Imaging of coronary atherosclerosis with multi-slice computed tomography

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Chapter 6

Head-to-Head Comparison Between Bicycle Exercise Testing and Coronary Calcium Score and Coronary Stenoses on Multi-Slice Computed Tomography

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Abstract

Aims: To perform a head-to-head comparison between signs of ischemia during bicycle exercise testing and coronary atherosclerosis on multi-slice computed tomography (MSCT) in patients with suspected coronary artery disease (CAD).

Methods: 201 patients underwent exercise testing, followed by 64-slice MSCT. A subgroup of 63 (31%) patients also underwent conventional coronary angiography. The exercise test was positive or negative based on electrocardiographic signs of ischemia. On MSCT, total calcium score was obtained. Based on MSCT angiography, the patients were classified as having normal MSCT or coronary atherosclerosis (with non-obstructive and obstructive CAD (≥50% luminal narrowing) present).

Results: In 178 patients with interpretable examinations, the exercise test was positive in 36 (20%) and negative in 142 (80%) patients. Calcium score was identical in patients with a positive (11 (0-343)) and a negative exercise test (18 (0-335), p=NS). The prevalence of non-obstructive CAD was the same in 2 patients groups (13 (36%) patients with a positive versus 54 (38%) patients with a negative exercise test, p=NS). Although obstructive CAD was observed in 15 (42%) patients having a positive exercise test, obstructive lesions were also present in 38 (27%) patients without ischemia on exercise testing. The findings were confirmed by conventional coronary angiography.

Conclusion: No correlation was observed between ischemia on exercise testing and both calcium scoring and non-obstructive CAD on MSCT. A large proportion of obstructive lesions on MSCT were not demonstrated on exercise testing. Potentially MSCT may provide additional information on CAD.

Introduction

For the initial evaluation of the presence of coronary artery disease (CAD) non-invasive testing modalities are typically used. Frequently, exercise testing is used as a first-line examination as it is robust, widely available, relatively safe and inexpensive.[1] The test provides an estimate of the presence of myocardial ischemia. Nevertheless, an important limitation of exercise testing is its limited diagnostic accuracy to detect obstructive CAD.[2] In addition, while a positive test result is associated with adverse outcome, the prognostic value of a negative exercise test is less well established.[1,2]

Multi-slice computed tomography (MSCT) has recently been introduced as a novel imaging modality allowing direct non-invasive assessment of coronary atherosclerosis. Since a high diagnostic accuracy to detect or exclude obstructive lesions has been demonstrated,[3] the technique has been suggested as a potential non-invasive modality to establish or rule out the presence of obstructive CAD. In addition, MSCT allows quantitative assessment of coronary calcium and visualization of coronary plaques.[3,4] Preliminary studies reporting on the prognostic value of MSCT have demonstrated that MSCT has an independent prognostic value over baseline patient characteristics.[5,6]

Since both exercise testing and MSCT may be used for detection of CAD and provide different type of information (functional versus anatomical), it is important to understand how these modalities correlate. Indeed, previous studies demonstrated superior diagnostic accuracy of MSCT in detecting obstructive CAD as compared with exercise testing.[7,8] Nevertheless, more detailed information on the correlation between both a positive and a negative exercise test result and the anatomical observations of CAD on MSCT is still lacking. Accordingly, the purpose of the study was to assess the relationship between exercise testing results and the presence of coronary atherosclerosis on MSCT in patients with suspected CAD.

Methods

Patients and study protocol

A total of 201 patients were initially included in the study who underwent bicycle exercise testing and MSCT for the evaluation of CAD. The 2 examinations were performed within a time interval of 4 weeks; patients who developed acute coronary events or worsening of angina between the 2 examinations were excluded. A subset of patients (63 (31%)) also underwent conventional coronary angiography within 4 weeks after MSCT coronary angiography; referral was at the discretion of a treating physician based on clinical symptoms and the presence of CAD risk factors. Only patients without contraindications to MSCT [9] or exercise testing [2] were included. Informed consent was obtained in all patients.

Exercise testing

Exercise testing was performed on a bicycle ergometer according to the standard protocols.[10] The tests were analyzed by an experienced reader who was unaware of the results of MSCT and were classified as positive or negative for ischemia. The exercise test was considered positive based on the presence of ≥0.1 mV horizontal or downsloping ST-segment depression on the electrocardiogram (ECG) at 80 milliseconds after the J point in 2 contiguous leads during exercise or recovery.[2] The exercise test was considered uninterpretable if the patient failed to attain at least 85% of the age-predicted maximum heart rate with the absence of ischemic changes, if the ECG recording artifacts were observed during testing or if ECG changes were equivocal.[2]

MSCT

The examinations were performed using Toshiba Multi-slice Aquilion System (Toshiba Medical Systems, Tokyo, Japan). Patients underwent a prospectively triggered coronary calcium scan without contrast enhancement first, followed by 64-slice MSCT coronary angiography.[11]

First, total Agatston calcium score was recorded for all patients while coronary artery calcium was identified as a dense area in the coronary artery exceeding the threshold of 130 HU. Based on the total coronary calcium score, the patients were classified as having no or minimal coronary calcification (total calcium score <10) or extensive calcification (total calcium score >400). Subsequently, MSCT angiograms were evaluated in consensus by 2 experienced observers. All coronary angiograms were evaluated for interpretability and patients were excluded from the analysis in case of 1. an uninterpretable proximal or mid coronary segment or 2. more than 3 uninterpretable segments in general. The presence of coronary plaques was visually evaluated using axial images and curved multiplanar reconstructions. If present, plaques were classified as non-obstructive and obstructive using a 50% threshold of luminal narrowing. The patients were first classified as A) having a normal MSCT (no plaques visible) or as B) having coronary atherosclerosis (at least 1 coronary plaque detectable). In case of the presence of atherosclerosis, the patients were further classified as follows: 1) patients with non-obstructive CAD*,* if exclusively non-obstructive plaques were present, 2) patients with obstructive CAD*,* if at least 1 obstructive plaque was present, 3) patients with left main and/or 3-vessel CAD*,* if obstructive plaques were located in left main coronary artery and/or in all 3 vessels.

Conventional coronary angiography

Conventional invasive coronary angiography was performed according to standard protocols.[12] Coronary angiograms were evaluated by an experienced observer blinded to the study results. Coronary segments were classified using a modified 17 segment American Heart Association classification.[13] The presence of an obstructive lesion was defined as ≥50% luminal narrowing. Accordingly, the patients were evaluated for the presence or absence of obstructive CAD *(*at least 1 obstructive lesion was present) and, if present, further classified as having left main and/or 3-vessel CAD (in case of an obstructive lesion located in the left main coronary artery and/or all 3 vessels).

Statistical analysis

Categorical variables are expressed as numbers (percentages) and compared between groups with 2-tailed Chi-square test. Continuous variables are expressed as mean (standard deviation). When not normally distributed, continuous variables are expressed as medians (interquartile range) and compared between groups with 2-tailed non-parametric Mann-Whitney test.

P-values of <0.05 were considered as statistically significant. Statistical analyses were performed using SPSS software (version 14.0, SPSS Inc, Chicago, Ill, USA).

Results

Patient population

A total of 201 patients were initially enrolled. The clinical characteristics of the patients at the time of inclusion in the study are presented in Table 1. MSCT was performed successfully in all but 2 (1%) patients, who had an elevated heart rate during the scan rendering the examination uninterpretable. In 21 (10%) patients, the exercise test was deemed uninterpretable: 12 patients did not reach 85% of the maximum predicted heart rate, ECG recording artifacts during exercise testing were observed in 2 patients and 7 patients developed equivocal ECG changes during exercise testing.

Table 1 Characteristics of the study population

	n=201
CAD risk factors	
Age (yrs, mean±SD)	56±11
Male gender	100 (50%)
Type 2 diabetes	28 (14%)
Hypercholesterolemia	121 (60%)
Hypertension	98 (49%)
Family history of CAD	100 (50%)
Smoking	67 (33%)
Body mass index (kg/m^2)	26±4
Obesity	65 (32%)
Previous history of CAD	
Previous PCI	22 (11%)
Previous MI	21 (10%)
Medications	
Use of ACEI/ARB	68 (34%)
Use of β-blockers	78 (39%)
Use of nitrates	23 (11%)
Use of statins	79 (39%)
Use of aspirin	75 (37%)

Data are absolute numbers (%), unless otherwise indicated.
ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Exercise testing, MSCT and conventional coronary angiography findings

The exercise test was positive in 36 (20%) of 178 patients with interpretable results, whereas the test was negative in 142 (80%) patients.

The coronary calcium score was available in 177 (99%) patients (35 (20%) with a positive exercise test and 142 (80%) with a negative exercise test). The median coronary calcium score per patient was 18 (0-338). Minimal coronary calcifications (total calcium score <10) were observed in 81 (46%) patients, whereas extensive coronary calcifications (total calcium score >400) were detected in 37 (21%) patients.

On MSCT coronary angiography, 58 (32%) patients were classified as normal, whereas 120 (68%) patients had atherosclerosis. Non-obstructive CAD was observed in 67 (38%) patients, whereas obstructive CAD was present in 53 (30%) patients, 12 (23%) of these patients having left main and/or 3-vessel CAD.

A subset of 63 (35%) patients underwent conventional invasive coronary angiography. In total, obstructive CAD was detected in 35 (56%) patients, 11 (31%) of these patients having left main and/or 3-vessel CAD.

Exercise testing versus coronary calcium score

The total calcium score was identical among patients with a positive and a negative exercise test (Figure 1). The median calcium score in patients with a positive exercise test was 11 (0-343), whereas the median calcium score in patients with a negative exercise test was 18 (0-335) (p=NS). Minimal coronary calcification (total calcium score <10) was observed in 18 (51%) patients with a positive exercise test and in 63 (44%) patients with a negative exercise test (p=NS). Vice versa, extensive coronary calcification (total calcium score >400) was observed in 7 (20%) patients with a positive exercise test and in 30 (21%) patients with a negative exercise test (p=NS).

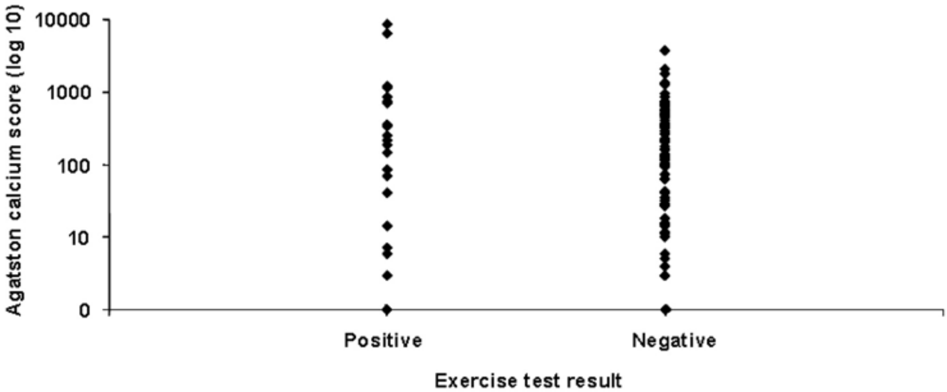

Figure 1. The results of exercise testing versus total Agatston calcium score on MSCT. Identical calcium scores were observed in patients with a positive and a negative exercise test.

Exercise testing versus stenoses on MSCT

The comparison between the findings on exercise testing and MSCT are presented in Figure 2. In patients with a positive exercise test, coronary atherosclerosis on MSCT was observed in 28 (78%) patients. Obstructive CAD was present in 15 (42%) patients (of which 5 (33%) had left main and/or 3-vessel CAD). Non-obstructive CAD was detected in 13 (36%) patients. In 8 (22%) patients with a positive exercise test, a normal MSCT was observed (no plaques visible).

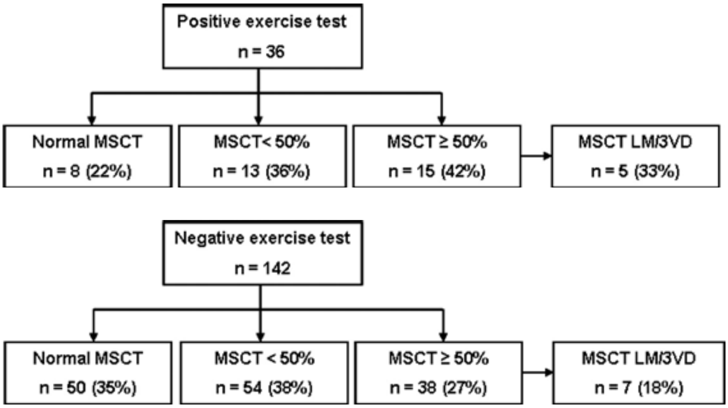

Figure 2. Relationship between the findings on exercise testing and MSCT.
Normal MSCT indicates the absence of any coronary plaques; MSCT <50% indicates the presence of exclusively non-obstructive CAD; MSCT ≥50% indicates the presence of obstructive CAD; MSCT LM/3VD indicates the presence of obstructive CAD in the left main coronary artery and/or all 3 coronary vessels.
CAD, coronary artery disease; LM, left main coronary artery; 3VD, 3-vessel disease.

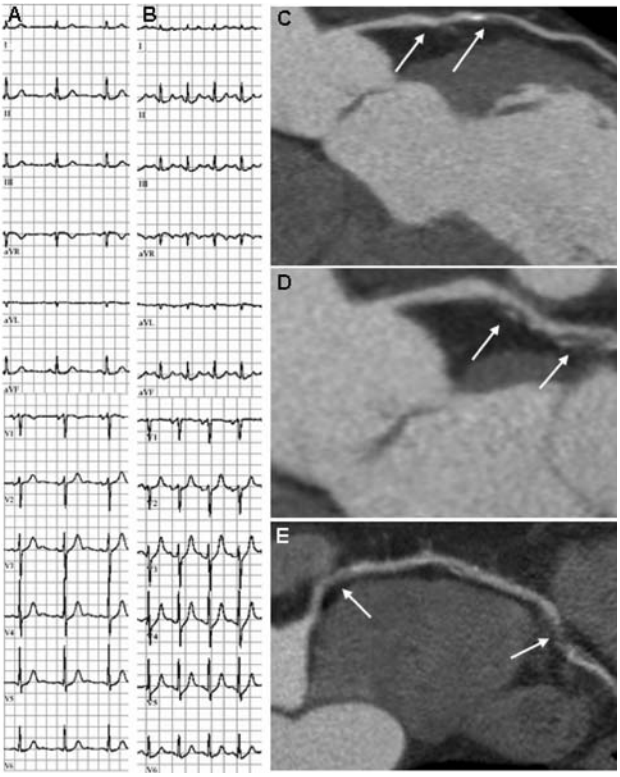

Figure 3. An example of a patient with 3-vessel coronary artery disease on MSCT and a negative exercise test. No signs of ischemia were observed on the electrocardiogram either at rest (A) or during maximal exercise (B). On MSCT, obstructive lesions were demonstrated in proximal left anterior descending coronary artery (arrows) (C), proximal left circumflex coronary artery (arrows) (D) and proximal and distal right coronary artery (arrows) (E).

In patients with a negative exercise test, a normal MSCT was obtained in 50 (35%) patients. Nevertheless, coronary atherosclerosis was identified in 92 (65%) patients. In these patients, non-obstructive CAD was observed in 54 (38%). Obstructive CAD was present in 38 (27%) patients, in which MSCT identified left main and/or 3-vessel CAD in 7 (18%). An example of a patient with 3-vessel CAD on MSCT coronary angiography despite a negative exercise test is provided in Figure 3.

Comparison of exercise testing and stenoses on MSCT to conventional coronary angiography

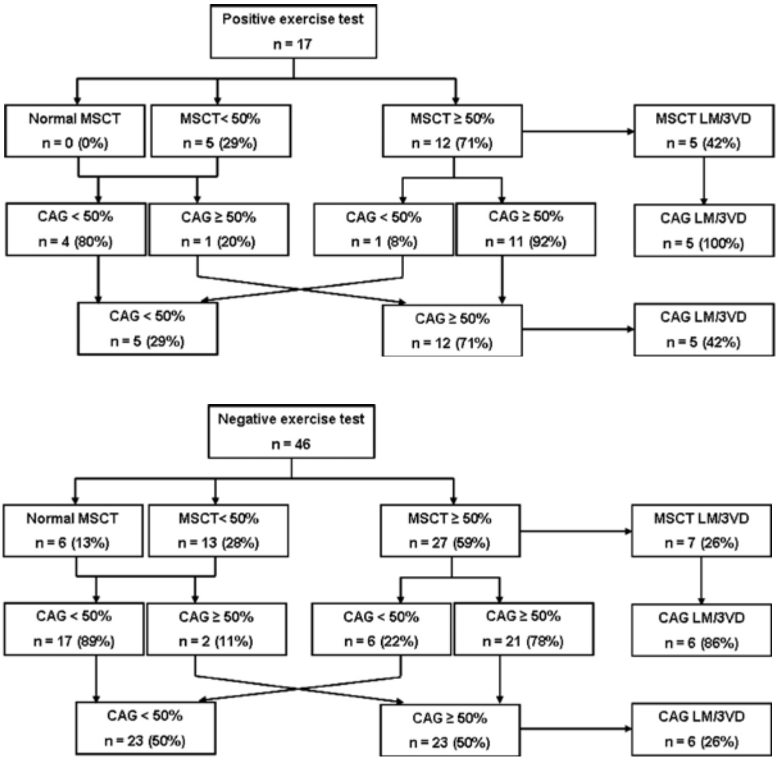

Figure 4. Relationship between the findings on exercise testing, MSCT and conventional coronary angiography. Normal MSCT indicates the absence of any coronary plaques; MSCT <50% indicates the presence of exclusively non-obstructive CAD; MSCT ≥50% indicates the presence of obstructive CAD; MSCT LM/3VD indicates the presence of obstructive CAD in the left main coronary artery and/or all 3 coronary vessels.
CAG <50% indicates the absence of obstructive CAD; CAG ≥50% indicates the presence of obstructive CAD; CAG LM/3VD indicates the presence of obstructive CAD in the left main coronary artery and/or all 3 coronary vessels.
CAD, coronary artery disease; CAG, conventional coronary angiography; LM, left main coronary artery; 3VD, 3-vessel disease.

The comparison between the findings on exercise testing, MSCT coronary angiography and conventional invasive coronary angiography is provided in Figure 4. The majority of patients with a positive exercise test had obstructive CAD on conventional coronary angiography (12 (71%)). All but 1 patient with obstructive lesions were correctly identified by MSCT (11 of 12 (92%)). However, absence of obstructive CAD was still observed in 5 (29%) patients with a positive exercise test.

Concerning patients with a negative exercise test, obstructive CAD was absent on conventional coronary angiography in 23 (50%) of patients. All but 2 patients without obstructive lesions were correctly identified on MSCT (17 of 19 (89%)). Nevertheless, the exercise test was false negative in 23 (50%) patients and 6 (26%) of these patients had left main and/or 3-vessel CAD confirmed by conventional coronary angiography.

Uninterpretable exercise test versus MSCT coronary angiography

In 21 patients with an uninterpretable exercise test, obstructive CAD was observed in 6 (29%) patients. Four (67%) of these patients had left main and/or 3-vessel CAD. Non-obstructive CAD was identified in 10 (47%) patients, whereas a normal MSCT was observed in 5 (24%) patients.

Discussion

The findings of the study may be summarized as follows. Exercise testing and MSCT, which are frequently used for the primary evaluation of CAD, provide discrepant information. First, no evident relationship between the results of exercise testing and the presence of coronary calcium and non-obstructive atherosclerosis was observed. Second, although obstructive CAD was observed in a large proportion of patients with a positive exercise test, obstructive CAD was also detected in nearly one third of patients with a negative exercise test. Moreover, MSCT even identified a small but not negligible proportion of patients with left main and/or 3-vessel CAD despite the absence of ischemia on exercise testing.

Exercise testing versus coronary atherosclerosis

The present study failed to demonstrate an evident relationship between the presence of coronary atherosclerosis as determined on calcium scoring and MSCT angiography and results from exercise testing. Indeed, the median calcium score in patients with a positive exercise test result was comparable to the median calcium score in patients with a negative exercise test. At first sight, this observation contradicts previous observations comparing calcium scoring to myocardial perfusion imaging (MPI). In a large investigation including asymptomatic individuals, a significantly higher mean coronary calcium score of 1,175 was observed in the 76 patients exhibiting abnormal MPI versus an average of 389 in the remaining 1,119 patients with normal MPI studies.[14] In symptomatic patients,[15] higher mean coronary calcium scores have been observed in patients with abnormal MPI as compared to patients with no perfusion abnormalities as well. Nonetheless, in these studies functional imaging still failed to identify substantial atherosclerosis in a considerable proportion of patients. In the study by Berman et al, extensive calcifications (total calcium scores >400) were observed in 31% of normal MPI studies.[14] Similarly, in the present study, calcium scores of >400 were identified in 21% of patients without signs of ischemia on exercise testing. Moreover, the prevalence of atherosclerosis was only slightly higher in patients with abnormal exercise tests (78%) with still a substantial proportion of patients (65%) without signs of ischemia on exercise testing having atherosclerosis. Nevertheless, the ability of MSCT to detect both obstructive and non-obstructive lesions may be of clinical importance since it has been demonstrated that myocardial infarction frequently occurs due to rupture of previously non-obstructive lesions.[16-19] Accordingly, MSCT may provide additional information on the presence of atherosclerosis.

Exercise testing versus obstructive stenosis

In accordance with previous studies comparing MSCT to exercise testing, a larger proportion of patients with obstructive CAD was observed in patients having detectable ischemia on exercise testing. Indeed, obstructive lesions were demonstrated in 42% of patients with a positive exercise test result. Nevertheless, obstructive lesions were also observed in 27% of patients with a negative exercise test. This is in line with observations by Rubinshtein et al [20] who compared exercise testing in 100 patients with a negative or non-diagnostic exercise test. The authors reported a prevalence of obstructive lesions in 22% of patients with a negative exercise test result. Importantly, in our study MSCT revealed left main and/or 3-vessel CAD in 5% of patients with a negative exercise test result, comparable to the study by Rubinshtein et al.[20] These observations were confirmed in a subgroup of patients who underwent conventional invasive coronary angiography.

On the contrary, although the absence of flow limiting lesions was correctly detected in 73% of patients having a negative exercise test, as many as 58% of patients without obstructive lesions on MSCT (and 22% patients with completely normal MSCT) were observed to have ischemia on exercise testing. Indeed, it is well known, that results from exercise testing may be influenced by a variety of clinical conditions such as the presence of arterial hypertension or previous CAD as well as female gender.[2] In contrast, these conditions appear to have no significant influence on the diagnostic accuracy of MSCT coronary angiography.[21,22]

Importantly, the presence of obstructive CAD could be excluded by MSCT in the majority of patients with an uninterpretable exercise test result. Accordingly, MSCT could possibly also provide valuable information in patients with an uninterpretable exercise test as previously suggested.[7]

Clinical implications

The study demonstrated that exercise testing and MSCT provide discrepant information on CAD. While exercise testing provides a general estimate on the presence of myocardial ischemia, MSCT provides more detailed information on coronary atherosclerosis including the presence and location of both obstructive and non-obstructive plaques. Accordingly, MSCT may possibly become an important component in the primary diagnostic work-up of patients with suspected CAD. In particular, MSCT would be a valuable evaluation tool in patients either with previous inconclusive exercise test results or unable to exercise. In addition, exercise testing may be less accurate in detecting obstructive CAD in general. Accordingly, depending on the likelihood of the presence of CAD, MSCT coronary angiography could be used in conjunction with exercise testing. Nevertheless, to develop and support such diagnostic algorithms, comparative data on clinical utility of MSCT and exercise testing in large patient populations and including follow-up are highly needed.

Limitations

The observations of the study are based on a relatively small patient population. Moreover, only a limited number of patients also underwent conventional coronary angiography. In this subset of patients, referral bias may have influenced observations. Limitations of MSCT include the fact that the technique is still associated with an elevated X-ray dose, while also the administration of contrast material is required. However, dose reduction is currently a topic of extensive investigation and recent investigations have demonstrated the feasibility of low-dose protocols without loss in image quality.[23,24]

Conclusions

Exercise testing and MSCT are frequently used for the primary evaluation of CAD but provide discrepant information. Moreover, MSCT identified a small but not negligible proportion of patients with extensive obstructive coronary lesions despite a normal exercise test. Future larger studies should demonstrate whether the use of exercise testing in conjunction with MSCT may provide more accurate information for optimal patient management.

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