Assessment of Myocardial Ischemia with the Integrated Use of Multimodality Imaging

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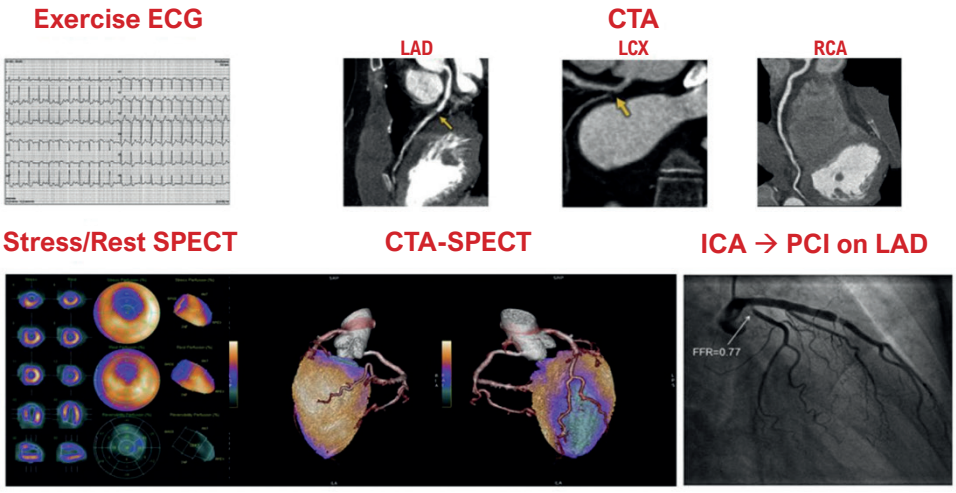
Central Illustration: Assessment of Myocardial Ischemia with the Integrated Use of Multimodality Imaging



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Example of multimodal assessment in the investigation of CAD in a patient with chronic coronary syndrome. CTA: coronary computed tomography angiography; ECG: electrocardiogram; ICA: invasive coronary angiography; LAD: left anterior descending artery; LCX: left circumflex artery; PCI: percutaneous coronary intervention; RCA: right coronary artery; SPECT: single-photon emission computed tomography.

Abstract

Myocardial ischemia, which is characterized by reduced oxygen supply to the myocardium, is a common manifestation of coronary artery disease (CAD), one of the leading causes of morbidity and mortality worldwide. Early and accurate detection of myocardial ischemia is essential for risk stratification, treatment planning, and improved clinical outcomes. In recent years, advances in cardiac imaging modalities have provided a more comprehensive assessment of myocardial ischemia. This article reviews recent advances in the assessment and detection of myocardial ischemia with a focus on the integrated use of multimodality imaging. The article discusses the main techniques available, their advantages and limitations, and their role in current clinical practice, in addition to future perspectives in this area. Cardiac imaging modalities for assessment of myocardial ischemia include exercise electrocardiography, stress echocardiography, single-photon emission computed tomography, positron emission tomography, cardiac magnetic resonance imaging, and coronary computed tomography angiography. When selected imaging tests, it is necessary to consider the pre-test probability (PTP) of CAD and patients' clinical characteristics. Non-invasive functional modalities are preferable for patients with intermediate probability of CAD. The integration of these modalities can improve sensitivity, specificity, and diagnostic accuracy, offering a more complete assessment of the patient's cardiovascular condition and allowing for more personalized therapeutic planning.

In conclusion, the multimodal approach to myocardial ischemia assessment improves early detection, risk stratification, and therapeutic planning. The combination

Keywords

Ischemia; Coronary Artery Disease; Echocardiography

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of several imaging modalities allows a holistic view of the cardiovascular condition, improving diagnostic accuracy and clinical outcomes in patients with suspected or established diagnosis of CAD.

Introduction

Myocardial ischemia, defined as reduced oxygen supply to the myocardium, is a common manifestation of coronary artery disease (CAD). CAD is one of the main causes of morbidity and mortality worldwide, and it can present clinically in different forms, from asymptomatic individuals with stable disease to those with symptomatic angina with different degrees of functional limitation, including unstable myocardial ischemic syndromes and sudden death.

CAD represents a significant challenge for healthcare systems globally. Early and accurate detection of myocardial ischemia plays a fundamental role in risk stratification, treatment planning, and improved clinical outcomes in patients with suspected or established diagnosis of CAD. In recent decades, there have been substantial advances in cardiac imaging modalities, providing a more comprehensive and accurate assessment of myocardial ischemia. The multimodal approach, which integrates these multiple imaging techniques, has emerged as a promising strategy to improve sensitivity, specificity, and diagnostic accuracy in the assessment of myocardial ischemia.

In this article, we review recent advances in the assessment and detection of myocardial ischemia with a focus on the integrated use of multimodality, highlighting the main techniques available, their advantages and limitations, and their role in current clinical practice. Additionally, we discuss emerging perspectives and directions in this area, aiming to further improve the detection and management of myocardial ischemia.

Cardiac imaging modalities in the assessment of myocardial ischemia

The distinctive pathophysiological characteristics of CAD can be assessed by means of various imaging modalities, such as exercise electrocardiography, stress echocardiography, single-photon emission computed tomography, positron emission tomography, cardiac magnetic resonance imaging, and coronary computed tomography angiography. When choosing a specific imaging test, it is necessary to consider the multiple factors that interact in the development of acute coronary syndrome and chronic CAD. The preferred imaging technique to confirm the diagnosis of acute or chronic CAD and guide treatment will depend on the clinical presentation, patient characteristics, local availability, and the clinical center's experience.[1] The objective of this article is to provide guidance on how to select the ideal imaging approach in the investigation of patients with clinical suspicion of CAD.

Pre-test probability (PTP) and selection of imaging tests

European and American guidelines recommend the Duke clinical score and the updated Diamond and Forrester models as preferred clinical tools for calculating the PTP of obstructive CAD in symptomatic patients without previous diagnosis. As the imaging tests used for the diagnosis of CAD have different performance characteristics, it is common to preferentially select tests with high sensitivity in groups with high disease prevalence and tests with high specificity in groups with lower prevalence, in order to reduce false negative and false positive results, respectively.[1]

Diagnostic tests are most useful and recommended when the likelihood of CAD is intermediate. According to the most current American and European guidelines, patients with intermediate PTP of CAD should undergo initial evaluation with non-invasive anatomical or functional diagnostic tests for assessment of CAD. Patients with very low PTP (< 5%) may not require assessment (a positive test would likely be a false positive) and patients with a high PTP (> 85%) may require direct assessment with coronary cineangiography (a negative test would likely be a false negative). In patients with a PTP of 5% to 15%, anatomical or functional tests can also be used in selected cases according to the clinical situation (Figure 1).

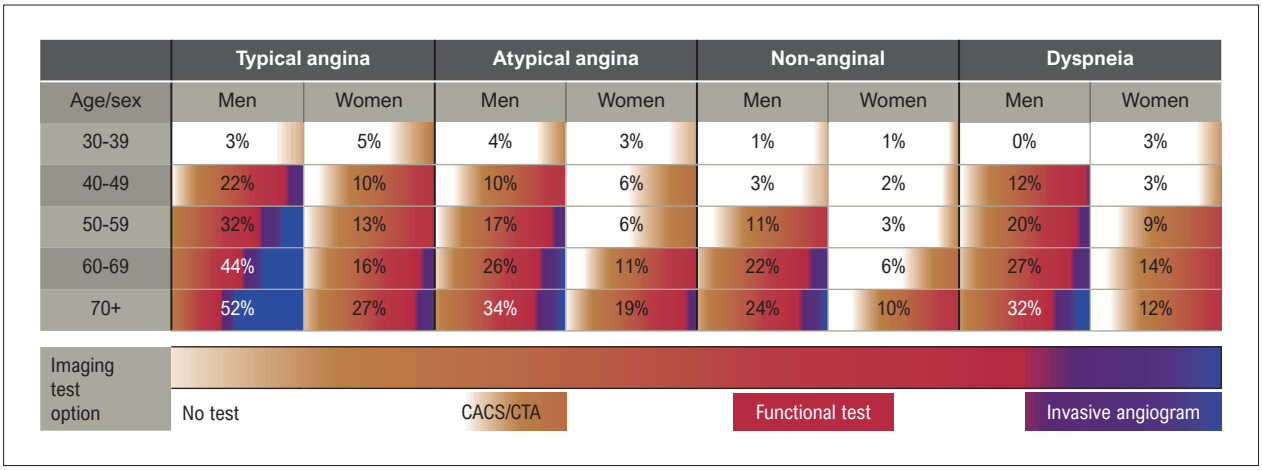

Figure 1 – *PTP of epicardial CAD (modified Diamond and Forrester model) and suggested imaging tests. PTP – very low: 0% to 5%; low 5% to 15%; intermediate: 15% to 85%; high: > 85%. CACS: coronary artery calcium score; CTA: coronary computed tomography angiography.*

Non-invasive functional imaging modalities

Non-invasive functional imaging tests serve not only to diagnose the presence of CAD, but also to guide clinical decision-making, and they are preferable in patients with PTP closer to the intermediate probability threshold. Documentation of ischemia involving more than 10% of the left ventricular myocardium or in a multivessel pattern are findings that define high risk, as reducing ischemia can favorably impact symptoms and clinical outcomes.[2]

Another outline suggested by the American College of Cardiology/American Heart Association for choosing the best CAD investigation method is based on a patient's clinical characteristics and individual risk factors, as shown in Figure 2.

Cardiac imaging modalities

Exercise electrocardiography

Advantages:

- Non-invasive and widely available.
- Lower cost compared to other imaging techniques.
- Possible identification of ischemic changes during exercise.
- Easily combined with other routine exams.

Limitations:

- Limited sensitivity and specificity, especially in patients with multivessel CAD or atypical angina subtypes.
- Depends on the patient's physical capacity to reach the target heart rate.
- Difficulties interpreting results in patients with underlying electrocardiogram abnormalities, such as bundle branch blocks, conduction disturbances, ventricular overload, or pre-excitation syndrome.[3]

Stress echocardiography

Advantages:

- Does not use ionizing radiation.
- Can provide information about myocardial contractile function during stress, valve changes, and changes in the pericardium.
- Can be performed with pharmacological stress or exercise.
- High temporal resolution, allowing dynamic assessment of the cardiac walls.

Limitations:

- Depends on ultrasound quality and operator skill.
- Limited by the patient's acoustic window.
- Lower sensitivity in patients with obesity and/or chronic obstructive pulmonary disease.
- Not capable of analyzing myocardial perfusion.

Myocardial scintigraphy

Advantages:

- High sensitivity in detecting myocardial ischemia.
- Able to assess myocardial perfusion at rest and under stress.
- Power in differentiating reversible from irreversible ischemia.
- Possible quantification of extent and severity of ischemia.

Limitations:

- Exposure to ionizing radiation.
- Depends on radiopharmaceuticals with possible side effects.
- Longer image acquisition time (resting and stress phases).
- Lower spatial resolution compared to other imaging modalities.

Cardiac magnetic resonance imaging

Advantages:

- Method with the highest spatial resolution and tissue contrast.
- Does not use ionizing radiation.
- Able to assess myocardial perfusion, ventricular function, and myocardial viability in a single session.
- Excellent visualization of anatomical structures and soft tissues.

Limitations:

- High cost and limited availability compared to other techniques.
- Depends on patient collaboration due to prolonged examination time and need for immobility.
- Lower sensitivity in detecting coronary obstructions compared to myocardial scintigraphy.
- Possible movement artifacts that could compromise image interpretation.

Coronary tomography angiography

Advantages:

- High sensitivity and specificity for detecting significant CAD.
- High negative predictive value: high power to rule out CAD in patients with low to intermediate PTP.
- Non-invasive test with quick acquisition time.
- Allows assessment of the presence, extent, and characterization of atherosclerotic plaques, including the quantification of coronary calcium.

Clinical Scenario Text	ECG Treadmill	Stress Nuclear MPI	Stress Echo	Stress CMR	CAC	CCTA	Cath	No Test
1. ■ Less-likely anginal symptoms with a noncardiac explanation	R (3)	R (2)	R (2)	R (2)	R (3)	R (1)	R (1)	A (8)
2. ■ Less-likely anginal symptoms, age <50 y and 0 and 1 CV risk factor	M (4)	R (3)	R (3)	R (3)	M (4)	R (3)	R (1)	A (7)
3. ■ Less-likely anginal symptoms, age 50 y or above and/or ≥ 2 CV risk factors	M (6)	M (6)	M (6)	M (5)	M (6)	M (5)	R (2)	M (4)
4. ■ Less-likely anginal symptoms, age <50 y and 0 or 1 CV risk factor	A (7)	A (7)	A (7)	A (7)	M (6)	A (7)	R (3)	R (3)
5. ■ Less-likely anginal symptoms, age 50 y or above and/or ≥2 CV risk factors	A (7)	A (8)	A (8)	A (7)		A (7)	A (7)	R (1)

Figure 2 – *Multimodal assessment for investigation of CAD based on clinical scenarios in symptomatic patients. CV risk factors: diabetes mellitus, smoking, family story of premature CAD, hypertension, dysplidemia. A: appropriate; CAC: coronary artery calcium score; CAD: coronary artery disease; Cath: cardiac catheterization; CCTA: coronary computed tomography angiography; CMR: cardiac magnetic resonance; CV: cardiovascular; ECG: electrocardiogram; echo: echocardiography; M: may be appropriate; MPI: myocardial perfusion imaging; R: rarely appropriate.*

– Widely available in many medical centers and hospitals.
– Although it does not directly evaluate ischemia in its conventional form, it can be performed with joint analysis of fractional flow reserve, providing anatomical and functional information.

Limitations:

– Exposure to ionizing radiation (cumulative effect).
– Requires iodinated contrast, which is a risk for patients with iodine allergy or renal failure.
– The presence of extensive coronary calcifications can limit the resolution of coronary tomography angiography, making it difficult to accurately assess the arterial lumen and determine stenosis severity.
– Lower utility in patients with high probability of CAD: negative result is less likely, and the need for confirmation by invasive angiography remains high.
– The quality of the images can be affected by factors such as elevated heart rate, arrhythmias, or the patient's inability to maintain breathing during the exam
– Relatively high cost.

Quantitative and qualitative analysis of atheromatous plaques

The awareness that certain plaque phenotypes are more closely associated with plaque rupture and myocardial infarction has sparked intense interest in the concept of vulnerable plaque and in the development of new methods to detect plaques with adverse characteristics in patients with stable CAD. Initial efforts were based on invasive imaging strategies, predominantly using intravascular ultrasound and optical coherence tomography, and more recently non-invasive imaging, through the enhancement of coronary tomography angiography. Using these methods, the total coronary atherosclerotic burden can be quantified, as well as the types of plaques (calcified or non-calcified, fibrous plaque, fibrofatty plaque, and low-attenuation plaque with necrotic core). These quantitative measures of plaque burden appear robust, with low interobserver variability and good reproducibility across scans with intravascular ultrasound assessment.[4]

Quantification of low-attenuation plaque, in particular, shows promise as a marker of adverse plaque burden and as a prognostic indicator. The concepts of vulnerable plaque and adverse or vulnerable plaque burden appear to be a continuous variable of worse prognosis throughout the coronary vasculature. A recent study demonstrated that low-attenuation plaque burden was the strongest predictor of adverse outcome in patients with stable chest pain. Patients with low-attenuation plaque burden greater than 4% were 5 times more likely to suffer a fatal or nonfatal infarction. This association occurred regardless of cardiovascular risk scores, Agatston coronary calcium score, or the presence of obstructive CAD.[5]

Integration of CAD assessment modalities

Initial screening

Initial assessment can begin with simpler, more widely available, and lower-cost tests, such as exercise electrocardiography, provided that it is appropriate for the patient. This allows for initial screening of patients with suspected myocardial ischemia and intermediate PTP. Patients with baseline electrocardiograms that are uninterpretable during exercise, inconclusive results, or significant risk factors may be referred for further evaluation using a different test modality.[2]

Anatomical-functional and myocardial perfusion assessment

Stress echocardiography can be performed to assess myocardial contractile function during stress induced by exercise or pharmacological agents, compared to function at rest. This provides valuable information regarding the presence and extent of myocardial ischemia. Cardiac magnetic

resonance imaging can also be used to assess ventricular function, myocardial perfusion, and tissue viability in a single session. Its high spatial resolution and tissue contrast provide a detailed assessment of cardiac anatomy and function.

Myocardial scintigraphy is a nuclear technique that allows for assessment of myocardial perfusion at rest and under stress, identifying areas of reversible and irreversible ischemia. Combining myocardial scintigraphy with other modalities, such as stress echocardiography or cardiac magnetic resonance imaging, can provide a more comprehensive assessment of myocardial perfusion and cardiac function. All of these methods can be used together, respecting their characteristics and particularities, in a complementary manner, for investigation of CAD in a patient, as exemplified in the Central Illustration.

Assessment of myocardial viability

Cardiac magnetic resonance imaging is particularly useful in the assessment of myocardial viability, making it possible to differentiate between viable and non-viable tissue after an acute ischemic event. The combination of cardiac magnetic resonance imaging with other ischemia assessment modalities may assist in the identification of patients who will potentially benefit from myocardial revascularization.

Benefits of integrating different imaging methods

The combination of multiple imaging modalities can increase the sensitivity and specificity in detecting myocardial ischemia, improving diagnostic accuracy.

The integration of techniques allows for a more comprehensive assessment of cardiac anatomy, function, and perfusion, providing a holistic view of the patient's cardiovascular condition.

Combined information obtained from different imaging modalities can assist with more accurate risk stratification, identifying patients with a higher likelihood of adverse cardiovascular events (Figure 3).

The integration of multiple assessment modalities allows for more personalized therapeutic planning, adapted to each patient's individual needs.

Conclusion

The integration of multiple modalities for myocardial ischemia assessment into the clinical investigation of patients represents a promising approach to enhancing early detection, risk stratification, and therapeutic planning. By combining and complementing information from different imaging techniques, physicians can obtain a more complete picture of patients' cardiovascular conditions, providing a solid foundation for informed clinical decision-making and optimization of clinical outcomes.

Assessment of myocardial ischemia plays a crucial role in the management of patients with CAD. The integrated use of multimodality imaging offers a comprehensive and accurate approach to the detection and characterization of myocardial ischemia, allowing for more refined risk stratification, early diagnosis, and optimization of therapeutic management. Although each imaging

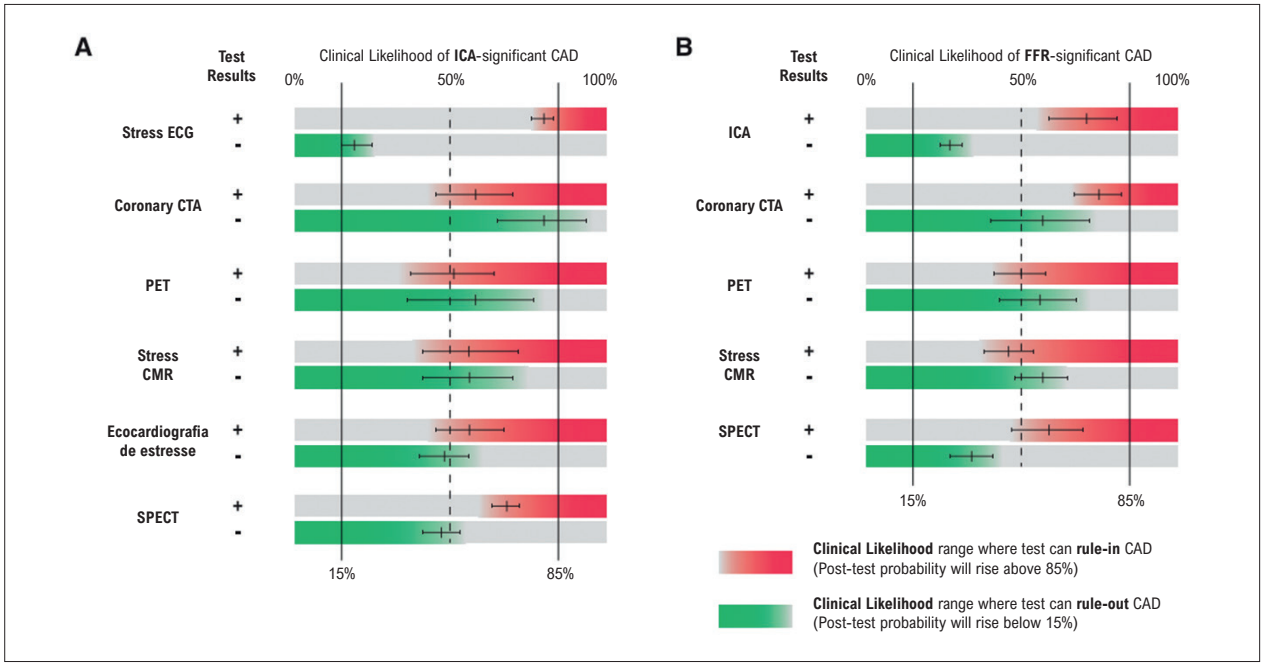

Figure 3 – *Ranges of clinical likelihood of CAD in which a determined test can rule-in (red) or rule-out (green) obstructive CAD. (A) The reference standard is anatomical assessment by means of ICA. (B) The reference standard is functional assessment using FFR. CAD: coronary artery disease; CMR: cardiac magnetic resonance; CTA: computed tomography angiography; ECG: electrocardiogram; FFR: fractional flow reserve; ICA: invasive coronary angiography; PET: positron emission tomography; SPECT: single-photon emission computed tomography.*[6]

technique has its specific advantages and limitations, the combination and complementarity between them can significantly improve diagnostic accuracy and clinical outcomes in patients with suspected or established diagnosis of CAD. The integration of biomarkers, the use of new technologies, and the development of new imaging modalities are expected to promote advances in the assessment of myocardial ischemia, thus improving the quality of cardiovascular care worldwide.

Author Contributions

Conception and design of the research, writing of the manuscript and critical revision of the manuscript for intellectual content: Leite TNP, Gowdak LHW.

Potential Conflict of Interest

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This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Edvardsen T, Asch FM, Davidson B, Delgado V, Maria A, Dilsizian V, et al. Non-invasive Imaging in Coronary Syndromes: Recommendations of the European Association of Cardiovascular Imaging and the American Society of Echocardiography, in Collaboration with the American Society of Nuclear Cardiology, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. Eur Heart J Cardiovasc Imaging. 2022;23(2):e6-e33. doi: 10.1093/ehjci/jeab244.
2. Winchester DE, Maron DJ, Blankstein R, Chang IC, Kirtane AJ, Kwong RY, et al. ACC/AHA/ASE/ASNC/ASPC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2023 Multimodality Appropriate Use Criteria for the Detection and Risk Assessment of Chronic Coronary Disease. J Cardiovasc Magn Reson. 2023;25(1):58. doi: 10.1186/s12968-023-00958-5.
3. Lopez DM, Divakaran S, Gupta A, Bajaj NS, Osborne MT, Zhou W, et al. Role of Exercise Treadmill Testing in the Assessment of Coronary Microvascular Disease. JACC Cardiovasc Imaging. 2022;15(2):312-21. doi: 10.1016/j.jcmg.2021.07.013.
4. Kwiecinski J, Tzolos E, Williams MC, Dey D, Berman D, Slomka P, et al. Noninvasive Coronary Atherosclerotic Plaque Imaging. JACC Cardiovasc Imaging. 2023;16(12):1608-22. doi: 10.1016/j.jcmg.2023.08.021.
5. Williams MC, Kwiecinski J, Doris M, McElhinney P, D'Souza MS, Cadet S, et al. Low-Attenuation Noncalcified Plaque on Coronary Computed Tomography Angiography Predicts Myocardial Infarction: Results from the Multicenter SCOT-HEART Trial (Scottish Computed Tomography of the HEART). Circulation. 2020;141(18):1452-62. doi: 10.1161/CIRCULATIONAHA.119.044720.
6. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes. Eur Heart J. 2020;41(3):407-77. doi: 10.1093/eurheartj/ehz425.