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## Multimodality Imaging of Anatomy and Function in Coronary Artery Disease

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# Chapter 7

## **Non-Invasive Evaluation of the Coronary Arteries with Multi-Slice Computed Tomography in Hypertensive Patients**

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# Abstract

## Background

Because patients with hypertension are at increased risk for developing coronary artery disease, early and non-invasive identification of the disease in patients with hypertension is important. Recently, multi-slice computed tomography (MSCT) has been demonstrated to allow both non-invasive coronary angiography and assessment of left ventricular function. The purpose of the present study therefore was to demonstrate the feasibility of this approach in patients with hypertension with known or suspected coronary artery disease and compare the results to invasive coronary angiography and 2D-echocardiography respectively.

## Methods

MSCT was performed in 31 patients with confirmed hypertension. From the MSCT images, the presence of significant coronary stenoses ( $\geq 50\%$  luminal narrowing) and regional wall motion abnormalities were evaluated and compared with invasive coronary angiography and 2D-echocardiography. In addition, left ventricular ejection fraction was calculated from the MSCT images.

## Results

A total of 243 (88%) coronary artery segments could be evaluated with MSCT. Sensitivity and specificity for the detection of significant coronary artery stenoses were 93% and 96%. On a per patient basis, multi-slice computed tomography was accurate in 28 (90%) patients. Mean left ventricular ejection fraction was  $46 \pm 14\%$  (range: 16% to 64%). The agreement for assessing regional wall motion was 91% (kappa statistic 0.81).

## Conclusion

Simultaneous, non-invasive evaluation of coronary artery stenoses and left ventricular function with MSCT is accurate in patients with hypertension. This non-invasive approach may allow triage of patient treatment in terms of conservative versus invasive management.

## Introduction

Coronary artery disease (CAD) is the major cause of morbidity and mortality in hypertensive patients, especially since patients with hypertension are at increased risk for developing CAD as compared to normotensive individuals<sup>1,2</sup>. Moreover, since hypertension is present in 1 of every 5 adults, non-invasive detection of CAD in this particular patient group has become a clinically important issue<sup>3</sup>. However, of several non-invasive tests, including exercise ECG and myocardial perfusion imaging, a limited specificity in hypertensive patients has been reported due to an increased occurrence of false positive results in this particular patient group<sup>4-7</sup>. These positive test results may represent impaired vasodilator reserve and increased myocardial oxygen demand as a consequence of microvascular disease, and thus myocardial ischemia in the absence of significant coronary artery abnormalities<sup>4-9</sup>. A non-invasive test therefore should ideally allow direct visualization of the coronary arteries to detect or exclude obstructive CAD to triage patients for optimal medical therapy or invasive evaluation.

Over the recent years, Multi-Slice Computed Tomography (MSCT) has emerged as a potential non-invasive imaging method that allows the acquisition of high-quality images of the entire heart within a single breath-hold. High sensitivities and specificities in the detection of coronary artery stenoses have been reported, ranging from 72% to 95% and 75% to 99%, respectively<sup>10-19</sup>. Furthermore, the simultaneous recording of ECG data permits the reconstruction of images at any moment of the cardiac cycle, thus allowing cardiac function analysis in addition to the evaluation of the coronary arteries, although data are scarce<sup>20-23</sup>.

Since no specific data are available on the performance of MSCT in patients with hypertension, the purpose of the present study was to demonstrate the feasibility of evaluation of the coronary arteries and left ventricular (LV) function using MSCT in patients with hypertension. Conventional coronary angiography and 2D-echocardiography served as reference standards.

## Methods

### Patients and study protocol

The study group comprised 31 patients with 1). chest pain and/or dyspnea, 2). confirmed hypertension (defined by sequential (on separate occasions) blood pressure measurements using an arm cuff and a mercury manometer). All patients were scheduled for conventional coronary angiography for the evaluation of chest pain/dyspnea complaints. Hypertension was defined as systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg, and/or use of antihypertensive medication.

Patients with atrial fibrillation were excluded, and additional exclusion criteria were renal insufficiency (serum creatinine  $> 120$  mmol/L), known allergy to iodine contrast media, severe claustrophobia, and pregnancy.

All patients gave informed consent to the study protocol, which was approved by the local ethics committee.

## Multi-slice computed tomography

### *Data acquisition*

In the initial 17 patients, MSCT angiography was performed with a Toshiba Multi-Slice Aquilion 0.5 system and in the remaining patients with a Toshiba Multi-slice Aquilion 16 system (Toshiba Medical Systems, Otawara, Japan). Thus, detector collimation was either 4 x 2.0 mm or 16 x 0.5 mm. Other parameters were: rotation time 400, 500 or 600 ms (depending on the heart rate), tube current 250 mA, and tube voltage 120 kV. A bolus non-ionic contrast (Xenetix 300<sup>®</sup>, Guerbet, Aulnay S. Bois, France) was injected in the antecubital vein at a flow rate of 4.0 ml/s, resulting in a total administered dose of 120-150 ml, depending on the scan time. Automated detection of peak enhancement in the aortic root was used for timing of the scan. During a breath hold of approximately 25s, cardiac images, from the aortic root to the apex, were acquired. Data were reconstructed using retrospective ECG gating. A multi-segment reconstruction algorithm was applied, meaning that data from up to 4 consecutive heartbeats were used to generate a single image, thereby resulting in a temporal resolution of 105 – 200 ms. Spatial resolution was 0.5 x 0.5 x 2.0 mm and 0.5 x 0.5 x 0.5 mm for the 4-slice and 16-slice system, respectively. No beta-blocking medication to reduce the heart rate was administered prior to the examination and patients were included regardless of heart rate.

To evaluate the presence of coronary artery stenoses, reconstructions in diastole (65% - 85% of the cardiac cycle) were generated with a reconstructed section thickness of either 1.0 mm (4-slice system) or 0.4 mm (16-slice system). Images were transferred to a remote workstation (Vitrea2, Vital Images, Plymouth, Minn. USA) for post-processing and evaluation. Images containing the fewest motion artifacts were used for evaluation.

For the evaluation of LV function, the same original raw data set (acquired for the evaluation of the coronary arteries) was used. Images were reconstructed retrospectively at 20 time points, starting at early systole (0% of the cardiac cycle) to the end of diastole (95% of the cardiac cycle). Subsequently, short-axis images with a slice thickness of 2.00 mm were generated and transferred to a remote workstation with dedicated cardiac function analysis software (MR Analytical Software System [MASS], Medis, Leiden, the Netherlands).

### *Data analysis*

The images were evaluated by an experienced observer, blinded to the catheterization results. A modified AHA-ACC segmentation model was used for stenosis assessment: the left main coronary artery (segment 5), the right coronary artery (segments 1, 2, 3), the left anterior descending coronary artery (segments 6, 7, and 8), and the left circumflex artery (segment 11, 13)<sup>24</sup>. If present and of sufficient size (diameter larger than 2.0 mm), distal segments and side-branches (segments 4, 9, 10, 12, 14, 15, 16 and 17) were also evaluated.

In addition to the original axial slices, curved multiplanar reconstructions and 3D volume rendered

reconstructions were used to assess the presence of luminal narrowing. First, assessability was determined for each segment. Interpretable segments were subsequently classified as having significant stenosis ( $\geq 50\%$  reduction of lumen diameter) or not.

An experienced observer blinded to all other data evaluated the presence of regional wall motion abnormalities visually on the short-axis slices (displayed in cine-loop format) using a previously described 17-segment model<sup>25</sup>. Each segment was graded on a 4-point scale (1= normokinesia, 2= hypokinesia, 3= akinesia and 4= dyskinesia).

In order to calculate LV ejection fractions, endocardial contours were manually drawn on both the end-systolic and end-diastolic short-axis images. Papillary muscles were regarded as being part of the LV cavity. LV end-systolic and end-diastolic volumes were calculated using commercially available software (MASS) developed at our institution by summation of the product (area  $\times$  slice distance) of all slices. Finally, the related LV ejection fraction was derived by subtracting the end-systolic volume from the volume at end-diastole and dividing the result by the end-diastolic volume.

## Invasive coronary angiography

Invasive coronary angiography was performed according to standard techniques. Vascular access was obtained through the femoral approach with Seldinger's technique and a 6 Fr or 7 Fr catheter. Coronary angiograms were visually evaluated by an experienced observer without knowledge of the MSCT data. The same segmentation as described above for MSCT was applied to determine the presence of significant luminal reduction in each coronary segment.

## 2D-echocardiography

2D-echocardiography was performed in the left lateral decubitus position using a commercially available system (Vingmed System FiVe/Vivid-7, GE-Vingmed, Milwaukee, WI, USA). Images were acquired using 3.5 MHz transducer at a depth of 16 cm in standard parasternal and apical views.

Regional wall motion was scored using the 17-segment model and 4-point scale as described above for MSCT.

## Statistical analysis

Sensitivity, specificity, positive and negative predictive values with their corresponding 95% Confidence Intervals (CIs) for the detection of significant coronary artery stenoses were calculated. The 95% CIs were calculated using the following formula:  $p \pm 1.96 \cdot \sqrt{\{p \cdot (100-p)/n\}}$ , where  $p$  = sensitivity or specificity (%) and  $n$  = the total number of segments. Additionally, data were analyzed on a per patient basis. MSCT was considered correct in the individual patient analysis if at least one significant stenosis was detected on the MSCT images or if MSCT ruled out the presence of any significant stenosis. Agreement for regional wall motion was expressed in a 4x4 table using weighted kappa

statistics. A kappa value of <0.4 represents poor agreement, a kappa value between 0.4 and 0.75 fair to good agreement, and a kappa value of >0.75 is considered an excellent agreement based on the Fleiss' classification<sup>26</sup>. A p-value <0.05 was considered to indicate statistical significance.

## Results

### Patient characteristics

The patient characteristics are listed in Table 1. The study group consisted of 31 patients with confirmed hypertension; mean systolic blood pressure was  $138 \pm 21$  mmHg (range: 110-167 mmHg), whereas mean diastolic blood pressure was  $81 \pm 10$  mmHg (range: 67-105 mmHg). Average duration of hypertension at the time of MSCT was  $3.1 \pm 5.8$  years (range: 0 - 9 years). Mean LV mass, as determined by echocardiography was  $197 \pm 68$  g. Mean body mass index was  $25 \pm 3$  kg/m<sup>2</sup>. Cardiac medication was continued during the study period. A total of 23 patients (74%) used beta-blocking agents. Other medications included angiotensin converting enzyme inhibitors (n=25), calcium-antagonists (n=16), nitrates (n=13), diuretics (n=10), oral anticoagulants (n=30) and statins (n=30). The average interval between conventional coronary angiography and MSCT was  $1.9 \pm 2.7$  days. The interval between 2D-echocardiography and MSCT was  $2.2 \pm 1.8$  days.

**Table 1.** Clinical characteristics of the study population (n=31).

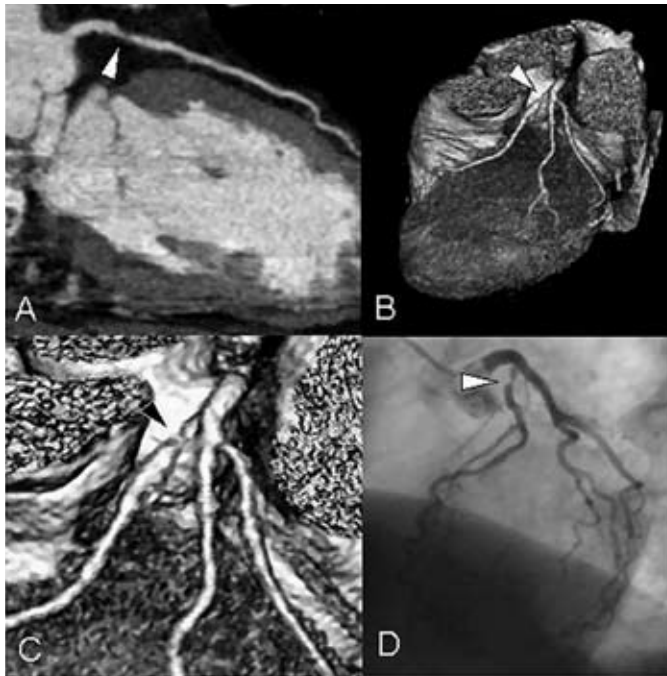
| Characteristic                           | Value            |
|------------------------------------------|------------------|
| Gender (M/F)                             | 28/3             |
| Age (yrs)                                | $63 \pm 11$      |
| Hypertension                             | 31 (100)         |
| Heart rate during data acquisition (bpm) | $68 \pm 14$      |
| Beta blocker medication                  | 23 (74)          |
| Angina Pectoris                          |                  |
| CCS class 1/2                            | 7 (23)           |
| CCS class 3/4                            | 24 (77)          |
| Heart Failure                            |                  |
| NYHA class 1/2                           | 23 (74)          |
| NYHA class 3/4                           | 8 (26)           |
| History                                  |                  |
| Previous MI                              | 15 (48)          |
| Previous PCI/CABG                        | 25 (81)/ 10 (34) |
| Other risk factors for CAD               |                  |
| Diabetes type 2                          | 16 (52)          |
| Smoking                                  | 15 (48)          |
| Hypercholesterolemia                     | 29 (94)          |
| Family with CAD                          | 17 (55)          |

Data between parentheses are %.

*Bpm: beats per minute; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CCS: Canadian Cardiovascular Society; MI: myocardial infarction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention.*

## Coronary artery stenoses

A total of 277 coronary segments was available for comparison between conventional angiography and MSCT. Of these segments, 243 (88%) were of sufficient quality to evaluate the presence of significant ( $\geq 50\%$ ) narrowing. Reasons of uninterpretability were predominantly the presence of coronary stents and motion artifacts. Furthermore, the majority of uninterpretable segments was located in distal segments (segments 3, 8 and 13). Conventional angiography revealed 57 significant stenoses in the interpretable segments. Of these lesions, 53 were correctly detected by MSCT. The presence of significant stenosis was correctly ruled out in 179 out of 186 non-diseased segments. Accordingly, the sensitivity and specificity for the detection of coronary artery stenoses were 93% and 96%, respectively. Details per coronary artery, including positive and negative predictive values, are summarized in Table 7.2; among the different coronary arteries, no significant differences were noted. On a per patient basis, MSCT was accurate in 28 (90%) patients. Of 21 patients with significant lesions on conventional angiography, 20 (95%) patients were correctly identified. In the remaining 10 patients with no significant abnormalities, MSCT was accurate in 8 (80%) patients. In Figures 1 and 2, MSCT images of both stenotic and normal coronary arteries are shown. Of note, to obtain a multiplanar reconstruction, each vessel needs to be reconstructed separately. Thus, no side-branches are visible, since only multiplanar reconstructions of the three major vessels are provided.



**Figure 1.** Severe lesion in the left anterior descending coronary artery (LAD). In Panel A, a curved multiplanar MSCT reconstruction of the LAD is shown, demonstrating a severe stenosis (white arrowhead) in the proximal part of the vessel. A 3D volume rendered reconstruction is provided in Panel B. The severe lesion is also clearly visible in Panel C (black arrowhead), an enlargement of Panel B. Findings were confirmed by conventional angiography (panel D).

**Table 2.** Diagnostic accuracy (with 95% Confidence Intervals) of MSCT in the detection of stenoses.

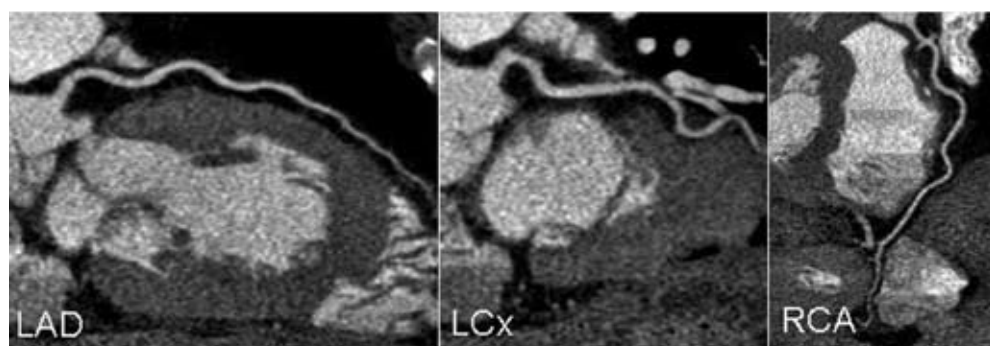
| Parameter     | All segments            | LM                    | LAD                   | LCx                   | RCA                   |
|---------------|-------------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Interpretable | 243/277<br>(88, 84-92)  | 30/31<br>(97, 91-100) | 84/97<br>(87, 80-94)  | 59/66<br>(89, 81-97)  | 70/83<br>(84, 76-92)  |
| Sensitivity   | 53/57<br>(93, 86-100)   | 1/1<br>(100, NA)      | 22/23<br>(96, 88-100) | 11/14<br>(79, 58-100) | 19/19<br>(100, NA)    |
| Specificity   | 179/186<br>(96, 93-99)  | 27/29<br>(93, 84-100) | 58/61<br>(95, 90-100) | 45/45<br>(100, NA)    | 49/51<br>(96, 91-100) |
| PPV           | 53/60<br>(88, 80-96)    | 1/3<br>(33, 0-86)     | 22/25<br>(88, 75-100) | 11/11<br>(100, NA)    | 19/21<br>(90, 77-100) |
| NPV           | 179/183<br>(98, 96-100) | 27/27<br>(100, NA)    | 58/59<br>(98, 94-100) | 45/48<br>(94, 87-100) | 49/49<br>(100, NA)    |

Values are the absolute values used to calculate the percentages. Numbers in parentheses are the percentages with the corresponding 95% CIs.

LAD: left anterior descending coronary artery; LCx: left circumflex coronary artery; LM: left main coronary artery; MSCT: multi-slice computed tomography; NPV: negative predictive value; PPV: positive predictive value; RCA: right coronary artery.

## LV function

LV ejection fraction, as determined by MSCT, ranged from 16% to 64% (mean  $46 \pm 14\%$ ), respectively. Abnormal wall motion was observed in 158 (30%) of 527 segments, with 86 (54%) of these segments showing hypokinesia, 55 (35%) akinesia and 17 (11%) dyskinesia. In 148 (94%) of these segments, MSCT also demonstrated abnormal wall motion. Overall, 91% of segments were scored identically on both modalities (kappa statistic 0.81, Table 3), indicating an excellent agreement between 2D-echocardiography and MSCT. For the individual wall motion scores (1-4), agreements were 97%, 78%, 71% and 94%, respectively. Examples of short-axis reconstructions are shown in Figure 3 and 4, showing patients with normal and abnormal LV function.



**Figure 2.** Patent coronary arteries. Curved multiplanar MSCT reconstructions of the left anterior descending artery, left circumflex artery and right coronary artery, respectively, showing the absence of significant luminal narrowing in all vessels.

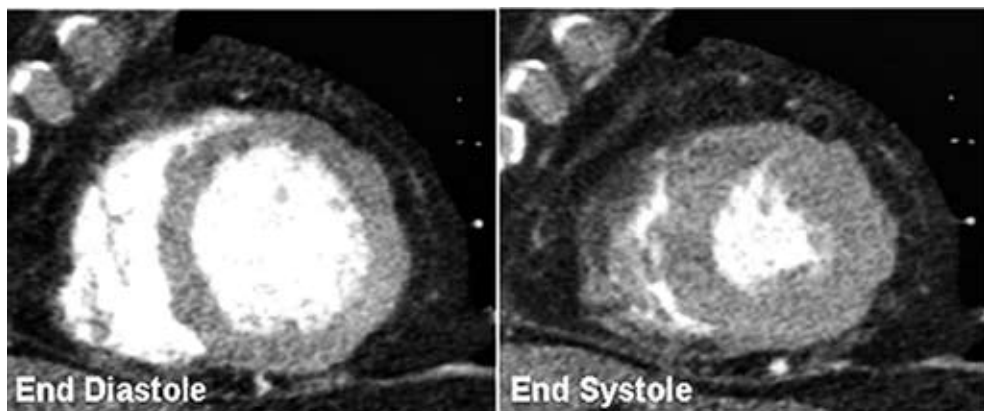
**Table 3.** Relation between regional wall motion as determined by echocardiography and MSCT (agreement 91%, kappa statistic 0.81).

| MSCT  | Echocardiography |    |    |    | Total |
|-------|------------------|----|----|----|-------|
|       | 1                | 2  | 3  | 4  |       |
| 1     | 357              | 10 | 0  | 0  | 367   |
| 2     | 12               | 67 | 13 | 0  | 92    |
| 3     | 0                | 9  | 39 | 1  | 49    |
| 4     | 0                | 0  | 3  | 16 | 19    |
| Total | 369              | 86 | 55 | 17 | 527   |

1= normokinesia, 2=hypokinesia, 3= akinesia, and 4= dyskinesia

## Discussion

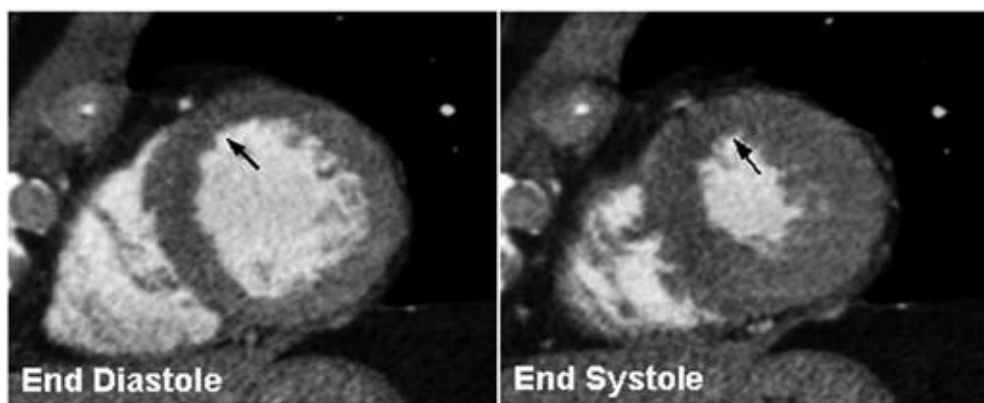
The results of the current study demonstrate that accurate evaluation of the coronary arteries and LV function in patients with hypertension using contrast-enhanced MSCT is feasible. In the detection of significant coronary artery stenoses, an excellent sensitivity and specificity of 93% and 96% were demonstrated. These results are in line with previous studies obtained in the general patient population. In a study by Ropers et al <sup>19</sup>, coronary artery stenoses were detected with a sensitivity and specificity of 91% and 93%, respectively. A somewhat higher sensitivity (95%) and slightly lower specificity (89%) were reported by Nieman et al <sup>16</sup>. In both studies a negative predictive value of 97% was reported, similar to our results (98%). These findings demonstrate the potential of MSCT to function as a diagnostic tool to rule out the presence of CAD. This may improve the non-invasive work up of patients with hypertension in particular, since in these patients false positive test results in the absence of coronary artery stenoses are frequently encountered with other non-invasive imaging modalities, including nuclear perfusion imaging and stress echocardiography <sup>5</sup>. These imaging modalities visualize the consequences of ischemia (induction of perfusion abnormalities or systolic wall motion abnormalities). In contrast, direct visualization of the coronary arteries is allowed by MSCT.

**Figure 3.** MSCT short-axis reconstructions in end-diastole and end-systole. Normal systolic wall motion is clearly present in all segments.

Thus, by ruling out the presence of CAD, non-invasive angiography with MSCT may substantially reduce the number of patients that will need diagnostic invasive coronary angiography. However, when significant abnormalities are observed on the MSCT images, this information could be used for a more efficiently targeted (interventional) treatment strategy. Still, further prognostic studies are needed in larger cohorts before MSCT can become an established diagnostic modality and replace conventional coronary angiography in certain patient groups.

In addition to non-invasive coronary angiography, LV function analysis was performed. Agreement of regional wall motion scores was excellent with 91% of segments scored identically, resulting in a kappa statistic of 0.81. For the individual wall motion scores, agreement was highest for segments with either normal contractility (97%) or dyskinesia (94%), whereas it was slightly lower in segments with intermediate motion abnormalities (75%). This phenomenon may be attributed to the temporal resolution of the technique (105–200 ms), which may be insufficient to allow detection of subtler wall motion abnormalities in some cases. For echo, wall motion was derived from parasternal and apical views whereas only short-axis views were used with MSCT and this may also account for discrepancies.

In contrast to several other studies<sup>16,19</sup>, no beta-blocking agents were administered prior to the MSCT data acquisition in order to lower heart rates higher than 65 beats per minute. The use of a multi-segmented reconstruction algorithm, available on our MSCT equipment, allowed the inclusion of patients with higher heart rates without compromise to temporal resolution.



**Figure 4.** Example of MSCT short-axis reconstructions of a patient with reduced wall motion in the anteroseptal region (black arrow).

Several limitations of the present study need to be addressed.

First, both a 4-slice system and 16-slice system were used for data acquisition. Since 16-slice systems have been demonstrated to result in both better assessability and accuracy as compared to 4-slice systems, the use of 2 different systems is likely to have influenced our results. Moreover, of the 34 coronary artery segments with insufficient quality to assess the presence or absence of significant coronary artery stenoses, 68% was acquired with the 4-slice system. As expected, assessability was

lowest in the right coronary artery, since this vessel displays the fastest movement during the cardiac cycle. In addition, the presence of coronary stents also frequently resulted in degraded image quality. Similar percentages have been reported previously<sup>13;19;27</sup>. In the near future however, this limitation may be overcome by the introduction of 32- and 64-detector row scanners in combination with faster rotation times, which are likely to reduce the percentage of non-assessable segments.

Second, an important drawback of MSCT is the radiation dose that is still considerably high; approximately 8 mSv. However, with the use of new filters the radiation dose will decrease substantially. Third, precise quantification of luminal stenosis (as can be performed with angiography) is currently not possible with MSCT, since the spatial resolution is still suboptimal and validated software is currently not available. Finally, the prevalence of CAD in the present population was high and validation of the technique in patients with lower prevalence of CAD is warranted. Similarly, patients with late-stage as well as early stage hypertension were included, since the purpose of the present study was to demonstrate the feasibility of the technique in this population. Thus, further testing of the technique in patients with early-stage hypertension is needed.

In conclusion, accurate, simultaneous evaluation of both the coronary arteries and LV function in patients with hypertension is feasible.

## Perspectives

This combined strategy may offer a new approach for a non-invasive, conclusive workup in patients with hypertension and known or suspected CAD. Direct visualization of the coronary arteries may result in improved identification of patients at risk for cardiovascular events. However, whether this translates into improved clinical management still needs to be tested, particularly in patient groups with early-stage hypertension and lower prevalence of CAD.

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