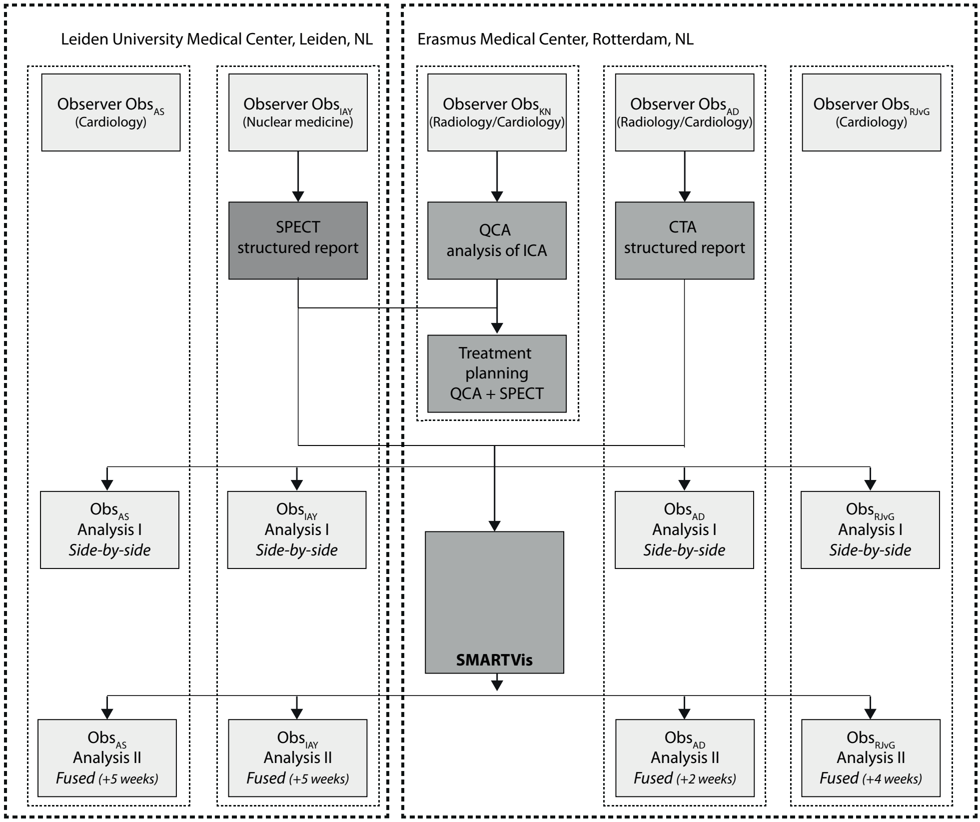

Figure 6.4: Overview of the multi-center evaluation study design. First, structured reports were created for CTA and SPECT-MPI of the 17 patients. QCA analysis was performed for 7 patients. A treatment strategy (i.e. medical treatment or revascularization of specific coronary segment(s)) was further derived from QCA and SPECT-MPI findings and served as reference standard. As the guidelines recommend proof of ischemia prior to revascularization of coronary stenoses [137], the expert considered medical therapy indicated for significant lesions detected on QCA which resulted in infarction and no further complaints. During individual sessions, the four experts examined the 17 patients and performed 1) a side-by-side analysis, using CTA and SPECT-MPI reports, and 2) an integrated analysis, using the SMARTVis fusion system in addition to the reports. The side-by-side analysis was performed 2 to 5 weeks prior to the integrated analysis to minimize the chance of recalling patient cases; the patients were analyzed in a different order and the expert analyzed several other cases in the elapsed time.

6.2.4 Findings of Side-by-Side analysis

6.2.4.1 Detection of coronary lesions requiring revascularization

For the seven patients in whom QCA was available, there was on average 81% agreement with regard to the therapeutic decision between the observers and the QCA/SPECT-MPI

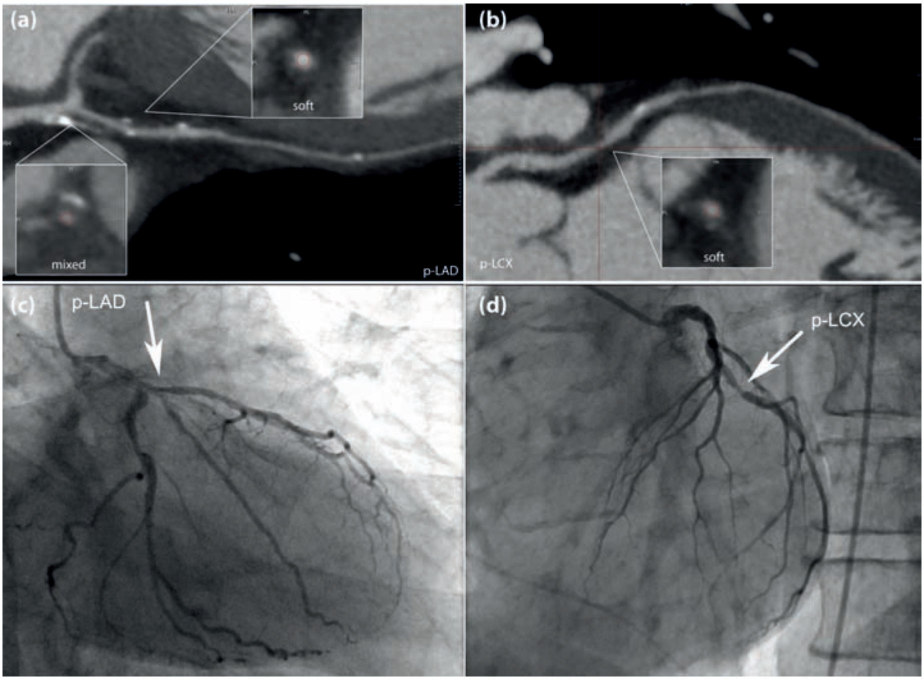

Figure 6.5: Example of patient01 (61 y.o. male). The CTA report indicates only mild (20-50%) stenoses in the LAD (a) and one significant stenosis in p-LCX segment (suspected single-vessel disease) (b). The QCA analysis reveals a 46% stenosis in the proximal LAD coronary segment (c) and a 63% stenosis in the proximal LCX segment (d). The SPECT-MPI report indicates two reversible perfusion defects located in the anterior basal-mid and inferior mid-apical walls (suspected double-vessel disease).

reference standard. Over the 4 (vessels) x 7 (patients) = 28 therapeutic decisions, the four observers agreed in fourteen cases (50%) with the QCA/SPECT-MPI therapeutic decision and three observer agreed in nine cases (32%). For the remaining five cases (18%), there was no consensus. The vessel-based sensitivities of the four observers to correctly refer for revascularization were 80%, 80%, 50% and 60% respectively; the vessel-based specificities were 83%, 83%, 100% and 84% respectively.

6.2.4.2 Inter-observer agreement

Over all patients, the averaged inter-observer therapeutic decision agreement was 74%. Over the 4 (vessels) x 17 (patients) = 68 therapeutic decisions, the four observers agreed in 41 cases (60%) and one observer disagreed in nineteen cases (28%). For the remaining eight cases (12%), no consensus was reached.

6.2.5 Findings of fused analysis

Figures 6.3, 6.5 and 6.6 present cases of two patients with its visualizations provided by the SMARTVis system for integrated analysis of CTA/SPECT-MPI.

6.2.5.1 Detection of coronary lesions requiring revascularization

For the seven patients in whom QCA was available, there was on an average 91% agreement with regard to the therapeutic decision between the observers and the QCA/SPECT-MPI reference standard. Over the 4 (vessels) x 7 (patients) = 28 therapeutic decisions, the four observers agreed in 20 cases (72%) with the QCA/SPECT-MPI therapeutic decision and three observers agreed in 6 cases (21%). For the remaining 2 cases (7%), there was no consensus. The vessel-based sensitivities of the four observers to correctly refer for revascularization were 100%, 90%, 70% and 80% respectively; the vessel-based specificities were 94%, 83%, 100% and 100% respectively.

6.2.5.2 Inter-observer agreement

Over all patients, the averaged inter-observer therapeutic decision agreement was 84%. Over the 4 (vessels) x 17 (patients) = 68 therapeutic decisions, the four observers agreed in 53 cases (78%) and one of the observer disagreed in eight cases (12%). For the remaining seven cases (10%), no consensus could be reached.

6.2.6 Comparison of Fused and Side-by-Side Analysis

6.2.6.1 Detection of coronary lesions requiring revascularization

By analyzing the integrated SPECT-MPI/CTA information using the SMARTVis system, the averaged therapeutic decision agreement improved in four cases (patients 01,04,13,14) and remained the same in the remaining three cases (patients 03,12,16). For all observers, it resulted in an increase of their sensitivity and specificity to correctly refer for revascularization.

6.2.6.2 Inter-observer agreement

The inter-observer therapeutic decision agreement increased in eight of the cases (patients 01,04,05, 08, 10,11,13,14), remained the same in seven of the cases (patients 02,03,07,09,12,15,16), and decreased in two cases (patients 06,17). Over all patients, the inter-observer agreement rose from 74% during the side-by-side analysis to 84% during the integrated analysis using the SMARTVis system; over the seven patients who underwent ICA, it increased from 66% to 82%, suggesting that increased observer agreement is also towards more correct therapeutic decisions using the SMARTVis system.

6.3 Discussion

6.3.1 Additional diagnostic value of cardiac CTA and SPECT-MPI fused analysis

The results of our case-study demonstrated that in several cases the integrated analysis of cardiac CTA and SPECT-MPI has a clinical benefit, in the sense that both the inter-observer agreement increased and the therapy planning decisions were in better agreement with the reference standard. Specifically, we found the tool to be of additional value in the diagnosis of patients who have perfusion defect(s) in fewer coronary territories than suspected vessel disease on CTA, i.e. who have a perfusion defect in one coronary territory and suspected double-/triple-vessel disease on CTA (diagnosis of patients 08,10,13 improved; diagnosis of patients 02,07 remained identical), a perfusion defect in two coronary territories and suspected double-/triple-vessel disease on CTA (diagnosis of patients 01,04,11,14 improved). In such cases, the relation between the coronary territories with

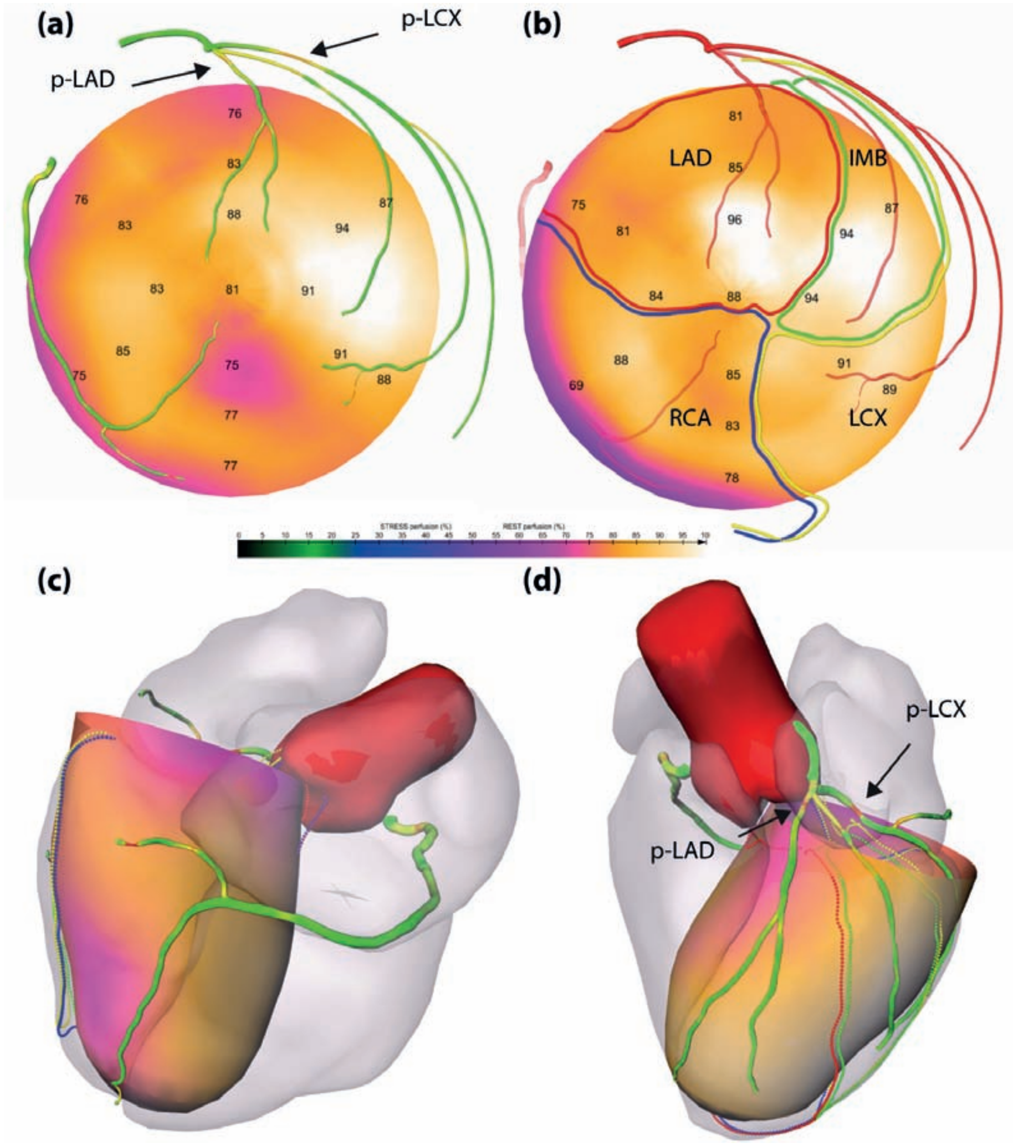

Figure 6.6: Example of patient01 (61 y.o. male). (a) Stress polar map: the coronary vessel tree is color-coded with the automatically estimated degree of stenosis. (b) Rest polar map: the coronary arteries are coded with the distance to the epicardium: the more transparent the artery, the further it is from the epicardium. Patient-specific perfusion territories are also projected: LAD in red, LCX in yellow, MO in green and RCA in blue. (c)(d) 3D model of the heart and coronary artery tree extracted from CTA fused with 3D stress polar map

a perfusion defect and its supplying coronary arteries is uncertain, thus making the use of the patient-specific SMARTVis system helpful.

The case study further revealed that the image fusion as implemented in the SMARTVis system does not have additional diagnostic value for patients with 1) no coronary stenoses (diagnosis of patients 03,09,15 remained identical), 2) suspected single-vessel disease on both CTA and SPECT-MPI (diagnosis of patient 16 remained identical), and 3) triple-vessel disease (diagnosis of patient 12 remained identical; diagnosis of patient 17 got worse). In fact, if a patient has no significant stenoses reported, but the SPECT-MPI study reveals the presence of perfusion defect(s), the observers consider that the perfusion defect(s) is/are caused by non-coronary diseases, such as micro-vascular disease. In case of suspected single-vessel disease, it is clear which coronary is causing the perfusion defect, and, thus, integrating information in a patient-specific way leads to the same diagnosis as during side-by-side analysis. Also, patients with suspected triple-vessel disease do not benefit from such a combined approach.

To summarize, integrated analysis of cardiac CTA and SPECT-MPI using the SMARTVis system results in an additional diagnostic value primarily for patients presenting coronary artery disease in more vessels than the number of reported perfusion defects.

6.3.2 Comparison to previous studies

Our work differs from previously published ones [81–83, 115, 163, 197, 199, 221] primarily by the way the information from CTA and SPECT-MPI is fused, and how the evaluation has been carried out. Previously, CTA images were registered (i.e. aligned) with SPECT-MPI images to provide fused 3D SPECT/CT images. We introduce a comprehensive visualization system to fuse multi-modal imaging data, and provide fused representations in both 2D and 3D for the convenience of the observer. Such an integration of cardiac CTA and SPECT-MPI anatomical and functional information into a single coordinated visual analysis tool is novel, maximizing the diagnostic complementarities of CTA and SPECT-MPI imaging modalities. The results of the presented work are consistent with the conclusions presented in previously published work on fusion of cardiac CTA and SPECT-MPI for assessment of CAD, where fused CTA/SPECT-MI interpretation appears to provide added diagnostic information on the hemodynamically relevance of coronary artery lesions.

Fusion of cardiac anatomical and functional information for the assessment of CAD has been introduced by Nakaura et al. [163]. Based on four cases, the study suggested that fused interpretation improves the relationship of relevant coronary arteries and abnormal perfusion territory. Also, Sato et al. [199] demonstrated that, based on a population of 130 patients, side-by-side combined interpretation of CTA and SPECT-MPI provides added diagnostic value, as compared to stand-alone CTA interpretation. Recently, Gaemperli et al. [81–83] further investigated the incremental diagnostic value of fused CTA/SPECT-MPI interpretation. In [82], thirty-eight patients who underwent both CTA and SPECT-MPI (twenty-five additionally underwent ICA) and presented with at least one perfusion defect on SPECT-MPI were included in an evaluation study similar to ours (i.e. side-by-side vs. fused). The authors demonstrated that fused analysis provides added diagnostic information on pathophysiologic lesion severity not obtained with side-by-side analysis. The evaluations were performed by a consensus of two observers. In our work, four independent observers were involved in the evaluation, which allowed us to also investigate the added diagnostic value of fused analysis to reduce inter-observer variability in revascularization strategy and target vessel selection decisions. Also, Gaemperli et al. [83] demonstrated that fusion of CTA and SPECT-MPI allows accurate detection of flow-limiting coronary stenoses (i.e. significant stenoses inducing ischemia) and that it is thus a potential gatekeeper for ICA and coronary revascularization. In our work, we provide additional insights concerning which patients are more likely to benefit from integrated analysis of fused CTA/SPECT-MPI.

6.3.3 Limitations and strengths of the study design

One limitation of our study is that it contains relatively few cases. However, results were consistent among observers and datasets. A strength of our study was the use of four independent observers in the evaluation study.

Whether integrated analysis of fused CTA/SPECT-MPI using the SMARTVis system is more time-efficient than side-by-side interpretation remains to be investigated. The interpretation using the SMARTVis system took from 3 to 15 minutes, depending on the complexity of the case and on the observer. In the current study, the observers only had a training session of a few minutes using one excluded patient to get familiar with the SMARTVis system. A reliable investigation of the time-efficiency would require a substantial longer time of use in clinical practice. Over all, the observers were enthusiastic about the presented integrated visualization tool and some were eager to use the SMARTVis system in clinical practice.

Further investigation also remains to be done to determine which patients should undergo such examination (increased imaging costs and radiation dose versus patient's benefits). We do not recommend all patients to undergo both CTA and SPECT-MPI examination, but underline that if both tests are performed, integrated analysis is to be preferred.

6.4 Conclusion

Integrated analysis of fused cardiac CTA and SPECT-MPI using the SMARTVis system primarily results in additional diagnostic value for patients presenting coronary artery disease in more vessels than the number of reported perfusion defects. The SMARTVis comprehensive visualization system can be effectively used to assess disease status in multi-vessel CAD patients, offering valuable new options for the diagnosis and management of these patients.

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