Artigo

Myocardial perfusion scintigraphy for the evaluation of atypical chest pain - likely non-cardiac - in type 2 diabetic individuals with systemic hypertension

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Abstract. Myocardial perfusion scintigraphy (MPS) is an essential diagnostic tool for evaluating coronary artery disease (CAD), particularly in high-risk populations such as hypertensive type 2 diabetic (T2DM) patients**.** Despite its clinical relevance, there remains a significant gap in understanding its optimal application and diagnostic accuracy in this subgroup, warranting further research to refine risk stratification and improve patient outcomes. This study aimed to assess the prevalence of myocardial ischemic abnormalities in hypertensive T2DM patients presenting with atypical chest pain and either a normal resting electrocardiogram (ECG) or ventricular repolarization disturbances, through MPS. A total of 165 participants, comprising 50 men (30.3%) and 115 women (69.7%), with a mean age of 65.6 ± 6 years, underwent MPS using a 2-day protocol. The results revealed that 63.0% of patients exhibited normal perfusion scans, while 37.0% demonstrated findings consistent with myocardial ischemia. Additionally, a subset of the cohort underwent exercise stress testing (90.9%), which yielded positive results for ischemia in 33.3% of cases. The agreement between MPS and exercise ECG was analyzed, revealing a moderate correlation (Kappa = 0.52; $P < 0.001$). In patients with T2DM and systemic arterial hypertension presenting with atypical chest pain, MPS revealed ischemic changes suggestive of the presence of CAD, thereby assisting in the screening process for the indication of more invasive diagnostic procedures.

Keywords: myocardial perfusion scintigraphy, type 2 diabetes mellitus, hypertension, myocardial ischemia, atypical angina.

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Cintilografia de perfusão miocárdica para avaliação de dor torácica atípica - provavelmente não cardíaca - em indivíduos diabéticos tipo 2 com hipertensão sistêmica

Resumo. A cintilografia de perfusão miocárdica (CPM) é uma ferramenta diagnóstica essencial para a avaliação da doença arterial coronariana (DAC), especialmente em populações de alto risco, como pacientes com diabetes mellitus tipo 2 (DMT2) e hipertensão arterial. Apesar de sua relevância clínica, persiste uma lacuna significativa no entendimento de sua aplicação ideal e acurácia diagnóstica nesse subgrupo, o que justifica a realização de pesquisas adicionais para aprimorar a estratifi-

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cação de risco e melhorar os desfechos clínicos. Este estudo teve como objetivo avaliar a prevalência de anormalidades isquêmicas miocárdicas, por meio da CPM, em pacientes hipertensos com DMT2, que apresentavam dor torácica atípica e eletrocardiograma (ECG) de repouso normal ou com distúrbios de repolarização ventricular. Um total de 165 participantes, sendo 50 homens (30,3%) e 115 mulheres (69,7%), com média de idade de 65,6 ± 6 anos, foi submetido à CPM utilizando protocolo de dois dias. Os resultados revelaram que 63,0% dos pacientes apresentaram cintilografias com perfusão normal, enquanto 37,0% demonstraram achados compatíveis com isquemia miocárdica. Adicionalmente, um subgrupo da coorte foi submetido ao teste ergométrico (90,9%), que indicou resultados positivos para isquemia em 33,3% dos casos. A concordância entre a CPM e o ECG de esforço foi analisada, revelando correlação moderada (Kappa = 0,52; P < 0,001). Em pacientes com DMT2 e hipertensão arterial sistêmica que apresentam dor torácica atípica, a CPM evidenciou alterações isquêmicas sugestivas de DAC, auxiliando no rastreamento para a indicação de exames diagnósticos mais invasivos.

Palavras-chave: cintilografia de perfusão miocárdica, diabetes mellitus tipo 2, hipertensão, isquemia miocárdica, angina atípica.

1. Introduction

Atypical chest pain is a frequent manifestation, yet diagnostically challenging, particularly in high-risk patients such as hypertensive individuals with type 2 diabetes mellitus (T2DM). Unlike typical angina, which follows predictable patterns, atypical chest pain often lacks clear characteristics, making it difficult to differentiate between cardiac and non-cardiac causes[1]. This diagnostic ambiguity is exacerbated in diabetic patients, who frequently experience silent ischemia due to autonomic neuropathy, leading to delayed diagnosis and increased cardiovascular morbidity and mortality[2]. The presence of systemic arterial hypertension (SAH) further complicates the clinical scenario, as it accelerates atherosclerosis and increases myocardial oxygen demand, predisposing these patients to ischemic events[3].

Coronary artery disease (CAD) is a leading cause of death in T2DM patients, with SAH serving as a significant comorbid factor that amplifies cardiovascular risk[4]. Studies have shown that the prevalence of CAD in diabetic patients is two to four times higher than in the general population, highlighting the need for accurate diagnostic tools to detect ischemia early[5]. Myocardial perfusion scintigraphy (MPS) has emerged as a powerful non-invasive imaging technique, offering high sensitivity and specificity for identifying myocardial ischemia, even in patients with atypical symptoms or inconclusive electrocardiographic findings[6].

The pathophysiology of CAD in diabetic patients is distinct, characterized by diffuse atherosclerosis, endothelial dysfunction, and microvascular disease, which often result in atypical presentations of ischemia[7]. Hypertensive diabetic patients are particularly vulnerable to these changes, as chronic SAH promotes vascular remodeling and increases myocardial workload, further complicating the clinical picture. Traditional diagnostic methods, such as stress electrocardiography (ECG), may fail to detect ischemia in this population due to the high prevalence of silent ischemia and baseline ECG abnormalities, such as repolarization disturbances[8]. It is important to consider that ischemic non-obstructive coronary artery disease is frequently observed in patients with SAH and T2DM, manifested by typical or atypical angina and even ischemic alterations in MPS.

Since the most important exams for diagnosing obstructive CAD are coronary CT angiography, which involves contrast infusion, and invasive coronary angiography, it is essential to use non-invasive methods such as MPS or exercise stress test for better patient screening and selection prior to these procedures.

Despite its clinical utility, the application of MPS in hypertensive T2DM patients with atypical chest pain remains underutilized. This gap is partly due to limited awareness of its diagnostic benefits, concerns about radiation exposure, and the lack of standardized protocols for this specific patient population[9]. Furthermore, there is a paucity of large-scale studies evaluating the prevalence of ischemic abnormalities in hypertensive T2DM patients with atypical chest pain and normal resting ECG or repolarization disturbances. This represents a critical knowledge gap, as early detection of ischemia in this high-risk group could significantly improve outcomes through timely intervention[10].

Recent advancements in imaging technology, such as hybrid single-photon emission computed tomography (SPECT/CT) systems, have enhanced the diagnostic accuracy of MPS by integrating anatomical and functional data, providing a more comprehensive assessment of myocardial perfusion[11]. Additionally, the prognostic value of MPS in diabetic patients has been well documented, with studies demonstrating its ability to identify high-risk individuals who may benefit from revascularization or intensified medical therapy.[12]

This study aimed to assess the prevalence of myocardial ischemic abnormalities in hypertensive T2DM patients presenting with atypical chest pain and either normal resting ECG or ventricular repolarization disturbances, through MPS.

2. Methods

According to the guidelines of the Brazilian Diabetes Society and the Brazilian Hypertension Society, the diagnosis of type 2 diabetes mellitus (T2DM) is primarily based

on glycemic criteria, including fasting plasma glucose, HbA1c, and the oral glucose tolerance test, with particular emphasis on early detection in high-risk individuals. Systemic arterial hypertension (SAH) is diagnosed through consistent blood pressure measurements above 140/90 mmHg in clinical settings, supported by additional methods such as ambulatory blood pressure monitoring or home blood pressure monitoring to confirm the diagnosis and guide management. Both guidelines stress the importance of integrating clinical history, physical examination, and complementary tests to identify metabolic and cardiovascular comorbidities commonly associated with these conditions.

- The study included 165 patients with T2DM who underwent myocardial perfusion scintigraphy (MPS) at rest and under stress, induced either by treadmill exercise testing or pharmacological stress for those unable to perform physical exercise. To be eligible, patients had to present with atypical chest pain, a normal resting electrocardiogram (ECG), or ventricular repolarization abnormalities, along with SAH and age over 40 years.
- Myocardial perfusion imaging was performed using single-photon emission computed tomography/computed tomography (SPECT/CT) with technetium-99m sestamibi (99mTc-MIBI) as the radiotracer. The tracer was administered intravenously at a dose adjusted to the patient's body weight, both at rest and during stress. Stress was induced either by treadmill exercise testing or by pharmacological agents (dipyridamole) for patients with physical limitations or contraindications to exercise. Imaging was conducted using a VARICAM gamma camera (Elscint®) equipped with two detectors in an L-mode configuration (90 degrees). Images were acquired 45 min after radiotracer administration, using standardized parameters: 140 keV photopeak, 20% energy window, 64 x 64 matrix, low-energy high-resolution parallel collimators, and a 180° rotation with 64 steps. Gated SPECT, synchronized with ECG, was employed during stress imaging for selected patients, with an R-R acceptance window of 20%.
- For image processing, an XPERT workstation (APEX 5.0 software, Elscint®) was utilized, complemented by Quantitative Gated SPECT (QGS) software for gated studies. Images were analyzed in paired stress-rest views across short-axis, vertical long-axis, and horizontal long-axis orientations. Additional three-dimensional end-systolic and end-diastolic images, along with polar maps (Bull's Eye), were generated to enhance diagnostic accuracy. A two-day protocol was followed, with rest imaging performed first, followed by stress imaging, maintaining consistent acquisition parameters throughout.
- Qualitative and quantitative criteria were applied to interpret the scintigraphic findings. Normal myocardium exhibited uniform radiotracer uptake in both stress and rest/redistribution phases, while ischemic myocardium demonstrated reduced uptake during stress with normalization at rest. Fibrotic tissue showed persistently reduced uptake in both phases, whereas viable ischemic tissue displayed partial improvement during redistribution. Quantitative analysis utilized polar maps to quantify perfusion defects based on pixel counts and standard deviations from normal perfusion areas, providing supplementary data to support visual interpretation.
- Exercise treadmill testing (ETT) was conducted using the ramp protocol[13], with modifications for patients unable to achieve maximal effort due to physical or clinical limitations. Test positivity was defined by specific ECG criteria, including ST-segment depression ≥ 2.0 mm, ST depression > 1.0 mm in the first stage, multi-lead ST changes, persistent ST abnormalities for over 5 min during recovery, maximal workload < 4 METs, abnormal blood pressure response, or ventricular arrhythmias. Pharmacological stress with dipyridamole (0.5 mg/kg intravenously over 4 min) was employed for patients with orthopedic, neurological, or vascular limitations.
- Statistical analyses were performed using PSPP software, with results expressed as mean ± standard deviation and relative frequency. The Chi-square test was used for proportion comparisons, and the Mann-Whitney test for mean comparisons. The Kappa index assessed agreement between MPS and exercise ECG results. A 95% confidence interval was applied, with statistical significance set at $p < 0.05$.
- Ø The study protocol was approved by the Ethics Committee of Santa Casa de Itabuna, Bahia.

3. Results

The study included 165 patients, comprising 50 men (30.3%) and 115 women (69.7%), with ages ranging from 40 to 75 years and a mean age of 65.6 ± 6.0 years. Men were significantly older than women (67.6 ± 10.0 years vs. 63.2 ± 8.1 years; P = 0.031) (Table 1).

Tabela 1 - Demographic date.

Characteristics	Women	Men	Total
Gender	115 (69.7%)	50 (30.3%)	165
Average age (years)	63.2 ± 8.1	67.6 ± 10.0	65.6 ± 6.0
Obesity	26	10	36
Dyslipidemia	50	30	80
Tobacco use	8	6	14
Chronic kidney disease	-	-	-

Of the total cohort, 150 patients (90.9%) underwent exercise stress testing, while pharmacological stress with dipyridamole was used in 15 patients (9.1%). Among those who performed the exercise treadmill test (ETT), 55 patients (33.3%) had negative results, whereas 55 (33.3%) tested positive for myocardial ischemia. Of the 61 individuals who presented with ischemia, 18 (29.5%) exhibited transient ischemia, whereas 43 (70.5%) showed persistent ischemia, with diaphragmatic wall ischemia being the most frequently observed type in the study.Myocardial perfusion scintigraphy (MPS) was performed in all patients, revealing normal perfusion in 104 cases (63.0%) (Figure 1), and ischemia in 61 (37.0%) (Figure 2).

Among the 15 patients who underwent pharmacological stress testing, 4.8% showed evidence of ischemia (Table 2).

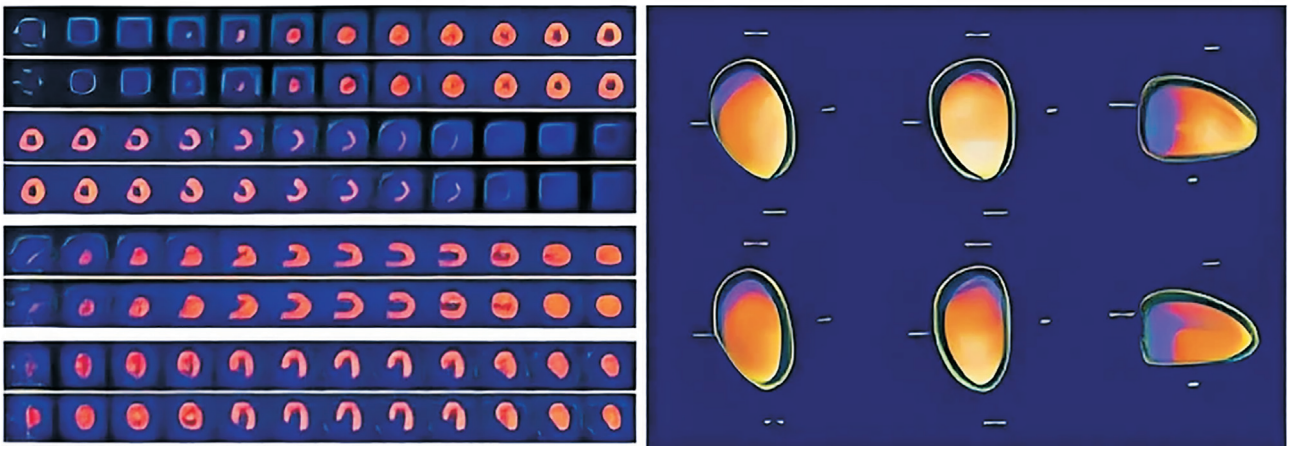
Notably, 15.7% of patients with normal exercise ECG results demonstrated ischemia on MPS, highlighting the superior sensitivity of scintigraphy in detecting myocardial ischemia. Of the 50 patients with positive exercise tests, 32 had concordant positive MPS findings, while 18 showed normal perfusion on scintigraphy.

Tabela 2 - Association among MPS, ETT and Pharmacological stress.

	MPS	ETT	Pharmacological stress
Normal	104 (63.0%)	55 (33.3%)	7 (4.2%)
Ischemia	61 (37.0%)	55 (33.3%)	8 (4.8%)
Total	165	110	15

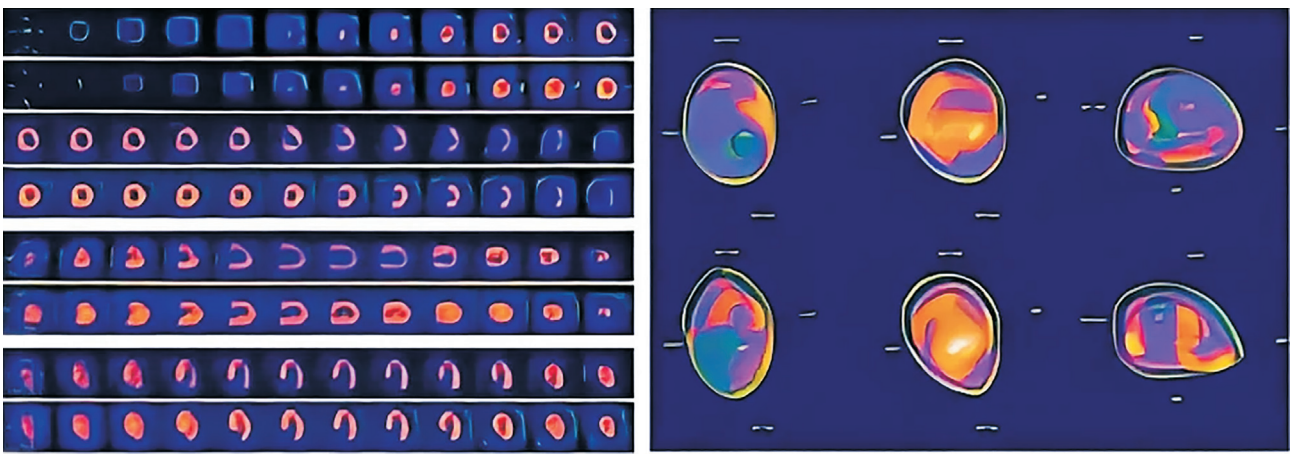
The agreement between MPS and ETT was assessed using the Kappa index, which revealed a moderate correlation between the two tests (Kappa = 0.52, P = 0.0001). No statistically significant differences were observed in the proportion of abnormal MPS findings between men and women (43.5% vs. 35.2%, P = 0.53). Similarly, the prevalence of abnormal ETT results did not differ significantly by gender (37.7% in men vs. 29.2% in women, P = 0.52).

Figura 1 - Normal myocardial perfusion scintigraphy.



Source: Study result.

Figura 2 - Anormal myocardial perfusion scintigraphy.



Source: Study result.

4. Discussion

In this study, we investigated the diagnostic utility of MPS in patients with concomitant T2DM and SAH who presented with atypical chest pain, normal baseline ECG, or nonspecific ventricular repolarization abnormalities. Our findings highlight the significant value of MPS in identifying ischemic changes that may otherwise go undetected in this high-risk population, particularly when resting ECG results are inconclusive. By accurately detecting inducible myocardial ischemia, MPS emerges as a reliable and clinically relevant tool for risk stratification and further diagnostic workup. These results underscore the importance of incorporating MPS into the early evaluation of T2DM and SAH patients with atypical angina, guiding appropriate selection for subsequent invasive coronary angiography. Thus, this approach may improve diagnostic accuracy and clinical outcomes by enabling timely intervention in those most likely to benefit.

Ischemia with no obstructive coronary arteries (INOCA) presents a complex clinical challenge, characterized by angina and objective evidence of myocardial ischemia despite the absence of significant coronary artery stenosis[14]. The underlying mechanisms are multifactorial, with coronary microvascular dysfunction and epicardial coronary vasospasm predominating, often leading to recurrent symptoms and a heightened risk for adverse cardiovascular outcomes, including heart failure with preserved ejection fraction and major adverse cardiovascular events[15]. Diagnostic evaluation relies on advanced invasive and non-invasive modalities to assess coronary flow reserve, microvascular resistance, and vasoreactivity, as conventional angiography frequently fails to reveal the microvascular or functional abnormalities responsible for ischemia. The recognition of INOCA is fundamental, as tailored, mechanism-specific management strategies can improve prognosis and quality of life, yet the condition remains underdiagnosed and undertreated in routine practice[16].

Individuals with T2DM experience higher rates of mortality and complications linked to myocardial infarction when compared to those without diabetes[17]. The occurrence of silent myocardial ischemia is notably more common among diabetic patients than in the broader population. Consequently, diabetic individuals with myocardial ischemia often lack the hallmark symptom of typical chest pain, resulting in delays in diagnosis and treatment[18]. This atypical clinical manifestation plays a significant role in the increased morbidity and mortality rates seen in this patient group.

CAD continues to be a leading contributor to morbidity and death among individuals with DM. Beyond the elevated risk of mortality inherently associated with diabetes, the presence of cardiovascular disease manifestations exacerbates this risk, doubling the mortality rate. This combination results in an estimated decline in life expectancy of roughly 12 years. Genetic factors also play a significant role as a risk indicator in the link between T2DM and CAD[19]. Comprehensive global epidemiological research, particularly the landmark Framingham study, has demonstrated that the prevalence of CAD is significantly elevated in individuals with diabetes. Specifically, diabetic men exhibit a twofold increase in CAD incidence, while diabetic women experience a threefold rise compared to their non-diabetic counterparts in the general population[20]. These results underscore the heightened cardiovascular risk associated with diabetes across genders.

Chest pain poses a considerable diagnostic challenge within emergency care settings, necessitating a thorough and meticulous clinical evaluation. The distinctions between “atypical” and “typical” chest pain are often inadequate, as they may fail to account for clinical scenarios unrelated to ischemic events. An innovative framework, which classifies underlying causes into cardiac, potentially cardiac, and likely non-cardiac origins, provides a more holistic and collaborative approach to developing a symptom-driven diagnostic algorithm[21]. Our investigation encompassed hypertensive diabetic patients presenting with atypical chest pain, likely attributable to non-cardiac etiologies.

In diabetic patients, CAD frequently presents without noticeable symptoms, largely due to the presence of autonomic neuropathy. Additionally, a standard twelve-lead resting ECG may appear normal even when CAD has progressed to advanced stages. Consequently, a normal ECG reading, particularly in individuals with T2DM, does not eliminate the possibility of significant CAD. However, it may still reveal subtle indicators of the condition, such as evidence of a prior myocardial infarction or abnormalities in ventricular repolarization[22,23]. In our investigation, the patient cohort not only included individuals with diabetes and SAH but also those reporting atypical chest pain. This group encompassed patients with both normal ECG and those displaying ventricular repolarization abnormalities, all of whom showed no signs of myocardial ischemia. These findings highlight the complexity of diagnosing CAD in T2DM populations, even in the absence of clear ischemic indicators.

A highly reliable and well-established method for evaluating CAD is the exercise stress test, which boasts high specificity and is endorsed by international clinical guidelines[24]. This diagnostic tool is particularly valuable for diabetic patients experiencing atypical chest pain, as well as for those with non-cardiac pain but presenting coronary risk factors.[25] However, it is important to note that a positive result on an exercise stress test may carry a higher likelihood of being a false positive, especially in women, due to the increased prevalence of vasospastic effects in this demographic compared to men[26,27]. Additionally, a normal exercise stress test result in diabetic individuals does not entirely rule out the possibility of underlying myocardial ischemia, emphasizing the need for a comprehensive diagnostic approach in this high-risk population[28]. In our study, ETT was performed on 90.8% of the participants, with 33.3% of these individuals yielding positive results indicative of myocardial ischemia. This highlights the utility of stress testing as a diagnostic tool in identifying ischemic conditions within the studied population.

MPS is a well-established and frequently used non-invasive imaging modality for evaluating CAD, providing both diagnostic and prognostic information. The technique involves the administration of radiopharmaceuticals to assess myocardial blood flow under both stress and rest conditions. This allows for the identification of myocardial ischemia and infarction with high sensitivity and specificity[29]. Contemporary clinical practice often incorporates hybrid imaging, combining SPECT with coronary computed tomography angiography. This integrated approach, merging functional perfusion data with anatomical coronary vessel information, leads to improved diagnostic performance[30]. Beyond qualitative assessment, quantitative perfusion analysis, including the calculation of myocardial flow reserve, offers additional prognostic value, particularly in complex CAD presentations such as multivessel disease[31] are available, MPS remains a clinically relevant tool, supported by substantial evidence from large-scale clinical trials[32]. It continues to be an important component in the diagnosis and risk stratification of patients with suspected or known CAD. Our research investigated hypertensive patients with T2DM presenting with atypical chest pain. We employed SPECT/CT with 99mTc-MIBI as the radiotracer to evaluate myocardial ischemia, given its established high sensitivity and specificity in diagnosing CAD.

The integration of ETT with MPS represents a highly effective approach for diagnosing myocardial ischemia. Conducting ETT immediately prior to MPS ensures the preservation of physiological stress parameters, such as heart rate, blood pressure, and symptom manifestation, in addition to diagnosing myocardial ischemia, thereby optimizing the alignment between functional and imaging data[33]. ETT delivers essential insights into exercise capacity and hemodynamic performance, whereas MPS detects perfusion abnormalities with greater diagnostic accuracy, especially in individuals with intermediate clinical risk or indeterminate ETT outcomes[34]. In our study, the agreement between MPS and ETT was assessed using the Kappa index, which demonstrated a moderate correlation between the two methods.

Pharmacological stress MPS identifies alterations in coronary flow resulting from arterial obstruction without the necessity of inducing ischemia through physical exertion[35]. This approach employs pharmacological agents such as vasodilators (e.g., dipyridamole or adenosine) or inotropic agents like dobutamine. The diagnostic rationale for vasodilator use lies in the disparity in blood flow between regions supplied by healthy coronary arteries and those affected by stenosis, making it highly compatible with scintigraphy, which relies on the visualization of flow distribution patterns[36]. To ensure test efficacy, it is critical to achieve at least a 10% increase in baseline heart rate during pharmacological stress, as this enhances the detection of flow discrepancies[37]. In our investigation, MPS was conducted using pharmacological stress with dipyridamole as the inducing agent. This approach was selected because certain physical limitations, such as joint-related issues or exercise intolerance, rendered traditional exercise stress testing impractical or unreliable. Among the fifteen patients who underwent pharmacological stress, eight exhibited positive findings, indicating detectable perfusion abnormalities consistent with ischemic pathology.

A principal limitation of this study lies in the absence of anatomical correlation for patients exhibiting ischemic abnormalities on MPS, as coronary angiography was not systematically performed to confirm or characterize the presence, extent, or severity of coronary artery disease. This omission precludes definitive assessment of whether perfusion defects detected by MPS truly reflect obstructive coronary lesions or are attributable to microvascular dysfunction, balanced ischemia, or other non-atherosclerotic etiologies, particularly relevant in populations with diabetes and hypertension[38]. Consequently, the diagnostic accuracy and specificity of MPS findings remain uncertain, and the potential for both false-positive and false-negative results cannot be excluded without anatomical validation[39]. This limitation underscores the need for integrative diagnostic strategies that combine functional imaging with anatomical assessment to optimize risk stratification and clinical decision-making in this high-risk cohort.

In patients with T2DM and SAH presenting with atypical chest pain of likely non-cardiac origin, the strategic incorporation of MPS significantly enhances diagnostic accuracy compared to relying solely on clinical evaluation. MPS, with its ability to identify subtle alterations in myocardial blood flow, uncovers occult ischemic processes, enabling timely interventions and potentially improving long-term cardiovascular outcomes in this high-risk population. This study underscores the value of MPS in refining risk stratification to guide therapeutic strategies, highlighting its role as an essential adjunct in the comprehensive management of these patients. By integrating MPS with clinical assessment, we can obtain a more precise diagnosis and optimize care for individuals with complex comorbidities.

5. Conclusion

In individuals with T2DM and systemic arterial hypertension experiencing atypical chest pain, MPS revealed ischemic alterations indicative of CAD, thereby facilitating the triage process for considering more invasive diagnostic interventions.

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UMA MISSÃO, UM PARCEIRO:

Aprimorar o controle & adesão para um cuidado melhor com o paciente

Apresentamos AS ONE by Servier, uma iniciativa global que une nossos produtos e serviços personalizados em um único portifólio para ajudar a melhorar o controle e a adesão dos pacientes agora e no futuro.[1,2A]

1. .Campano E. et al. Impact of SEvierPatient Solution: "Sempre Cuidando" program aNd dIGital Solution "Elfie" on Adherence among hypERtensive patients – the ENGAGE real-world study – Poster apresentado no II Congresso Internacional SOBREXP 2024, 18 a 20 de setembro de 2024. Disponível em :file:///C:/Users/ER22_BR1/Downloads/20240814_Servier_Engage_Poster_SOBREXP%202024_V0.1.pdf
2. BARROSO, Weimar Kunz Sebba et al. Diretrizes Brasileiras de Hipertensão Arterial–2020. Arquivos Brasileiros de Cardiologia, v. 116, p. 516-658, 2021.
A- Um programa completo de educação e engajamento para ajudar seus pacientes no tratamento, com programas de suporte ao paciente, parcerias para melhora da adesão e programas de conscientização. Com isso, há uma melhora na adesão ao tratamento, por meio da educação em saúde e da facilitação de acesso ao medicamento, evitando desfechos negativos, sendo o único promovido pela Servier do Brasil. Comprovado pelo ESTUDO ENGAGE. Imagem ilustrativa

Material destinado a profissionais de saúde habilitados a prescrever e/ou dispensar medicamentos. M-NO-BR-202505-00081. MAIO/2025