

Assessing Myocardial Viability in Clinical Practice

Viabilidade Miocárdica na Prática Clínica

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Abstract

Although assessing myocardial viability is a common cardiology practice, many physicians question the results of diagnostic methods. Nuclear medicine plays an important role in viability studies, but the reports require interpretation in a clinical and pathophysiological context. This article was aimed at reviewing the origin and evolution of myocardial viability. Here we present diagnostic methods by emphasizing nuclear medicine and provide a functional explanation of each test type using example images. We also propose how to act in these cases based on clinic examination findings, the percentage of affected myocardium, and coronary lesion topography (proximal or distal).

"Do not declare that the stars are dead just because the sky is cloudy."

Arabic proverb

Introduction

The most common question in the cardiologist's daily routine regarding interventions in patients with a previous history of infarction or left ventricular dysfunction is as follows: Is the myocardium viable or unviable? However, answering this question is not so simple. In addition to a variety of methods of assessing viability, there are several anatomical possibilities for lesions within the same muscle area. Cases referred by the physician for a viability test are usually complex to diagnose. As René Descartes said: "There are no easy methods to solve difficult problems." Thus, this review aimed at explaining the principles of viability, especially those used in nuclear medicine tests.

Theoretical background

The concept of myocardial viability emerged in the early 1980s. Prior to that point, left ventricular dysfunction was considered an "irreversible" process. The term "hibernating myocardium" was created after the perception that some patients had improved ejection fractions after coronary artery bypass graft surgery.¹

Keywords

Myocardial Viability; Myocardial Infarction; Cardiology; Nuclear Medicine.

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An important study at that time was the Coronary Artery Surgery Study (CASS),² which divided 780 three-vessel disease patients with left ventricular dysfunction into two treatment groups: 1) clinical and 2) surgical. The CASS study showed a significant advantage of surgical therapy. The survival rate was 88% for the surgical group versus 65% for the clinical group ($p = 0.009$). The pharmacological treatment used at the time of the CASS included no beta-blockers, statins, and angiotensin-converting-enzyme (ACE) inhibitors; moreover, no mammary grafts were used (only saphenous). Thus, the results cannot be fully extrapolated to the present day, although the concept of left ventricular dysfunction and three-vessel disease are still considered by many as synonymous with surgical therapy.

But why do patients with coronary lesions develop left ventricular dysfunction? Contractility loss is part of what we call "programmed cell survival."² The decreased blood flow decreases oxygenation and the cell increases its anaerobic metabolism to survive. Scarce adenosine triphosphate (ATP)³ (energy) is recruited to maintain vital functions and not contractility. ATP use in the myocyte is divided into 60% for systolic function, 15% for diastolic function, 5% for electrical activity, and 20% for cell membrane integrity.³

The so-called hibernating myocardium ceases contractility but maintains cellular metabolism.⁴ The muscle reduces its contraction as a protective factor to consume minimal energy and prevent cell death. A histological analysis of hibernating myocardium demonstrated non-contractile myocytes with intact membranes and little or no evidence of metabolic apoptosis.⁴ The stunned myocardium is also a mechanism of programmed cell survival, being characterized by contractile dysfunction that follows brief episodes of myocardial ischemia after blood flow has been restored.⁵ Briefly, hibernation is a protective phenomenon that reduces contractility in the setting of a persistently decreased blood flow. On the other hand, stunned myocardium is a consequence of injury in cases in which contractility remains temporarily reduced despite the return of coronary flow.

It is not always simple to differentiate hibernated from fibrotic myocardium through tests. Each method assesses it according to the following principles of viability⁴:

Presence of myocardial blood flow

Myocardial blood flow can be assessed by capturing ^{99m}technetium-2-methoxyisobutyl-isonitrile (^{99m}Tc-MIBI).⁶ MIBI (sestamibi) is a monovalent cation that along with ^{99m}Tc, forms a radiopharmaceutical that lodges in the mitochondria of myocardial cells. The retention of this tracer in intact mitochondria reflects viable myocytes. In cases of decreased cardiac uptake with ^{99m}Tc-MIBI, imaging can be acquired after the administration of nitrate to improve perfusion with

vasodilator stimulation.⁷ ^{99m}Tc -MIBI is not the best method for assessing viability, as viable regions with low blood flow can be misclassified as scars (Figure 1).

Cell membrane integrity

Cell membrane integrity can be assessed using thallium (on single photon emission computed tomography) and rubidium (on positron emission tomography [PET]) scans, which have a physiology similar to potassium ion. Thallium is not a radiopharmaceutical like ^{99m}Tc -MIBI but rather a radioisotope produced in cyclotron. The physical half-life of thallium-201 is 73 hours. The sodium-potassium pump acts on the cell membrane, enabling the assessment of its integrity through these substances, which are analogous to potassium.⁸ Potassium, the main intracellular cation, is absent in scar tissue. As thallium does not bind to organelles within myocytes, it is pushed out of the cell by the same entry mechanism. Thallium excretion from the cell is called redistribution. In this process, normal tissues redistribute thallium faster than ischemic tissues. Therefore, most thallium protocols include only one tracer injection with two image acquisitions, which can consist of rest and redistribution or stress and redistribution.

The following scenarios are possible:

- Changed rest with improved redistribution, leading to necrosis with viability.
- Changed rest without improved redistribution, leading to necrosis without viability.
- Changed stress with improved redistribution, leading to ischemia with viability.
- Changed stress without improved redistribution, leading to necrosis without viability.
- Normal stress, leading to normal test findings (no redistribution image required).

In some cases, an additional 24-hour late imaging test may be performed after a low-dose reinjection. However, this does

not happen with ^{99m}Tc -MIBI, which does not redistribute; therefore, separate injections are required for stress and rest studies at intervals of up to several days between steps.

Figure 2 shows the test performed on a patient admitted to the hospital with a history of infarction and catheterization with an occluded left anterior descending coronary artery but the presence of collaterals. The initial image taken after stress shows significant apical anterior hypoperfusion, while redistribution images show mild reversibility. As the reversibility area was small in the first acquisitions and the patient experienced symptoms and electrocardiographic changes during stress, late redistribution was performed. Normal tissues redistribute thallium faster than ischemic tissues, so perfusion improvement (viability sign) can be seen on images only after 24 hours.

Figure 3 shows a test performed with thallium-201. The top line shows rest images with hypoperfusion at the apex and distal portions of the anterior, septal, and inferior walls. The bottom line shows redistribution images (3 hours post-injection) with improved perfusion - a sign of viability.

Preserved metabolic activity

Metabolic myocyte activity can be measured by PET.⁹ In the viability protocol, the patient is injected with ^{18}F -fluorodeoxyglucose (^{18}F -FDG), a glucose analog labeled with fluorine-18 when associated with a carbohydrate-free diet. In the situation of chronic ischemia of the hibernated myocardium, the oxygen supply is low and the myocardium partly uses the glycolytic (anaerobic) pathway for energy production, which may be inadequate to maintain contractility but sufficient to maintain cellular metabolism. If the patient is taking a ketotic diet (low in sugars), cellular uptake of this tracer will be low. The hibernated myocardium, unlike normal muscle, involves a chronically activated glycolytic pathway and will be able to capture ^{18}F -FDG through its residual glucose metabolism, showing viable areas.

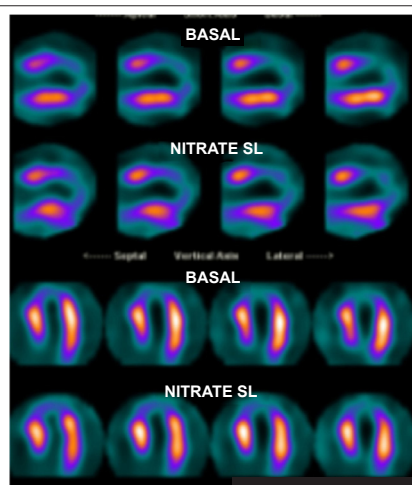


Image courtesy of Cardionuclear.

Figure 1 – Test showing significant necrosis in the territory of the anterior descending coronary artery using ^{99m}Tc -methoxyisobutyl-isonitrite, with no significant improvement in perfusion noted after nitrate administration.

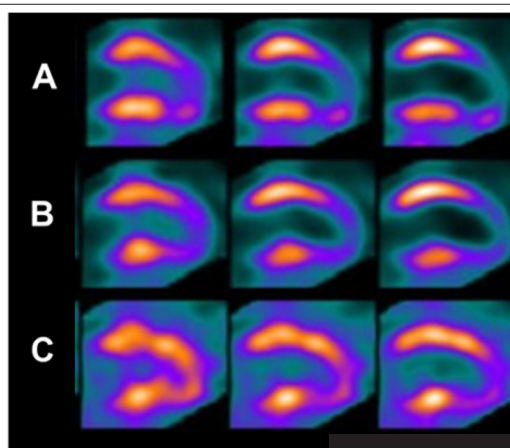


Image courtesy of Cardionuclear.

Figure 2 – Test of an inpatient with a history of infarction and catheterization with an occluded left anterior descending coronary artery and the presence of collaterals. A) Image taken immediately after stress. B) Image taken after 3 hours of redistribution. C) Image taken after 24 hours of redistribution using thallium-201.

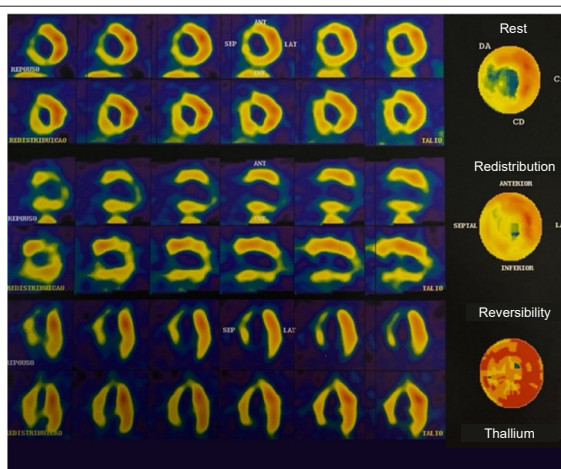


Image courtesy of Cardionuclear.

Figure 3 – Test using thallium-201.

The top line in Figure 4 shows a test with thallium-201 evidencing an area of perfusion defect⁴ in the territory of the anterior descending coronary artery. The bottom line shows a test with ^{18}F -FDG evidencing increased capture⁵ and, therefore, preserved metabolism precisely in areas deficient in thallium-201. These test results are compatible with myocardial viability. Mismatch (viable myocardium) occurs when the perfusion image is changed and metabolism is improved. Match (absent viability) occurs when cases are changed in both studies and, therefore, demonstrate defect pattern agreement (Figure 5).

^{18}F -FDG PET associated with cardiac magnetic resonance imaging (MRI) is considered the best method for detecting myocardial viability since MRI assesses the absence of myocytes using late gadolinium enhancement.¹⁰ Interpretation of the results is based on analysis of the transmural extension of the enhancement in relation to the healthy region. When the

length of the same segment is less than 50%, the myocardium is viable. When the extension of the same segment is greater than 50%, the myocardium is not viable.

Finally, viability can also be analyzed through the “contractile reserve” by dobutamine echocardiography.¹¹ Viable myocardium in this situation will have the following characteristics:

- Abnormal contractility at rest
- Improved contractility at a low dose of dobutamine
- Unchanged contractility at a high dose of dobutamine

A myocardium with ischemia and viability benefits most from revascularization. In such cases, the stress echocardiogram will have the following findings:

- Abnormal contractility at rest
- Improved contractility at a low dose of dobutamine
- Worsened contractility at a high dose of dobutamine

A viability study is not indicated in cases of a myocardium with normal contractility at rest. If there is some degree of kinesis, necrosis does not predominate. Knowledge of the concept of hibernation is essential to prevent an erroneous request for viability test based only on a previous history of infarction or some electrocardiographic changes. Table 1 summarizes the main viability assessment methods.¹²

Considerations about myocardial perfusion

Myocardial perfusion changes are not always segmented and homogeneous. Reports would be less complex if the areas

without viability were exactly in segments irrigated by a single coronary artery. However, areas of necrosis surrounded by areas of ischemia (or even normal myocardium) in the same topography are a common finding on scintigraphy. For example, a patient may have necrosis without viability in the medial and apical anterior segments that totals 12% of the extension. However, other viable areas are irrigated by the anterior descending coronary artery, such as the basal anterior segments and the entire septal wall. The attending physician may consider not revascularizing this artery since the report showed no viability. However, the territory of the anterior descending coronary artery extends beyond the 12% described; thus, this

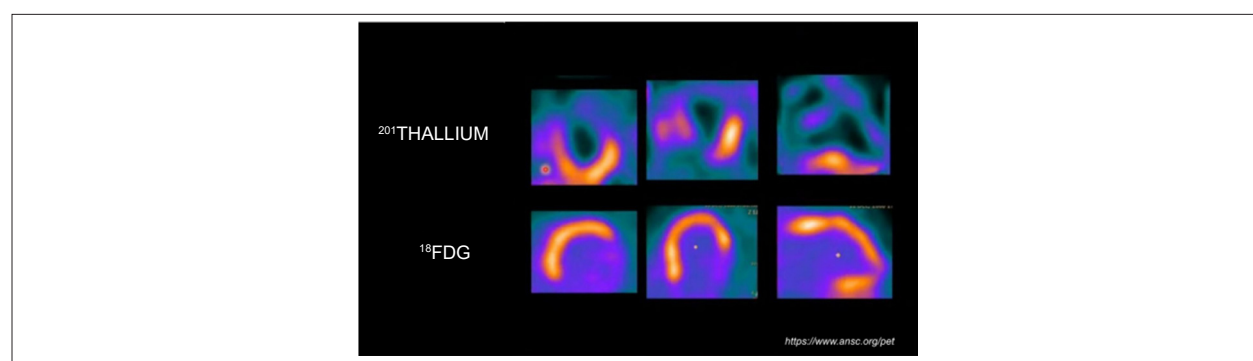


Figure 4 – Image on the top line taken with thallium-201 showing an area of necrosis in the territory of the anterior descending coronary artery.

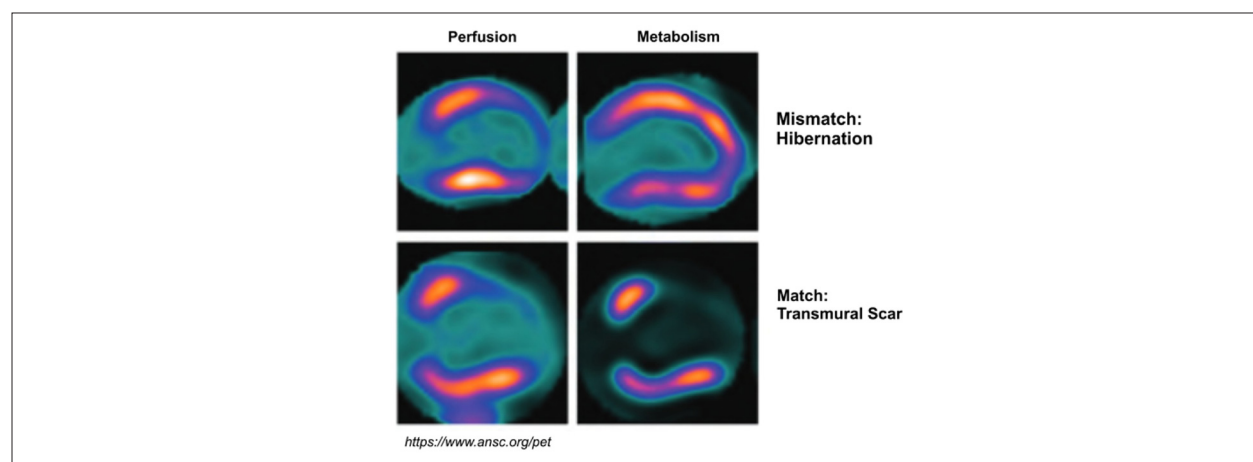


Figure 5 – Image mismatch and match.

Table 1 - Summary of the main viability assessment methods.

Methods	Radiation	Duration	Number of phases	Sensitivity	Specificity
Echocardiography with dobutamine	Absent	30 min	-----	77-89%	68-93%
^{99m} Tc-MIBI SPECT	Moderate	90-120 min	2 injections	81%	69%
Resonance	Absent	35 min	2 injections	92%	51-89%
Thallium-201	Discharge	3 h with additional 24-h IN image	1 injection	87%	54%
¹⁸ F-FDG PET	Moderate	1 h	1 injection	92%	63%

¹⁸F-FDG PET, ¹⁸F-fluorodeoxyglucose positron emission tomography; SPECT, single photon emission computed tomography; ^{99m}Tc-MIBI, ^{99m}technetium-2-methoxyisobutyl-isonitrile, IN, if necessary.

decision could compromise an important part of the muscle. If we consider three territories in the left ventricular myocardium, the percentage of each main coronary artery will be about 33% of the total. Therefore, the 12% proportion without viability in this area does not represent the physiological importance of the left anterior descending coronary artery. If a patient has lesions in the three main coronary arteries, coronary artery bypass graft surgery cannot be avoided due to a non-viable area of 10–15% and viable area of more than 80%. In addition, the Stich study already showed that a lack of viability was associated with no differences between drug therapy and revascularization.¹³ The presence of viability proved to be a good prognostic factor regardless of the approach used.¹⁴

Most methods divide the myocardium into 17 segments, but there are only three main coronary arteries. Therefore, it is necessary to analyze exactly which segments are being irrigated by each of the coronary arteries in each case. Apical necrosis is a very common scintigraphic finding because tissue suffering almost always occurs firstly at the tip of the heart. When a vascular occlusion occurs in the leg, for example, fibrosis starts at the tip of the toes and may extend throughout the foot. The same occurs with the heart, justifying a high prevalence of tissue suffering in the apical region of the left ventricle.

The apical region comprises the apex (segment 17) and the distal portion of all walls (anterior, septal, inferior, and lateral).¹⁵

For example, necrosis may develop if the patient has an infarction involving medial occlusion of the anterior descending coronary artery. If short time is available to open the coronary artery, the fibrotic area is likely to be only at the apex. If the delta T is greater, this fibrosis will extend from the apex to the medial portion of the anterior wall and affect the septum.

A very relevant analysis involves determining whether the coronary lesion(s) is proximal or distal. If the patient has distal lesions and necrosis is present in the periapical segments, the absence of viability is less important even by a method that is not the gold standard, as a smaller tissue area is at risk.

However, if the patient has proximal or left main coronary

lesions, necrosis in the distal portions of the left ventricle should not be decisive for ruling out revascularization. In these cases, a stress test or analysis of clinical and electrocardiographic changes is often more important in the choice of a particular therapy than a viability test alone.

Imaging tests were performed of a patient with a history of inferior wall infarction and three-vessel lesion. The tests were performed after coronary artery bypass graft surgery and showed necrosis sequelae in the apex and lower basal segment (Figure 6).

Figure 7 shows the case of a patient with a history of anterior wall infarction and lesions in the anterior and right descending coronary arteries. A viability test quantified necrosis in 15% of the apical anterior extension (bottom line). The use of a stress test was suggested (top row) as the lesions were proximal. Perfusion worsened in the middle and basal anterior segments beyond the bottom wall. The report indicated necrosis with ischemia and viability in the territory of the anterior descending coronary artery and ischemia in the territory of the right coronary artery.

Figure 8 shows the case of a patient with lesions in the three coronary arteries and an occluded anterior descending coronary artery. A viability test was requested, but a stress test (top row) was suggested to better guide treatment.

Despite the significant area of necrosis at rest, worsening that occurs after stress indicates the presence of viable myocardial peri-necrosis. Ischemia also occurs in the other periapical segments (septal, lateral, and inferior).

Another important change is right ventricular uptake only on post-stress images as a sign of severe ischemia. These findings indicate the need for myocardial revascularization surgery.

Final messages

No imaging method can assess viability with 100% sensitivity and specificity, so if it is clinically justified, the physician should consider revascularization.

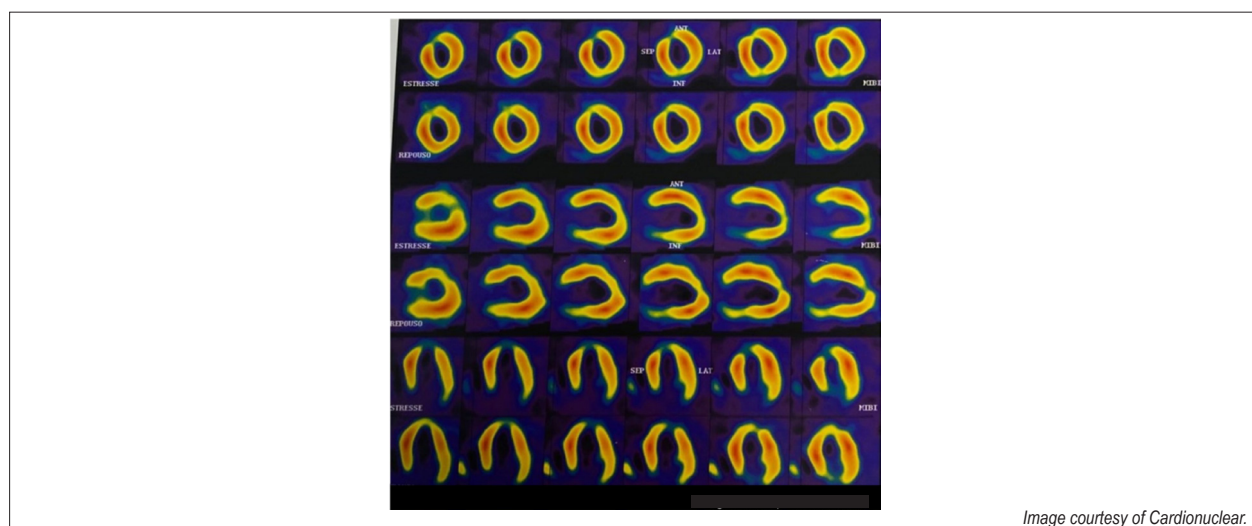


Image courtesy of Cardionuclear.

Figure 6 – Imaging tests of a patient with a history of inferior wall infarction and a three-vessel lesion.

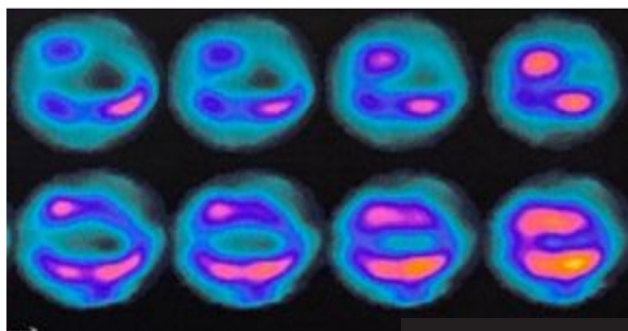


Image courtesy of Cardionuclear.

Figure 7 – Image of a patient with a history of anterior wall infarction and lesions in the anterior and right descending coronary arteries.

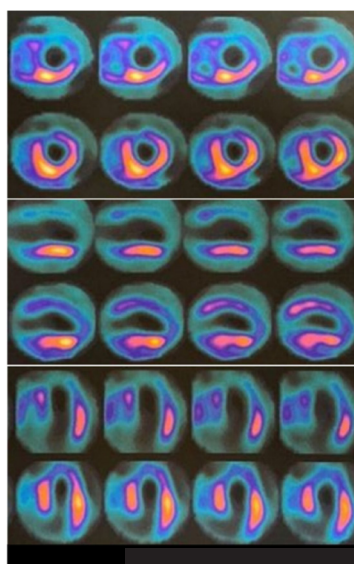


Image courtesy of Cardionuclear.

Figure 8 – Test of a patient with lesions in the three coronary arteries and an occluded anterior descending coronary artery.

The Stich study¹³ showed that the absence of viability was associated with no differences between drug therapy and revascularization. However, an analysis performed 10 years after that study showed that the ejection fraction increase was greater in patients with viability (regardless of treatment approach).¹⁶

The Christmas study also reported that patients with heart failure using carvedilol experienced a greater increase in ejection fraction when viability was present.¹⁷ Therefore, viability can be considered a useful indicator of good prognosis regardless of assessment method.

Areas with less than 30% viability should be analyzed very carefully, as each of the three main coronary territories corresponds to approximately 33% of the left ventricle. Not revascularizing a coronary artery due to a small percentage of fibrosis may compromise other segments also supplied by the same coronary artery.

When the fibrotic area is restricted to the apex and surrounding segments, it is important to analyze whether the coronary lesion(s) are proximal or distal. If they are distal, clinical treatment is indicated. If they are proximal, there is a greater tendency to perform invasive therapy due to the higher percentage of myocardium at risk, a stress test may aid in therapeutic decision.

Author's contributions

Data analysis and interpretation, statistical analysis, manuscript writing, and critical review of the manuscript for important intellectual content: GOMES MB.

Conflict of interest

the author has declared that she has no conflict of interest.

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