American Heart Journal Plus: Cardiology Research and Practice 54 (2025) 100541

Contents lists available at ScienceDirect

American Heart Journal Plus: Cardiology Research and Practice

journal homepage: www.sciencedirect.com/journal/american-heart-journal-plus-cardiology-research-and-practice

Research Paper

A comparison of magnetocardiography with noninvasive cardiac testing in the evaluation of patients with chest pain☆

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A B S T R A C T

Objectives: Chest pain is a common complaint of outpatients and emergency department patients. These patients are often referred for noninvasive cardiac imaging (NCI). Problems with NCI include limited availability, lengthy test delays, test duration, radiation exposure, adverse events, NPO (holding medications, caffeine/food/liquids/tobacco), exercise requirement, limitations for certain populations, inability to assess for ischemia with no obstructive coronary artery disease (INOCA), contrast/medication/needlestick-intravenous (IV) line needed.

Magnetocardiography (MCG) advantages include faster, easier test administration, radiation avoidance, less resource utilization, safer, no needlestick/IV requirement, no NPO for caffeine/food/liquids/tobacco, and no holding medications. By avoiding medications and/or exercise, MCG avoids risk of provoking myocardial injury and dangerous events (arrhythmias). No contrast or pharmacologic agents are needed with MCG, eliminating side effects/complications: tissue necrosis from extravasation, contrast-induced nephropathy, allergic reactions including life threatening anaphylaxis.

Design: MCG comparison with NCI: exercise stress test, stress echo, dobutamine stress echocardiogram, myocardial perfusion imaging: single photon emission computed tomography (SPECT) or positron emission tomography (PET), cardiac magnetic resonance imaging (cMRI), coronary computed tomography angiography (CCTA).

Outcome measures: Literature review: NCI versus MCG.

Conclusion: MCG is a rapid, safe, effective, painless and radiation-free test, does not require contrast/medication administration. MCG by avoiding provocative medications and/or exercise eliminates the risk of provoking myocardial injury and causing dangerous events such as arrhythmias. MCG avoids testing delays, has higher patient satisfaction, no NPO requirement, no holding medications or caffeine/food/liquids/tobacco, with similar sensitivity and specificity. Additional clinical research is needed to validate its utility. MCG may be a complementary modality alongside current NCI.

1. Introduction

Chest pain is a common complaint of patients seen in emergency departments (EDs) and in outpatient facilities in the U.S. and worldwide [1–3]. In the U.S. alone, there are 7.8 million ED visits [1,2] and another 4 million outpatient visits [4] for a combined total of 11.8 million visits for chest pain on an annual basis. Despite advances in cardiac care over the past decades, cardiovascular disease remains the number one cause of morbidity and mortality worldwide [5]. This is also true for the U.S., where cardiovascular disease remains the leading cause of death, accounting for 23.1 % of annual deaths, almost one million deaths (928,741) in 2020, with $407.3 billion in direct and indirect costs in 2018 [6,7].

The evaluation of the patient presenting with chest pain can be challenging [8,9], yet rapid and accurate patient assessment is critical to differentiate cardiac from noncardiac causes of pain [5,10]. An initial electrocardiogram (ECG), chest x-ray and cardiac biomarkers are generally used with a history and physical examination to help risk stratify patients with acute chest pain [4]. Even using these tools, a significant proportion of patients, up to 40 %, fall into an intermediate grey zone for coronary ischemia and do not rule in or out [11]. For those patients who are classified into this intermediate risk for acute coronary syndrome (ACS), current chest pain guidelines recommend non-invasive cardiac testing [1].

There are limitations to initial testing strategies using ECG and high-sensitivity troponins (hsTn) [11–14]. Troponins may be elevated for

☆ This article is part of a Special issue entitled: 'Magnetocardiography Rediscovered' published in American Heart Journal Plus: Cardiology Research and Practice.

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https://doi.org/10.1016/j.ahjo.2025.100541
Received 26 June 2024; Received in revised form 6 February 2025; Accepted 4 April 2025
Available online 10 April 2025

many reasons other than ACS, for example, patients with chronic kidney disease or those who are septic or critically ill [14]. This could result in a misinterpretation of elevated hsTn and unnecessary downstream testing. In certain age groups, e.g., the elderly, hsTn have decreased specificity and positive predictive value [13]. An elevated hsTn may indicate myocardial injury. At the same time, patients may have ischemia without myocardial injury (e.g. unstable angina); they could have a "normal" hsTn and be a "false negative" for ACS. These individuals represent an opportunity for intervention by either conservative medical management or an invasive approach to prevent myocardial injury. Magnetocardiography (MCG) can detect patients with reversible ischemia and ACS who have not yet infarcted and not yet had myocardial damage but are at risk and could have reversible ACS [15].

MCG can detect the electrophysiological changes occurring with ischemia by measuring and mapping the magnetic fields emitted during the cardiac cycle. Since the early measurements of the cardiac magnetic fields in the 1960s at Syracuse University, there have been many technical improvements [16]. These include upgraded sensors, better shielding of extraneous magnetic waves, advanced intelligence, and highly developed computers; all of which have improved MCG scanning and imaging techniques and show promise in the use of MCG in the clinical setting [15,17,18].

MCG also has many advantages over other non-invasive cardiac imaging (NCI). MCG is very rapid with the actual test only taking 90 seconds and about five minutes from set up to finish (Table 1a). MCG avoids the pain and risks of a needlestick, which can be necessary in some NCI for medication administration (Table 1b). It also avoids the need for contrast injection, which carries the risks of extravasation, allergic reaction, and anaphylaxis (Table 1b). MCG also avoids radiation, which is associated with an increased lifetime risk of cancer (Table 1a). MCG has fewer side effects and complications than the other NCI (Table 1c) and, has no absolute contraindications (Table 1d). Importantly, MCG has comparable sensitivities to other standard of care (SOC) stress tests [15] (Table 1e).

Additionally, in the Magneto study, the median time to test was significantly shorter for MCG at 2.9 h versus 22.9 h for all other SOC NCI [15]. Patient experience was substantially greater for MCG than for other tests with mean patient experience on a 5-point Likert scale (5 = very satisfied, 3 = neutral, 1 = very unsatisfied) of 4.7 for MCG versus 3.0 for SOC stress tests [15].

However, despite these advantages, real-world clinical use of MCG remains relatively limited, necessitating further studies and broader adoption to fully understand its utility and optimize its application in clinical practice.

2. Noninvasive cardiac testing (Tables 1a–1f)

Stress tests can be classified into three types: electrocardiography exercise stress testing, stress echocardiography and nuclear medicine myocardial perfusion imaging (MPI) using single-photon emission CT (SPECT) or positron emission tomography (PET) [19]. Exercise stress testing evaluates the physiologic and electrocardiographic response to exercise, while stress echocardiography evaluates left ventricular (LV) wall motion abnormalities and MPI analyzes perfusion defects to determine if obstructive coronary artery disease (CAD) is present.

Coronary computed tomography angiography (coronary CTA or CCTA) is a noninvasive anatomic test that directly visualizes the coronary arteries and measures CAD severity by calculating the degree of stenosis and plaque characteristics [19]. Cardiac magnetic resonance imaging (cMRI) uses the MRI to provide an assessment of the coronary arteries [19].

According to the Centers for Medicare and Medicaid (CMS) 2024 Medicare payments fee schedule, the total cost, which includes the facility fee and the professional fee for interpretation and supervision of the test, is quite variable depending on the specific NCI test [20] (Table 1f). A recent study (that did not include MCG) indicated that "graded exercise stress testing and stress echocardiography were associated with the least downstream costs, whereas CCTA and MPI were associated with higher costs." [21]

3. Exercise stress test

The exercise stress test; also referred to as a clinical exercise test, graded exercise test (GXT), exercise tolerance test (ETT), treadmill or bicycle stress test, or functional stress test; is the most common stress test performed in the U.S. in patients with stable symptoms suspected of

Table 1a
Comparison of MCG with non-invasive cardiac tests: Test characteristics and utilization.

Cardiac Test	Functional or anatomical	Patient exercise	Radiation exposure	Medications given during test	Personnel required to perform test[a,b]	Time to perform test
ETT	Functional	Yes	No	None	Stress lab technician	1 h, 15 min for test itself
SE	Functional	Yes	No	None	Echocardiogram technician	45–120 min, average 60 min
DSE	Functional	No	No	Dobutamine, sometimes atropine to increase heart rate	Echocardiogram technician	60 min
MPI-SPECT	Functional	No	Yes	Technetium	Nuclear medicine technician	2–4 h
MPI-PET	Functional	No	Yes	Rubidium FDG	Nuclear medicine technician	1–3 h, average 2 h
cMRI	Functional	No	No	Perfusion stress uses vasodilators[c]	MRI technician	30 to 90 min, usually 90 min
cCTA	Anatomical unless with FFR	No	Yes	B blockers, calcium channel blockers, nitroglycerin	CT technician	15–75 min
MCG	Functional	No	No	None	ED technician trained to do MCG	5 min, 90 s scan time

ETT: exercise tolerance test; SE: stress echocardiogram; DSE: dobutamine stress echocardiogram; MPI-SPECT: cardiac myocardial perfusion imaging using single photon emission computed tomography; cMPI-PET: cardiac myocardial perfusion imaging using positron emission tomography; cMRI: cardiac magnetic resonance imaging; cCTA: coronary computed tomography angiography; FFR: fractional flow reserve; MCG: magnetocardiography.

[a] Excludes supervising professionals. Interpreting specialist needed for all the tests.

[b] May need second personnel when patients are exercising (see Clinical exercise testing and interpretation. In: Liguori G. ACSM's Guidelines for exercise testing and prescription, Philadelphia: Lippincott Williams & Wilkins, 2022, 11th ed., Ch. 4. pp. 113–141) and third personnel to administer drugs and/or contrast.

[c] "Perfusion stress cardiac MR uses vasodilator agents, such as adenosine, dypiridamole and regadenoson". May not need medications during test, but "sometimes, rate and/or rhythm control drugs should be prescribed few days before the MR exam, occasionally, acute IV administration of beta-blockers or other antiarrhythmic drugs (i.e. flecainide, propaphenone) could be considered right before or during the scanning". Barison A, Baritussio A, Cipriani A, et al. Cardiovascular magnetic resonance: What clinicians should know about safety and contraindications. Int J Cardiology 2021; 331:322–328.

Table 1b
Comparison of MCG with non-invasive cardiac tests: Test preparation.

Cardiac test	IV required	IV contrast or pharmacologic stress agent used	Medications held before testing	NPO status before testing	Abstinence from caffeine	Normal baseline ECG required
ETT	Yes	No	β blockers, calcium channel blockers, digoxin, nitrates	Yes, 4 h[a]	Yes, at least 12 h, preferably 24 h	Yes
SE	Yes	No	Per MD	Yes, 4 h[a]	Yes, at least 12 h, preferably 24 h	No
DSE	Yes	Yes, dobutamine	β blockers, nitrates	Yes, 4 h[a]	Yes, at least 12 h, preferably 24 h	No
cMPI-SPECT	Yes	Yes, technetium	Phosphodiesterase inhibitors	Yes, 4 h[a]	Yes, at least 12 h, preferably 24 h	No
cMPI-PET	Yes	Yes, rubidium FDG	Theophylline, persantine, aspirin-dipyridamole	Yes, 4 h[a]	Yes, at least 12 h, preferably 24 h	No
cMRI	Yes	Yes, if given late gadolinium	No	Depends[b]	Yes, at least 12 h, preferably 24 h	No
cCTA	Yes	Yes, iodinated contrast agent	Sildenafil and similar meds	Yes, 4 h[a]	Yes, at least 12 h, preferably 24 h	No
MCG	No	No	No	No	No	No

ETT: exercise tolerance test; SE: stress echocardiogram; DSE: dobutamine stress echocardiogram; MPI-SPECT: cardiac myocardial perfusion imaging using single photon emission computed tomography; cMPI-PET: cardiac myocardial perfusion imaging using positron emission tomography; cMRI: cardiac magnetic resonance imaging; cCTA: coronary computed tomography angiography; MCG: magnetocardiography.

[a] Fasting requirements vary from 4 or 6 or 8 h, especially if receiving IV contrast and/or medications especially sedatives. Most recommend NPO for 4 h. However, some have no NPO requirements.

[b] For cMRI, NPO depends. If the patient is claustrophic (and may need a sedative), is receiving contrast, or medications especially sedative, NPO for 2–4 h. Otherwise, may not need to be NPO.

having CAD [22,23]. It is non-invasive, relatively inexpensive, readily available in most settings, and has no radiation associated with its use [22,24]. The ability to exercise to a satisfactory workload, whether using a treadmill or stationary bicycle, is a requirement for exercise stress testing. The most commonly cited exercise test endpoint is 85 % of the patient's maximum predicted heart rate [19,25]. Two exercise stress test requirements are an interpretable resting ECG and the ability to exercise [9,22]. Women are said to be more likely to have a false positive exercise stress test [19,22]. However, this may indicate that women are more likely to have underlying coronary microvascular dysfunction (CMD). In a study of symptomatic men and women undergoing exercise ECG and subsequent angiography, the positive predictive value (PPV) of ST-segment depression with exercise testing in women was significantly lower than in men (47 % versus 77 %, respectively; $P < 0.05$) [26].

3.1. Technical considerations

Exercise stress testing should not be performed on individuals unable to exercise sufficiently for any reason and those with ECG changes at rest that may interfere with the interpretation of the exercise test. Some of the resting ECG abnormalities that preclude the diagnosis of ischemic heart disease are left bundle branch block, ventricular paced rhythm, >1 mm ST depression at rest, Wolff-Parkinson-White, and ST-T abnormalities associated with LV hypertrophy, electrolyte abnormality, or digoxin use [27]. Examples of conditions in which individuals may not be able to exercise sufficiently include deconditioning, arthritis, lower extremity amputation, leg claudication, various other lower extremity orthopedic, musculoskeletal or neurologic diseases/conditions, some heart disease (e.g., decompensated heart failure) and pulmonary disease (e.g., COPD) [27]. There should be a minimum of two personnel present during exercise stress testing: the test administrator (who may be a nurse) and "at least one support technician." [28] During an exercise stress test, the patient usually exercises for about 10–15 min with warm-up and cool-down periods necessary and the entire test usually lasts about one hour. The exercise stress test is a functional test that does not involve radiation or contrast administration.

3.2. Dietary and medication considerations

Ideally, to maximize exercise capacity, patients should not eat, drink or smoke for at least four hours prior to the exercise stress test. They should avoid caffeine; including coffee, tea, cola, energy drinks, and chocolate; for at least 12 h and preferably 24 h before the stress test. Multiple drugs preclude the ability to attain 85 % of the predicted maximum heart rate, which limits the ability to identify ischemic heart disease. Medications that restrict the chronotropic response include beta blockers, nondihydropyridine calcium channel blockers (e.g., diltiazem and verapamil), antiarrhythmic drugs including amiodarone and sotalol, and digoxin, which also decreases the specificity for angiographic CAD. Nitrates diminish the ischemic response to exercise in patients with CAD [27].

3.3. Side effects and complications

Fatigue, myalgias, arthralgias, malaise, dizziness, near-syncope, and syncope can occur. Exercise stress testing may precipitate claudication in the lower extremities. Patients may fall and sustain injuries during exercise testing, especially in patients with gait instability. Hypertension and hypotension may occur but are uncommon. Angina, myocardial infarction and cerebrovascular accidents are rare complications. Dysrhythmias "are the most common complication of exercise ECG testing." Premature ventricular contractions (PVCs) and premature atrial contractions (PACs) are the most common dysrhythmias, although bradycardias and tachycardias can occur. Ventricular tachycardia or ventricular fibrillation are rare but can precipitate sudden death [29].

3.4. Contraindications

Absolute contraindications are acute myocardial infarction within two to four days, ongoing unstable angina, dysrhythmias with hemodynamic compromise, severe symptomatic aortic valvular stenosis, decompensated heart failure, active endocarditis or myocarditis or pericarditis, acute aortic dissection, acute venous thromboembolism, and physical or mental limitations that prohibit safe and adequate testing [30].

Relative contraindications are known left main coronary artery stenosis, moderate to severe aortic stenosis, tachydysrhythmias with uncontrolled ventricular rates, complete heart block, obstructive cardiomyopathy with severe resting gradient, recent stroke or transient ischemic attack, mental impairment with limited ability to cooperate, uncontrolled hypertension (i.e., systolic BP > 200 mm Hg or diastolic > 110 mm Hg) and uncorrected medical conditions including significant

Table 1c
Comparison of MCG with non-invasive cardiac tests: Side effects and complications.

Cardiac test	Side effects	Potential complications during testing	Medication or contrast agent complications
ETT	Fatigue, myalgias, arthralgias, dizziness, near-syncope/syncope, claudication	Fall with injuries, hypotension, hypertension, dysrhythmias, MI, CVA, cardiac arrest	N/A
SE	Fatigue, myalgias, arthralgias, dizziness, near-syncope/syncope, claudication	Chest pain Hypotension Hypertension Dysrhythmia MI, CVA, cardiac arrest	N/A
DSE	Nausea, anxiety, headache, tremor, flushing, urinary urgency, palpitations, local reaction at IV site	Chest pain Hypotension Hypertension Dysrhythmia MI, CVA, cardiac arrest	Extravasation, allergic reaction, anaphylaxis
cMPI-SPECT	Flushing, headache, GI distress, lightheaded, local reaction at IV site claustrophobia	Chest pain Hypotension Hypertension Dysrhythmia MI, CVA, cardiac arrest	Extravasation, allergic reaction, anaphylaxis
cMPI-PET	Nausea, local reaction at IV site claustrophobia	Chest pain Hypotension Hypertension Dysrhythmia MI, CVA, cardiac arrest	Extravasation, allergic reaction, anaphylaxis
cMRI	Nausea/vomiting, dizzy, claustrophobia, headache, local reaction at IV site claustrophobia[a]	Chest pain Hypotension Hypertension Dysrhythmia MI, CVA, cardiac arrest	Extravasation, allergic reaction, anaphylaxis
cCTA	Flushing, metallic taste, urinary urgency, claustrophobia	Contrast nephropathy, contrast extravasation, allergic reaction, anaphylaxis	Extravasation, allergic reaction, anaphylaxis
MCG	Claustrophobia[a]	N/A	N/A

ETT: exercise tolerance test; SE: stress echocardiogram; DSE: dobutamine stress echocardiogram; MPI-SPECT: cardiac myocardial perfusion imaging using single photon emission computed tomography; cMPI-PET: cardiac myocardial perfusion imaging using positron emission tomography; cMRI: cardiac magnetic resonance imaging; cCTA: coronary computed tomography angiography; MCG: magnetocardiography; MI: myocardial infarction; CVA: cerebrovascular accident, N/A: not applicable.

[a] Claustrophobia with MCG is mitigated and eliminated by multiple factors: time < 5 min vs. 1 h., larger opening with MCG vs. MRI, patient is less enclosed with MCG, "no escape with MRI" while MCG has opening in front, technician in same room for MCG not for MRI, communication between patient and technician is better and possible with MCG vs. MRI, difficult almost impossible communication with MRI, loud clanking noise throughout MRI with earphones that are minimally distracting at best.

Table 1d
Comparison of MCG with non-invasive cardiac tests: Contraindications and comments.

Cardiac test	Contraindications	Typical testing hours of availability	Other comments
ETT	1, 2, 4 Abnormal ECG RBBB LBBB Aortic stenosis Inability to exercise	Typically weekdays AM to afternoon	Relatively inexpensive, widely available
SE	1, 2, 4 Aortic or mitral stenosis Inability to exercise Large body habitus, COPD, pre-existing WMA	Typically weekdays AM to afternoon	Readily available, less costly than other tests (except exercise stress), gives structural information
DSE	1, 2, 3, 4	If available, typically weekdays AM to afternoon	Can be used in patients with asthma, RAD, airway disease, or severe conduction disorders
cMPI-SPECT	1, 2, 3, 4	Typically weekdays AM to afternoon	Most commonly performed
cMPI-PET	1, 2, 3, 4	If available, typically weekdays AM to afternoon	Not available in most hospitals
cMRI	1, 2, 3, 4	If available, typically weekdays AM to afternoon	Least common test, fairly new, high cost, long scan time
cCTA	1, 2, 3, 4 High risk Prior CAD Atrial fibrillation/ flutter Unable to receive IV contrast Inability to lower heart rate	If available, typically weekdays AM to afternoon	
MCG	1	If available, 24/7 every day of the week	

ETT: exercise tolerance test; SE: stress echocardiogram; DSE: dobutamine stress echocardiogram; MPI-SPECT: cardiac myocardial perfusion imaging using single photon emission computed tomography; cMPI-PET: cardiac myocardial perfusion imaging using positron emission tomography; cMRI: cardiac magnetic resonance imaging; cCTA: coronary computed tomography angiography; MCG: magnetocardiography; COPD: chronic obstructive pulmonary disease; WMA: wall motion abnormality; RAD: reactive airway disease; LBBB: left bundle branch block; RBBB: right bundle branch block.

Contraindications

1. Absolute Contraindications: Acute MI within 2–4 days, unstable angina, symptomatic or hemodynamically compromised dysrhythmias, symptomatic severe aortic stenosis, decompensated heart failure, acute venous thromboembolism, severe pulmonary hypertension, acute myocarditis or pericarditis or endocarditis, acute aortic dissection.
2. Relative Contraindications: high grade AV blocks (2nd or 3rd degree), uncontrolled hypertension (systolic BP > 200 mm Hg and/or diastolic BP > 110 mm Hg), left ventricular outflow tract obstruction, hypertrophic cardiomyopathy, left main coronary artery stenosis, moderate valvular stenosis, electrolyte abnormalities.
3. Prior significant reaction to any contrast or medication used for the specific test is an absolute contraindication.
4. Note: Pregnancy is always a concern with any radiation or contrast agents so this is another contraindication when there is radiation and/or contrast agents given.

anemia, critical electrolyte imbalances, and hyperthyroidism [30].

4. Stress echocardiogram

A resting (baseline) echocardiogram can give information about chamber and valvular structure and function, aortic root diameter, LV wall thickness, pericardial effusions, and pulmonary artery pressure. This should be obtained before the stress testing [31]. Wall motion abnormalities and/or alterations in the LV contractility relative to the coronary artery anatomic distribution form the basis for the stress echocardiogram [19]. Infarcted or ischemic myocardium demonstrates poor contractility and wall motion abnormalities and alterations during stress and recovery compared to "normal" well-perfused myocardium [32]. Echo can be combined with exercise or pharmacological stress tests. Dobutamine is the most used pharmacologic agent when paired with a stress echocardiogram (SE), and atropine is administered if necessary to obtain the targeted heart rate. Nuclear MPI (e.g., SPECT) is deemed more sensitive than stress echocardiography, although stress

Table 1e
Comparison of MCG with non-invasive cardiac tests: Diagnostic test performance.

Cardiac test	Sensitivity	Specificity	PPV	NPV
EST	67 %[1]	72 %[1]	41 %[1]	89 %[1]
	65–80 %[2]	60–85 %[2]	10–31 %[2]	80–95 %[2]
	–80 %[a]	*60–85 %*[a]	*10–41 %*[a]	*80–95 %*[a]
SE	80 % (77–82 %)[1]	84 % (82–87 %)[1]	–	–
	80 % (77–83 %)[3]	86 % (84–88 %)[3]	–	–
	80–85 %[4]	80–88 %[4]	–	87 %[4]
	80–85 %[a]	*80–88 %*[a]	–	*87 %*[a]
DSE	79 % (71–87 %)[1]	85 % (83–88 %)[1]	73 %[1]	89 %[1]
	80 %[3]	84 %[3]	68 %[3]	92 %[3]
	83 %[5]	83 %[5]	58 %[5]	95 %[5]
	82 %[6]	84 %[6]	–	–
	79–83 %[a]	*83–85 %*[a]	*58–73 %*[a]	*89–95 %*[a]
cMPI-SPECT	52 % (37–66 %)[7]	57 % (48–65 %)[7]	–	82 % (74–88 %)[7]
	76 %[8]	–	–	50 %[8]
	81.8 %[9]	92.9 %[9]	90 %[9]	86.7 %[9]
	78 %[10]	52 %[10]	–	83 %[10]
	88.3 %[11]	75.8 %[11]	–	–
	52–88.3 %[a]	*52–92.9 %*[a]	*90 %*[a]	*50–86.7 %*[a]
cMPI-PET	–	–	–	84 % (75–90 %)[7]
	96.8 %[8]	92.6 %[8]	–	82.3 %[8]
	92.6 %[11]	81.3 %[11]	–	–
	92.6–96.8 %[a]	*81.3 %–92.6 %*[a]	–	*82.3–84 %*[a]
cMRI	–	84 % (77–89 %)[7]		79 % (71–86 %)[7]
	81 %[12]	86 %[12]		–
	89 %[10]	76 %[10]		92 %[10]
	81–89 %[a]	*76–86 %*[a]		79–92 %
cCTA	87 %[7]	79 %[7]	69 %[7]	92 %[7]
	94 %[8]	83 %[8]	72 %[8]	97 %[8]
	89 %[13]	83 %[13]	78 %[13]	94 %[13]
	85 %[14]	90 %[14]	91 %[14]	83 %[14]
	85–94 %[a]	*79–90 %*[a]	*69–91 %*	*83–97 %*
MCG	*91 % (87.1 %*[b]*)*[15]	*83 % (84.7 %)*[15]	*80.4 %*[15]	90.2 %[15]
	83 %[16]	77 %[16]		
	66.7 %[17]	*57.1 %*[17]		
	66.7–91 %[a]	*57.1–83 %*[a]	*80.4 %*[15]	90.2 %[15]

– indicates not given in the study.

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[a] Range for all the references for the given cardiac noninvasive test and is in italics.

[b] Percent in parenthesis is calculated from numbers given in text, first number is what authors listed as the percent (reference 15).

[c] https://e-jcvi.org/DOIx.php?id=10.4250/jcvi.2019.0109#B2.

[d] https://e-jcvi.org/DOIx.php?id=10.4250/jcvi.2019.0109#B3.

echocardiography is thought to be more specific than SPECT [19,33].

4.1. Technical considerations

Image quality is a function of the thoracic echo windows. In certain patients, especially those with obesity or COPD, images can be problematic and challenging to interpret [19]. Underlying conduction abnormalities, such as a bundle branch block, affect image quality [32]. Image quality is also a function of the skill of the individual performing the test. In addition to the echocardiographer, some laboratories require a stress ECG technician [28]. The dobutamine infusion usually takes about 15 min and the entire dobutamine stress echocardiogram usually takes about one hour. The SE is a functional test that does not involve radiation, although a pharmacologic stress agent is administered if a dobutamine stress echocardiogram is done.

Speckle tracking echocardiography, which uses myocardial strain analysis, has been suggested for diagnosing ischemia [34]. Unfortunately, "the diagnosis of ischemic myocardium by strain analysis is not widely performed in clinical practice at this time due to several limitations." [35] Limitations include poor image quality, use of highly variable segmental strain and blood pressure measurements, a lack of standardization of values, and dropout artifacts and reverberations, all of which can result in drift or miscalculation of myocardial strain [34,35].

4.2. Dietary and medication considerations

Again, to maximize exercise capacity, patients should not eat, drink or smoke for at least four hours before the SE. They should avoid caffeine; including coffee, tea, cola, energy drinks, and chocolate; for at least 12 h and preferably 24 h before the stress test [32]. Beta-blockers may lessen heart rate response and evidence of myocardial ischemia during stress echocardiography. However, using atropine can usually offset the effect of beta blockers to achieve the desired heart rate [31].

4.3. Side effects and complications

Echocardiography itself has no known adverse effects. With a dobutamine stress echocardiogram (DSE), palpitations occur in 10–30 % of patients [36]. Minor dysrhythmias, mostly PVCs or PACs can occur in up to 30 % of dobutamine stress tests [32,36]. Nausea, anxiety, headache, tremor, urinary urgency, hypertension, hypotension and tachycardia are side effects that can occur with dobutamine. About one-fourth (25 %) of those undergoing a DSE experience noncardiac side effects [32]. Chest pain has been reported in 15–20 % of patients undergoing dobutamine stress testing. However, complications from myocardial ischemia are infrequent and are treated by stopping the dobutamine and administering sublingual nitroglycerin and intravenous (IV) beta blockers [31,36]. LV mid-cavity and outflow tract obstruction can occur in 10–25 % of patients undergoing dobutamine stress echocardiography [31].

4.4. Contraindications

Contraindications for all stress testing modalities include acute coronary syndromes (e.g., acute myocardial infarction within two to four days, active unstable angina), severe cardiac arrhythmias, malignant hypertension, obstructive cardiomyopathy, symptomatic severe aortic stenosis, and significant LV outflow tract obstruction [31]. Uncontrolled tachydysrhythmias and systemic hypertension (e.g., systolic BP $>$ 180 mm Hg) are additional contraindications to dobutamine stress echocardiography [31,32].

5. Pharmacologic stress agents

Dobutamine, a beta-agonist, is a positive chronotropic and inotropic agent. Dobutamine is used to pharmacologically reproduce the effects of exercise. Its effects can be offset by IV metoprolol if necessary. It is the preferred pharmacologic stress agent for patients with inadequately controlled reactive airway disease or those on methyl xanthines [36,37]. Side effects that can occur with dobutamine include nausea, anxiety, headache, tremor, urinary urgency, premature ventricular contractions (PVCs) and premature atrial contractions (PACs). Complications seen with dobutamine are hypotension, hypertension, and tachycardia. Preferably, beta-blockers should be held within 24 to 48 h since they can impair the response to dobutamine. The following are contraindications to dobutamine: obstructive cardiomyopathy, significant aortic stenosis, uncontrolled hypertension and uncontrolled tachydysrhythmias. Dobutamine is commonly combined with echocardiography, SPECT, cardiac PET and cardiac MRI.

Adenosine, dipyridamole (Persantine) and regadenoson (Lexiscan) lead to coronary vasodilatation by adenosine receptor activation. Their effects can be counteracted by inhaled bronchodilators or IV aminophylline [37]. Regadenoson is thought to have fewer side effects than the other two coronary vasodilators. Side effects include nausea, flushing, lightheadedness, and headache. Complications that can occur with these coronary vasodilators include chest pain, dyspnea, bronchospasm, and dysrhythmias, specifically bradycardia and AV nodal blockade. Dietary restrictions include NPO for at least four hours and no caffeine within twelve to twenty-four hours. Hypotension (systolic BP $<$ 90 mm Hg), inadequately controlled bronchospastic disease, and dysrhythmias: sinus node dysfunction or second or third degree AV block are contraindications to using these three coronary vasodilators [37]. There has been a report of second-degree heart block followed by pulseless electrical activity and then asystole in an 84-year old male after the administration of regadenoson [38]. This indicates the potential danger of administering any contrast agent or medication.

Known hypersensitivity to the specific pharmacologic stress agent is a contraindication.

6. Nuclear myocardial perfusion imaging (MPI) stress tests

Nuclear myocardial perfusion imaging (MPI) can be implemented via single-photon emission CT (SPECT) or positron emission tomography (PET). MPI can be exercise or pharmacologically induced. The pharmacologic stress agents for MPI are the vasodilators: adenosine, dipyridamole (Persantine) and regadenoson (Lexiscan), with regadenoson as the primary agent used. MPI measures and compares the coronary blood flow before and after stress. A fixed perfusion defect at rest and after stress in a coronary distribution indicates scarring from a prior MI or hibernating myocardium, which could improve if revascularized. In contrast, normal flow at rest with a perfusion defect with stress signifies ischemia. Compared with exercise ECG, functional testing with imaging has improved sensitivity and specificity for the diagnosis of obstructive CAD [9]. SPECT is currently the most widely available and least expensive nuclear MPI modality [19].

6.1. Technical considerations

There are differences between SPECT and PET, including the intravenous radioactive tracers. SPECT scanners generally use technetium 99 (sestamibi) for their perfusion imaging [39]. Thallium has been replaced because of higher radiation. PET scanners commonly use rubidium or ammonia radionuclides for their perfusion imaging with fluorodeoxyglucose (FDG) employed to evaluate myocardial viability and inflammation. In September 2024, the FDA approved flurpiridaz F-18, a novel PET radiotracer with a longer half-life, offering expanded access to cardiac PET imaging and improved diagnostic accuracy for coronary artery disease [40,41].

SPECT functions by contrasting regional perfusion. Therefore, diffusely hypoperfused myocardial disease, for example, left main or triple-vessel disease, may be a false negative [37]. False-positive tests

may occur with attenuation artifacts as can occur from adipose tissue in obese patients, breast tissue or an elevated diaphragm [42–44]. "SPECT tests can often give equivocal results." [37]

PET has several advantages over SPECT. PET has less attenuation artifact (from gastrointestinal scatter and diaphragmatic attenuation especially in the obese patient) due to the higher energy photons emitted by the positron radiotracers compared with the SPECT radiotracers. PET can identify more minor perfusion defects than SPECT because of PET's greater spatial resolution. Additionally, PET has less radiation, and faster scan time [9,19]. PET's disadvantages are a higher cost and lesser availability since a PET scan can only be done at facilities with either an on-site cyclotron, which makes isotopes on site or acquires isotopes from radiopharmaceutical companies within a tight designated time frame, which is necessary because of the short half-life of the radioactive tracer [19]. The recent approval of flurpiridaz F-18 does provide an option that has a significantly longer half-life, about 12 times longer, compared to the other commonly used PET radiotracers which may facilitate more utilization and growth in cardiac PET [40,41].

The MPI tests are functional tests that involve radiation and contrast agents. During a SPECT test, a gamma camera takes images of the heart, first at rest and then following exercise. Each image takes about 15–20 min. There is a required waiting period between the rest and the exercise parts of the SPECT because of extensive hepatobiliary uptake relative to myocardial uptake so initial imaging after stress must be delayed for about one hour [39]. The exercise part alone takes another 20–30 min. Thus, the total test time can be 2 to 4 h. The scan time for the PET is about 30 min. However, the total PET test time may take 1 to 3 h with an average time of two hours. ECG-gated imaging is needed with technetium 99 (sestamibi) SPECT scanning and PET scanning with rubidium or ammonia radionucleotides. MPI is a functional test that involves radiation and contrast agents.

The sensitivity and specificity of MPI tests are affected by the skill/experience of the individual interpreting the test results, who should be able to identify imaging artifacts and normal variants [39]. The American College of Radiology standards for a SPECT scan include the involvement of multiple personnel including the nuclear cardiologist or radiologist to supervise the procedure, and a nuclear technologist with input from a nuclear pharmacist, medical physicist and radiation safety officer [45]. There is an expert consensus document regarding the use of ionizing radiation in cardiovascular imaging [46].

6.2. Dietary and medication considerations

Again, patients should be NPO for a minimum of 4 h before the test with no caffeinated beverages/foods for a minimum of 12 h but 24 h preferred before the test since caffeine counteracts the vasodilatory medications that may be administered during the test. Dipyridamole and other phosphodiesterase-3 inhibitors should be withheld for a minimum of 48 h to avoid the possibility of hypotension during the test from multiple vasodilator medications [45]. There are similar restrictions for PET scans, such as NPO for 4 h, no caffeine for 24 h, etc. Diabetics may not absorb the glucose in the radiotracer, which could affect the results.

6.3. Side effects and complications

The most common side effects are from the medications and include flushing, lightheadedness, headache, gastrointestinal upset, nausea, shakiness, and dyspnea. Discomfort can occur from tracer injections, as well as allergic reactions or anaphylaxis. Contrast extravasation from a peripheral IV line can cause local pain, swelling, irritations and more serious complications ranging from necrosis, contractures, and compartment syndrome. If exercise is performed during the test, then there is the possibility of dysrhythmia, chest pain, syncope, or even a myocardial infarction or stroke.

6.4. Contraindications

Obesity, specifically, exceeding the weight limit for the scanner table, is a relative contraindication. Since there is radiation involved, pregnancy is a contraindication. Breast feeding patients should stop breast feeding for 24 h before the cardiac MPI test. Other contraindications include autonomic dysfunction, hypovolemia, left main coronary artery stenosis, stenotic valvular heart disease, pericarditis, pericardial effusions, and carotid artery stenosis with cerebrovascular insufficiency. Acute MI within the previous 4 days, sinus bradycardia (i.e., heart rate $<$ 40 beats per minute), severe systemic hypertension, recent venous thromboembolism, active myocarditis or endocarditis or pericarditis are additional contraindications.

7. Cardiac magnetic resonance imaging with stress perfusion (cardiac MRI)

Cardiac magnetic resonance imaging (cMRI) is usually combined with a pharmacologic agent. Gadolinium contrast enhancement is a radionuclide-free stress test, although there is still the danger of allergic reaction or anaphylaxis to the contrast agent and nephrogenic systemic fibrosis. The MR-IMPACT II Trial reported that perfusion cMRI with gadolinium has better sensitivity but lower specificity than SPECT to detect CAD [47,48]. Late gadolinium enhancement (LGE) imaging was superior to SPECT for infarct detection in patients with known or suspected CAD [49]. A recent study indicates that cMRI can predict adverse cardiac events in patients with myocardial infarction with non-obstructive coronary arteries (MINOCA) at $\approx$ 3 year follow-up [50].

Stress cardiac MRI is a functional test, fairly new, the least commonly used non-invasive cardiac test, and is not yet widely available; experience is still somewhat limited with this imaging technique, and it has a high cost and a long scanning time (usually about 90 min) [19]. In patients with renal insufficiency, whether acute or chronic, gadolinium contrast agents are contraindicated [51].

7.1. Technical considerations

Cardiac gating is typically necessary for cardiac magnetic resonance (CMR) since the information is generally acquired during many cardiac cycles to improve resolution. Although ECG gating usually improves image quality, CMR may have poor-quality images in patients with dysrhythmias [52]. Respiratory gating may sometimes be needed in addition to ECG gating. Images can be obtained during breath holding.

CMR has three-dimensional, high spatial and temporal resolution, multiple imaging techniques in a single system and no lung or bone interference [19]. It requires ECG and respiratory gating, and acquisition time can be long [19].

The magnetic field can distort the ECG, which impedes the monitoring of acutely ill patients.

7.2. Dietary and medication restrictions

Products with caffeine should still be avoided for a minimum of 12 h but preferably for 24 h because it can lead to vasoconstriction. Dietary restrictions depend on the clinical scenario. If the patient is claustrophobic and may need sedation, or receiving IV contrast or IV medications, then NPO for 2–4 h is suggested. Otherwise, there may be no NPO restrictions.

7.3. Complications

Nephrogenic systemic fibrosis has occurred in rare cases when gadolinium contrast agents were administered to patients with moderate to severe kidney disease (e.g. estimated glomerular filtration rate [eGFR] $\leq$30 mL/min).

7.4. Contraindications

Relative contraindications are pregnancy, kidney dialysis or kidney problems, recent major surgery or illnesses. Since CMR involves MRI, absolute contraindications are MRI-incompatible devices including metallic implants, pacemakers, defibrillators, aneurysm clips, nerve stimulators, TENS, many other devices, foreign bodies, and any metal in the body.

The use of gadolinium-based contrast agents should be avoided in individuals with severe kidney disease because of the danger of contrast nephropathy and nephrogenic systemic fibrosis.

8. Noninvasive cardiac testing: anatomic, non-stress tests

8.1. Coronary computed tomography angiography (CCTA)

Coronary CT Angiography (CCTA) is not technically a "stress test" in that the heart is not imaged under an artificially altered blood flow so it is not a functional test, like exercise electrocardiography, or nuclear stress testing or stress echocardiography but is instead an anatomical noninvasive cardiac test. Coronary computed tomography angiography, also called coronary CT angiography or CCTA, requires an injection of iodine-containing contrast material followed by CT scanning, which carries the risk of an allergic reaction or anaphylaxis. Coronary CTA is an anatomic test requiring contrast administration and radiation exposure. Calculation of the CT-derived fractional flow reserve (CT-FFR) may yield additional functional information useful in specific patients [53]. One advantage CCTA offers is the ability to analyze the characteristic of atherosclerotic plaques to determine if these are hard calcified plaques or more vulnerable less stable, soft plaques. The PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) study compared anatomical testing with CTA vs. functional testing (exercise electrocardiography, nuclear stress testing or stress echocardiography) and reported "in symptomatic patients with suspected CAD who required noninvasive testing, an initial strategy of CTA did not improve clinical outcomes." [54]

8.1.1. Technical considerations

Technical considerations with CTA must be addressed to obtain adequate images. Due to the brief presence of IV contrast in the coronary arteries, there must be a particular heart rate and unique ECG timing with a prerequisite for ECG gating or ECG triggering availability with the -CT scanner, a property that not all CT scanners have. The desired heart rate is <60 bpm [19,55]. The patient must also be cooperative and able to hold their breath for 5 to 10 s [55].

The 3D CT scan images of the arteries of the heart, can detect plaque with narrowing of the coronary arteries. It may require a beta blocker to slow the heart rate and/or nitroglycerin to dilate and improve the visualization of the coronary arteries to get better images [19]. If no medications are needed, the test takes about 15 min. If the beta blocker is given PO, it takes at least an hour; if the beta blocker is given intravenously, it may require several doses and at least 20 min for the heart rate to slow and obtain adequate images. Thus, it takes about 15 min to complete if the heart rate is slow and steady, but an additional 20 to 60 min is needed if the heart rate is fast and a beta blocker is needed for the test to be completed. In summary, the time to completion is 15 min without a beta blocker and 35 to 75 minutes with a beta blocker.

8.1.2. Dietary and medication restrictions

Patients must avoid caffeinated products, sildenafil and similar medications for erectile dysfunction. Most recommend being NPO for four hours prior to the test. Caffeine should be withheld for at least 12 h and preferably 24 h prior to the test.

8.1.3. Side effects and complications

Side effects of the contrast include a flushed or warm feeling with contrast injections, a metallic taste in the mouth, and urinary urgency, which dissipates quickly. Extravasation of contrast from the IV site may lead to skin irritation, erythema and even skin necrosis with the need for plastic surgery consultation and skin grafts or a fasciotomy in the worst-case scenario [56–58]. There is the possibility of an allergic reaction and anaphylaxis to the contrast agent. In patients with kidney disease, contrast should be used with caution since it may worsen kidney function with resultant contrast nephropathy. There is a lifetime risk of malignancy from accumulated radiation [59,60].

8.1.4. Contraindications

Relative contraindications include individuals with a high body mass index (BMI) who may not fit into the opening of a conventional scanner or whose weight may be greater than the limits of the CT table, which is usually about 350 pounds. Those with dysrhythmias may have poor-quality scans. It may be challenging to interpret the scan if there are many regions of old calcified, hardened plaque, which is often the case in older patients. Other relative contraindications include pregnancy, acute thyroid storm, renal insufficiency (creatinine clearance $\leq$30 mL/min/1.73 m^2), acute decompensated heart failure, patients on radioactive iodine therapy and inability to hold one's breath for more than five seconds. History of a severe anaphylactoid reaction to iodinated contrast is an absolute contraindication.

The "triple rule-out" scan has been used to evaluate acute chest pain, especially in the emergency department setting [61]. This allows for contrast bolus with concomitant CT images to do a coronary CTA, a pulmonary CTA (to assess for pulmonary embolism), and a CT aortogram (to look for aortic dissection). However, this has the significant disadvantage of a large contrast bolus with a concern for nephrotoxicity and much larger radiation exposure. Additionally, there are concerns for overuse in patients that can be effectively evaluated using faster and safer alternatives.

8.2. Non-invasive cardiac testing: diagnostic test performance

The diagnostic performance of current non-invasive cardiac tests has variable ranges in test performance. For example, ETT has the lowest sensitivity (65 %–80 %), cardiac MPI with PET the highest sensitivity (92 % -97 %), and cardiac MPI with SPECT the widest range (52 % -88 %). See Table 1e for the ranges of sensitivity, specificity, positive and negative predictive value for each cardiac testing modality.

8.3. Non-invasive cardiac testing: radiation exposure and cost

Exposure to radiation during cardiac testing carries a lifetime risk of cancer and cancer deaths The risk may be small, but there is a cumulative effect over a person's lifetime [59,60]. The American Cancer Society notes that radiation exposure from all sources can add up over a lifetime, and "radiation can, indeed, increase cancer risk, imaging tests that use radiation should only be done for a good reason. In many cases, other imaging tests may be used." [59] MCG may be an alternative to imaging tests that use radiation.

One chest x-ray exposes a person to about 0.1 mSv radiation exposure. However, some non-invasive cardiac testing modalities, such as cardiac MPI with SPECT expose a person to radiation equivalent to 100 chest x-rays and CCTA exposes a person to a radiation equivalent of 30–50 chest x-rays. See Table 1f for comparison of radiation exposure by cardiac test.

There is significant variation in the cost of cardiac testing, ranging from about $86 to almost $1600, and factors such as the cost of professional interpretation and supervision in addition to the facility fee, need to be taken into consideration when considering the total cost for each test (Table 1f).

Fig. 1. Magnetocardiography device (Genetesis CardioFlux® MCG).

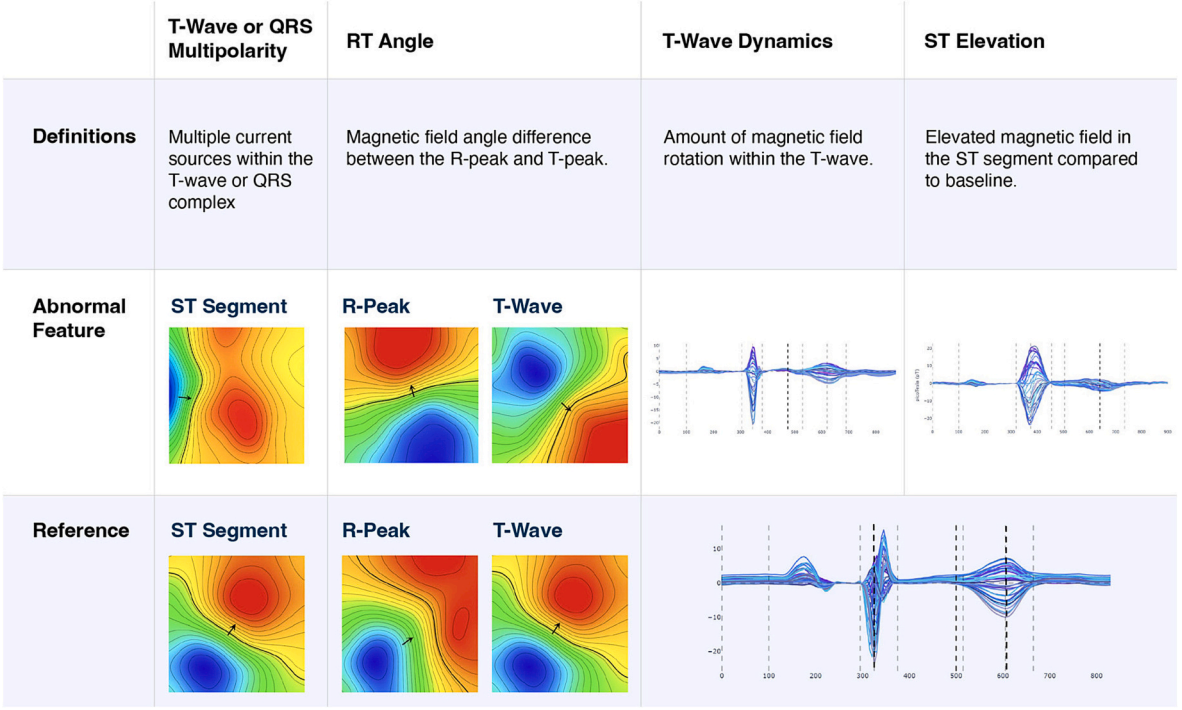

Fig. 2. Magnetocardiogram with normal or negative magnetocardiogram showing P wave, QRS, and T waves and positive magnetocardiogram with abnormalities indicating ischemia.

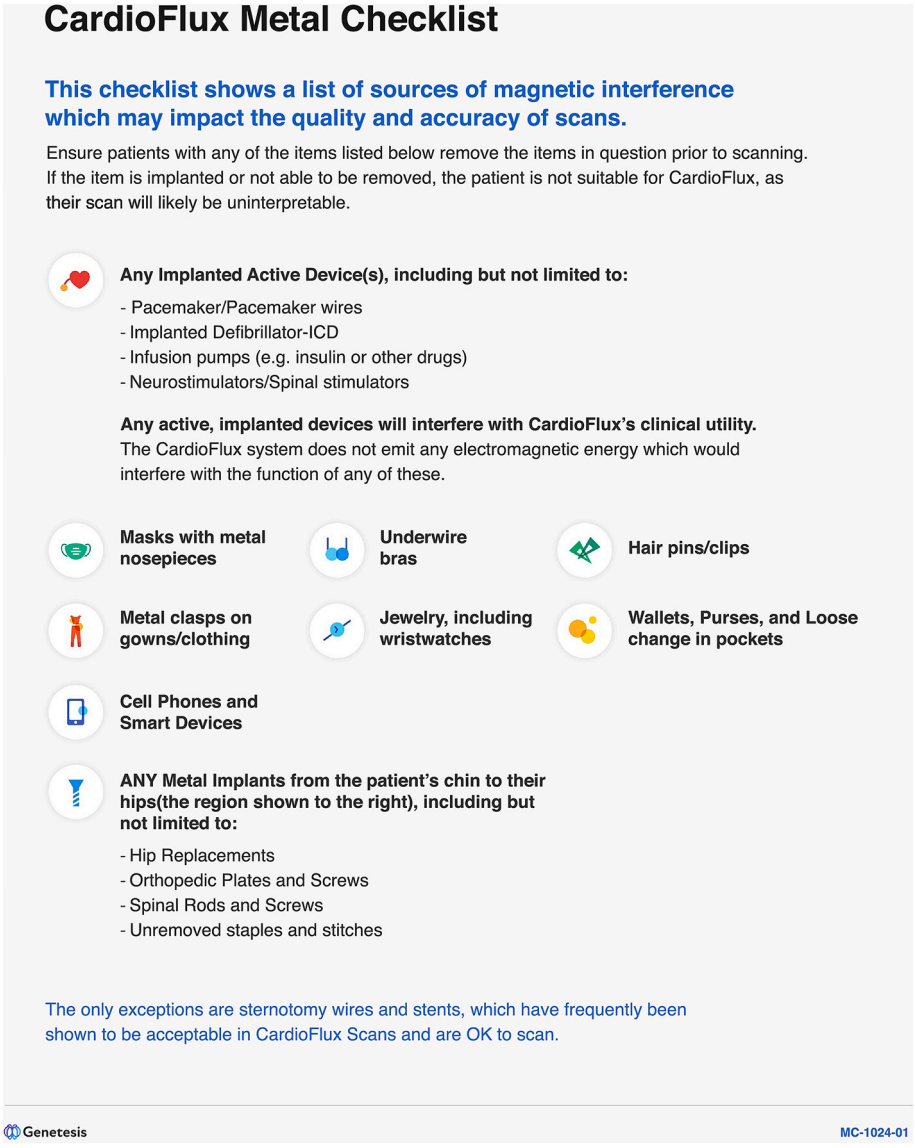

Fig. 3. Metal checklist.

8.4. *Non-invasive cardiac testing: clinical use*

The non-invasive cardiac tests: ETT, SE, DSE, MPI-SPECT, MPI-PET, cMRI and cCTA are clinically approved by the Food and Drug Administration (FDA). The CardioFlux® MCG technology is approved by Health Canada for the diagnosis of myocardial ischemia [62] (Fig. 1). In the United States, CardioFlux® has received FDA 510(k) clearance and is intended for use as a tool that non-invasively measures and displays the magnetic signals produced by the electrical currents of the heart [63]. It has not been cleared or approved by the FDA for the diagnosis of myocardial ischemia but is being investigated in that capacity. Two recent (2024) studies evaluated the clinical use of MCG. The Magneto Study by Mace et al. reported that MCG had a similar sensitivity and lower specificity as non-invasive stress testing in ED patients with suspected ACS, while having a significantly shorter time to test and significantly higher patient satisfaction scores [15]. The study by Ashokprabhu et al. concluded that in patients with angina but no obstructive coronary artery disease (ANOCA) patients, MCG was able to detect coronary microvascular dysfunction (CMD) [64]. There are also two ongoing trials registered at ClinicalTrials.Gov on MCG and coronary artery disease. The Micro2 trial is evaluating MCG as a noninvasive diagnostic strategy for suspected INOCA [65] and Magneto-PET is a registry of cardiac PET and CardioFlux MCG in patients with suspected coronary ischemia [66].

8.5. *Magnetocardiography*

MCG is a noninvasive cardiac test. Noninvasive cardiac tests that do not directly image any coronary arteries are considered functional tests. Current commonly used noninvasive cardiac functional imaging tests include exercise electrocardiography, stress echocardiography, and nuclear stress testing. CCTA, a commonly used noninvasive cardiac test, is classified as an anatomical test because it directly images the coronary arteries [19,54]. Stress testing, either by exercise or stimulant medication, works by increasing the heart rate and by making the heartbeat more forcibly (thus, increasing myocardial contractility), and thereby, artificially modifying blood flow to detect coronary ischemia. Although MCG does not involve exercise or stimulant medications, and thus, does not modify cardiac blood flow or "stress" the heart, it is still classified as a functional test because it does not directly image the coronary arteries.

MCG has existed since 1963 but has lacked clinical application due to challenges associated with older magnetic sensor technology and the

lack of computing power. Now with the advancements in magnetic sensors, as well as computing and machine learning capabilities, there is a resurgence in the interest and potential clinical application of this technology.

MCG is like an ECG in that both measure and map the physiological activity of the heart, with the ECG recording the heart's electrical signals and the MCG recording the heart's magnetic field. Both the ECG and MCG have similar morphological features including P waves, QRS complexes and T waves, and both obtain their information passively without requiring any patient cooperation or participation (Fig. 2).

However, MCG has several advantages over ECG [17]. Unlike the ECG, MCG does not require contact with the patient's skin so MCG is not affected by differences in body composition and variations in conductivity, which can affect the ECG measurement [17]. The ECG detects voltage across the chest wall in a two-dimensional plane, while MCG sensors measure the heart's magnetic waves in both planar and tangential directions, which likely increases the sensitivity of MCG in detecting coronary ischemia compared with ECG [18] (Fig. 2).

8.5.1. Technical considerations

There is no danger from metals in or on the patient's body, unlike with an MRI where metallic objects present during a MRI can result in significant morbidity and even, mortality [65]. Image quality, however, is affected by the presence of metal and may lead to inadequate or uninterpretable scans [15]. A cardioflux metal checklist has been developed to be used before scanning any MCG patient (Fig. 3). As with other noninvasive diagnostic cardiac testing modalities, a patient with a markedly increased BMI may not fit into the scanner. The current MCG table, rated for a weight limit of 300 pounds, can safely accommodate patients up to 750 pounds, which is 2.5 times its standard limit.

Recently, there has been an improvement is the usable scan rate for MCG. In the past few years, technical improvements have led to a marked improvement in the usable scan rate. In the Mace et al. study which began in January 2021 and ended in June 2023, because of technical limitations 22.8 % of MCG scans were not evaluable, while the Ashokprabhu et al. study which began later in November 2021 and ended later in June 2023, only 10.8 % of scans were not evaluable [15,64]. Over time, the incidence of unevaluable scans has decreased and we may see a further reduction in this rate. Currently. MCG evaluable scan yield is improving but still lags behind other NCI modalities. Ideally, the number of unevaluable scans should be limited, perhaps, at <5–10 %.

8.5.2. Dietary and medication considerations

There are no dietary or medication restrictions for MCG. Abstinence from caffeine is not required for MCG, although abstinence from caffeine is required for at least 12 h and preferably for 24 h for all other noninvasive cardiac diagnostic tests (Table 1b). There are no dietary restrictions for MCG, while six of the other noninvasive diagnostic cardiac tests require a minimum of four hours NPO prior to the test and the other NCI test may require NPO depending on the patient's clinical situation (Table 1b). Patients do not have to have any medications held prior to testing for MCG, while all of the other NCI tests (e.g. ETT, SE per MD, DSE, cMPI-SPECT, cMPI-PET, and cCTA) except for cMRI require medications be held (Table 1b). For patients seen in the ED and then placed in the observation unit or admitted to the hospital, many of whom have eaten or drank coffee or taken their medications, these dietary and medication requirements can lead to a delay in testing for many patients.

8.5.3. Side effects and complications

There is no risk of side effects or complications including allergic reaction and anaphylaxis and no pain or risk from a needlestick injury, since no medications and/or contrast agents are administered when an MCG study is performed (Table 1c). The design of the MCG has a much larger opening than with an MRI and the patient is not in an enclosed area separated from the technician performing the test as with an MRI, so claustrophobia is a potential but rare possibility (Fig. 1).

8.5.4. Contraindications

There are no contraindications including pregnancy.

9. Discussion: advantages of MCG over other non-invasive cardiac testing (Table 2)

9.1. Avoidance of medications and contrast agents, elimination of dietary restrictions and need for patient participation

As noted, MCG avoids the need for a needlestick and IV catheter, eliminates the risk of contrast and avoids radiation.

Needlesticks are painful and many patients have a needle phobia. Needlesticks also have an associated risk of needlestick injury and there is the risk of disease transmission.

Injection of contrast involves several risks. Extravasation of contract into the skin and subcutaneous tissue can cause local irritation, necrosis, pain, weakness, decreased range of motion, compartment syndrome, extremity deformities and contractures; which may necessitate further treatment including surgery procedures such as surgical debridement, skin grafting and fasciotomy [56–58]. According to the American College of Radiology, "there is no known effective treatment for contrast medium extravasation." [58]

Unlike other forms of NCI that use contrast or medications, there is no possibility of an acute allergic reaction or anaphylaxis with MCG. There is no danger of renal damage, such as worsening renal function with an elevated BUN and creatinine or a contrast-induced nephropathy. There is no risk of nephrogenic systemic fibrosis which can occur with gadolinium-based contrast agents.

MCG has no dietary restrictions, so individuals who have just had coffee, for example, do not have to wait hours before the test can be done. Similarly, there are no medication restrictions so that individuals on beta blockers or other medications don't need to have their medicines withheld so their noninvasive cardiac test can be done.

Unlike many other NCI, patient participation/cooperation is not a prerequisite for MCG. The patient does not need to hold their breath to obtain adequate images. The patient also does not need to be able to exercise, which many individuals are incapable of doing for various reasons ranging from orthopedic or musculoskeletal to pulmonary (e.g., COPD, interstitial lung disease), or even cardiac diseases such as decompensated heart failure.

9.2. Testing advantages: technical issues, decreased testing time, and decreased personnel time

MCG avoids multiple technical issues that are associated with other NCI. There is no need for ECG or respiratory gating. To improve image quality, multiple images or scans over a prolonged time are not averaged, and breath-holding is unnecessary.

In terms of time for the test, MCG is significantly faster than other NCI since the patient test involvement is completed within 5 min, while other NCI modalities take a minimum of 60 min to 4 h. (Table 1a) MCG is a very rapid test, which takes only 90 s to obtain the images and about 5 min for the entire test from set-up to completion. This can be compared to CCTA which can take up to 75 min if an oral beta-blocker is needed to slow the heart rate.

Moreover, the time to test is significantly less for MCG (2.9 h) than the other standard of care (SOC) NCI (22.9 h) [15]. This could convert into better turnaround times (TAT) with shorter lengths of stay (LOS) for patients awaiting NCI in the ED, observation unit or on an inpatient floor. The improved TATs and shorter LOS, creates the possibility of opening more beds for other patients, and lessening ED crowding and boarding.

Personnel considerations are less with MCG. With other SOC NCI,

because of the necessity for the medication administration, often highly trained personnel such as a nurse or an echocardiography technician (for stress echocardiogram) is necessary during the test and at times, a minimum of two personnel is required as with exercise stress testing [28]. With MCG, only one person is needed to perform the test and this individual does not need specialized training as required for nursing, an echocardiography technician, or a nuclear scan technician. This could translate into personnel cost savings needed to perform the test.

9.3. Patient safety and comfort

There are no pregnancy or lactation concerns. Evidence for the safety of MCG is illustrated by the fact that fetal magnetocardiography (fMCG) has been used to detect fetal arrhythmias, such as long QT syndrome, congenital atrioventricular block and several tachyarrhythmias, and cardiac defects. However, because of wider availability and lesser cost, fetal cardiac Doppler ultrasound is still the most widely used modality for diagnosing fetal arrhythmias, although fMCG has also been used to confirm or further elucidate findings on fetal cardiac Doppler ultrasound. It is possible, even likely, that as fMCG becomes more widely available and costs decrease, that fMCG will see wider usage [68–71].

The relative contraindication to MCG is the presence of metal, which results in poor quality images but carries no risk or danger unlike MRI [67]. Claustrophobia is a warning, which also occurs with other NCI including CCTA, and CMRI and can be alleviated with the use of anti-anxiety medications. However, MCG has multiple advantages that have rendered claustrophobia a non-issue. First, unlike an MRI, the patient is in the shielded bore for less than five minutes. Second, the standard bore diameter of an MRI is 60–70 cm versus 97.5 cm in the CardioFlux MCG scanner. Third, the design and set-up of the MCG and MRI are very different. The larger opening of the MCG allows for the patient to look forward and see his/her surroundings in the room versus the nearly complete enclosure of the MRI (Fig. 1). It is almost totally dark with MRI while MCG is in a bright open room. During the MRI, the technician doing the scan is in another area about 10 ft away behind a shield, while the technician doing the MCG is in the same room (within 60–70 cm of the patient). Fourth, the MRI emits loud, clanking noises during the MRI, which can be heard even with earphones that are supposed to block the noise but don't totally block the noise. Moreover, transient haring loss can occur with MRI if headphones or ear plugs are not used [67].

Weight restrictions apply for the CT scan, the MRI scan and the MCG. As with a CT scan or MRI, a patient with marked obesity may not fit in the MCG scanner. The weight restrictions for any CT or MRI scanner generally vary depending on the device and the model. There are industry standard table weight limits [72]. The industry standard table weight limit for CT scanners is 350 pounds (159 kg), although some,

Table 1f
Comparison of MCG with non-invasive cardiac tests: Radiation exposure and cost.

Cardiac test	Radiation exposure[a] CXR equivalent	CPT/HCPCS code[b]	Cost of professional interpretation and supervision[b]	Facility HCPCS code[b]	Cost of facility fees[b]	Total cost[b]
ETT	None	93015 + 93018	$71.90 $13.65	SI B always bundled		$85.55
SE	None	93351 (-26)	$80.56	93351	$526.17	$607.27
DSE	None	93351 (-26) + 93352	$80.56 $34.62	93351 93352 (SI M-not billable)	$526.17	$641.89
cMPI-SPECT	10 mSv ~100 CXRs	78454 (-26)	$62.25	78454	$1354.34	$1416.59
cMPI-PET	3 mSv ~30 CXRs	78942 (-26)	$82.55	78492	$1492.14	$1574.69 Does not include radiopharmaceuticals.
cMRI	None	75559 (-26)	$134.81	75559	$526.17	$660.98
cCTA	3–5 mSv ~30 to 50 CXRs	75574 (-26)	$111.18	75574	$175.24	$286.42
MCG	None	0542T	$0	0541T	$510.68	$520.68

ETT: exercise tolerance test; SE: stress echocardiogram; DSE: dobutamine stress echocardiogram; MPI-SPECT: cardiac myocardial perfusion imaging using single photon emission computed tomography; cMPI-PET: cardiac myocardial perfusion imaging using positron emission tomography; cMRI: cardiac magnetic resonance imaging; cCTA: coronary computed tomography angiography; CXR: chest x-ray; mSv: millisievert.

[a] Radiation exposure in mSv obtained from the Gulait M, Levy P, Mukherjee D, et al. 2021AHA/ACC/ASE/CHEST/SAEM/SCCT/SMR Guideline for the evaluation and diagnosis of CHEST pain: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circ 2021;1344:e368-e454.

One chest x-ray exposes the patient to about O.1 mSv.

[b] The codes and costs are obtained from the Healthcare Common Procedural Coding System (HCPCS), Current Procedural Terminology (CPT) Codes (see acknowledgement).

93015 Cardiovascular stress test using maximal or submaximal treadmill or bicycle exercise, continuous electrocardiographic monitoring, and/or pharmacological stress; with supervision, interpretation and report.

93018 Cardiovascular stress test using maximal or submaximal treadmill or bicycle exercise, continuous electrocardiographic monitoring, and/or pharmacological stress; interpretation and report only.

93351 Echocardiography, transthoracic, real-time with image documentation (2D), includes M-mode recording, when performed, during rest and cardiovascular stress test using treadmill, bicycle exercise and/or pharmacologically induced stress, with interpretation and report; including performance of continuous electrocardiographic monitoring, with supervision by a physician or other qualified health care professional.

93352 Use of echocardiographic contrast agent during stress echocardiography (List separately in addition to code for primary procedure).

78454 Myocardial perfusion imaging, planar (including qualitative or quantitative wall motion, ejection fraction by first pass or gated technique, additional quantification, when performed); multiple studies, at rest and/or stress (exercise or pharmacologic) and/or redistribution and/or rest reinjection.

78492 Myocardial imaging, positron emission tomography (PET), perfusion study (including ventricular wall motion[s] and/or ejection fraction[s], when performed); multiple studies at rest and stress (exercise or pharmacologic).

75559 Cardiac magnetic resonance imaging for morphology and function without contrast material; with stress imaging.

75574 Computed tomographic angiography, heart, coronary arteries and bypass grafts (when present), with contrast material, including 3D image postprocessing (including evaluation of cardiac structure and morphology, assessment of cardiac function, and evaluation of venous structures, if performed).

Modifier 26 indicates the professional component of a service, and includes the physician supervision, interpretation, and report. It does not include the technical component, which is the actual performance of the test.

Table 2
Advantages of magnetocardiography compared to other noninvasive cardiac tests.

Patient safety	• No absolute contraindication • No need for needlestick/intravenous line with needlestick pain and risk of needlestick injuries and infections/ disease transmission • No need for contrast administration with associated risk of contrast extravasation, allergic reaction, anaphylaxis • No need for medication administration whether to slow heart rate or cause vasodilatation etc. which avoids adverse events from medications • No radiation exposure • No need to be NPO (especially important in diabetics with risk of hypoglycemia)
No testing delays	• Can be done in individuals who have recently (<24 h) ingested caffeine (coffee, tea, caffeinated beverages, energy drinks, chocolate) • No need to hold cardiac, blood pressure, or other medications • No need to hold medications such as insulin or oral hypoglycemic drugs in a diabetic • No patient exclusion due to comorbid conditions such as reactive airway disease, asthma, COPD, decompensated heart failure, etc. • No exercise requirement (can be done in individuals with physical or mental limitations that impair their ability to exercise) • No need to hold test for 24 h in those who have smoked or used a nicotine patch
Improved ED turn-around-time and decreased ED and/or observation unit and/or hospital length of stay	• By avoiding testing delays and very short time needed for the test, turn-around-time is faster in the emergency department (ED) observation unit or hospital, and length of stay in the hospital is shorter, thereby decreasing patient exposure to hospital-associated risks (e.g. falls, infection, medication error, etc.) as well as decreasing ED crowding and opening more hospital beds
Less resources needed	• No need for a nurse to be present since no medications administered • No need for a specialized echo technician or nuclear stress test technician or CT scan radiology technician • Need only one person needed to administer the test, unlike some other noninvasive cardiac tests which require at least two personnel to be present
Ease of test administration	• No patient cooperation needed such as for breath holding or exercise • No special patient preparation needed • Extremely short time to complete the test (<5 min for entire test, only 90 s to obtain images)
Other	Can assess for coronary microvascular disease (CMD) or ischemia with no obstructive coronary artery disease (INOCA)

newer, larger CT scanners can accommodate patients weighing up to 680 pounds (309 kg) [72]. The industry standard table weight for MRI is generally 350 pounds (159 kg). However, the bore diameter is the more important factor for the MRI weight considerations. "The typical MRI bore length is typically longer than the gantry length of a CT scanner and patients can become claustrophobic laying inside a long MRI bore." [67] If the bore length is shortened, as with open MRI or a larger opening in a closed MRI, there is a lower field strength and lower image quality [67]. The MCG machine must be able to accommodate up to two and a half times the listed MCG table weight limit (750 pounds or 340 kg) for safety considerations, given a current MCG table weight limit of 300 pounds (136 kg).

The aperture opening may be a more critical factor than the table weight in allowing patients to undergo a CT or MRI scan. The usual CT diameter is 70 cm and up to 85 cm for the standard and bariatric gantry diameters, respectively [72]. The MRI bore diameter has been 60 cm for years, although this does not account for the placement of phased array coils. More recently, some closed bore MRIs diameters are 70 cm [67]. The MRI diameter does not take into consideration phased array coils which are usually placed on top of the patient to improve the scan images. A danger is that patients who are crammed into the MRI bore may suffer minor skin burns at the locations where the skin touches the MRI bore [67].

The opening for the MCG is about 98 cm (actual 97.53 cm), which is much larger than for the CT (typical 70 cm, bariatric 85 cm) or MRI bore diameter 60 cm (actual 59.944 cm), although few more recent MRIs have a bore diameter of 70 cm. This opening is an important factor in alleviating or eliminating claustrophia for the MCG compared to the CT or MRI scanner [67].

The Magneto study found that the mean patient experience on a 5-point Likert scale was significantly better with MCG at 4.7 versus 3.0 for SOC stress testing ($P < 0.0001$) and that the time to test was significantly less ($P < 0.001$) for MCG at 3.18 h (SD 1.91) vs. SOC stress testing 22.71 (SD 15.23) [15].

9.4. Advantages compared to ECG, high sensitivity troponins and other noninvasive diagnostic cardiac testing modalities

Both the ECG and MCG detect the heart's electrical activity, but unlike the ECG, MCG does not require contact with the skin. This non-contact property of MCG eliminates discrepancies caused by fluid or tissue conductivity, resulting in no alterations or distortion as can occur with other non-invasive cardiac tests such as SPECT [73].

There are pitfalls to the sole reliance on hsTn for evaluating chest pain patients. There are many causes of elevated hsTn ("troponinemia") with both noncardiac and non-ACS cardiac etiologies, and false negative high-sensitivity troponins in patients with ACS [74–76]. Chronic kidney disease, sepsis, stroke, chemotherapy, and pulmonary disease, including pulmonary emboli, are noncardiac causes of an elevated hsTn [14,74]. Cardiac causes that are not ACS that may have an elevated hsTn include heart failure and cardiomyopathy [74].

MCG may have a role in evaluating chest pain patients who are risk stratified into the "intermediate" or grey area or those with either elevated or false negative hsTn [77]. In specific patient populations, such as the elderly, the diagnostic accuracy of troponins falls off with a decreased positive predictive value and decreased specificity [13]. It is known that women have a higher incidence of false positive exercise stress tests [22]. MCG might be a valuable alternative to exercise stress testing in women.

MCG compares favorably with other NCI and could be a viable substitute for other NCI in certain situations. For example, CCTA has limitations in those with increased calcification, which is common in the elderly, and decreased sensitivity in individuals with known coronary artery disease and stents [78]. Renal damage from contrast administration is a real concern with some of the other NCI (e.g., CCTA, MPI: SPECT or PET, and cardiac MRI with late gadolinium). The need for medication administration, such as beta blockers and nitroglycerin for CCTA, adds other potential risks.

9.5. Sensitivities and specificities

MCG has comparable sensitivities and specificities with other noninvasive cardiac testing (Table 1e). The multicenter MAGNETO study by Mace et al. reported a sensitivity of 66.7 % and a specificity of 89.9 % for non-invasive stress testing versus the same sensitivity of 66.7 % and a specificity of 57.1 % for MCG [15]. In patients with acute chest pain, the negative predictive value and sensitivity of MCG was double that for ECG, troponin and echocardiography in the Park et al. study [79]. The echo specificity was 76.2 %, PPV 87.9 %, while MCG specificity 84.5 %, PPV 95.2 % (mean for readers 1 and 2) [79]. In the study by Wu et al., sensitivity for SPECT variables was 0.6966 to 0.8889 compared with MCG variables 0.7778 to 0.8611 [80]. In the systematic review and meta-analysis by Agarwal et al. MCG had a sensitivity of 83 % and a specificity of 77 % [81]. A recent systematic review and meta-analysis by Xu et al. found MCG had a sensitivity of 0.91 and a specificity of 0.83 [82]. A more recent study evaluating coronary microvascular dysfunction (CMD) using MCG reported a high sensitivity of 92 % to detect CMD in an ANOCA population when one abnormal MCG feature was detected and a high specificity of 93 % - 98 % when three and four abnormal MCG features were detected [64].

9.6. Limitations

Despite MCG's decades-long existence, its widespread clinical adoption has been limited. Recent advances in sensor technology and computing capabilities now necessitate larger, well-designed clinical trials to validate its efficacy. While studies by Mace, Wu, and others have been conducted, these are primarily feasibility and hypothesis-generating in nature, underscoring the need for more rigorous clinical investigations to fully explore MCG's potential. Robust, well-controlled clinical studies comparing MCG to current standard-of-care modalities are essential to establish its role in clinical practice.

10. Discussion: additional uses of magnetocardiography

Indeed, MCG's earliest clinical application and acceptance may be as an adjunctive diagnostic aid when combined with well validated existing modalities that are anatomical in nature such as CCTA especially in the evaluation of patients whose differential diagnosis includes INOCA. The completion of the on-going Micro2 trial may provide a path for real world clinical application and increased utilization.

In addition to its use for diagnosing myocardial ischemia and infarction [15,64], MCG has shown promise in the diagnosis, prognosis, and monitoring of treatment for other cardiovascular diseases. MCG has been used as a predictor of who can benefit from invasive coronary angiography and to determine if percutaneous coronary intervention (PCI) was successful [83]. MCG has been used for mapping of arrhythmias [84,85]. In patients with heart failure and reduced ejection fraction (HFrEF), MCG has been utilized for predicting which patient will respond to cardiac resynchronization therapy (CRT) and to determine long-term outcomes after CRT [86]. Patients with a malignant early repolarization pattern (ERP) are considered at risk for ventricular fibrillation. MCG has been shown to be an effective tool for distinguishing malignant from benign ERP [87]. In patients with orthotopic heart transplantation (OHT), MCG has been recommended as a non-invasive tool for detecting cardiac allograft vasculopathy [88]. Additional uses of MCG include the diagnosis of heart failure, hypertension, atrial fibrillation, hypertrophic cardiomyopathy [89,90], for diagnostic screening and treatment response for patients with inflammatory cardiomyopathy [91] and for myocarditis [92]. In patients with beta-thalassemia, MCG detected myocardial iron load and predicted adverse cardiac events [93]. In patients with amyloidosis, MCG has been used for monitoring therapy [94]. In pediatrics, fetal MCG has been used extensively over the past decades and has become an additional modality to ultrasound especially because of its safety during pregnancy [68–71].

11. Future studies

HsTn is elevated when there is myocardial injury but it does not detect ischemia. MCG can detect ischemia, which raises the possibility of intervention before infarction occurs [15]. It is recognized that certain patient populations, e.g. elderly and women, have lesser performance or reliability with certain studies, such as hsTn and exercise stress test, respectively. MCG, at present, has not demonstrated lesser performance with specific patient groups.

Questions have been raised about the "economic, ethical and sustainability of cardiac imaging." [95]. Issues related to the responsible use of healthcare dollars, limiting potential damage to patients (e.g., minimizing radiation exposure from medical imaging) and environmental impact have been raised. MCG compares favorably with these concerns in that there is no radiation exposure, the costs of MCG versus other modalities may be less, and there is no need to manufacture isotopes or contrast agents, which may have a lesser impact on the environment. The jury is still out regarding these concerns, although the initial implications appear favorable for MCG.

Most NCI tests are intended to evaluate chest pain patients for obstructive CAD [9,19,96]. What about ischemia with no obstructive CAD (INOCA)? There are no functional or structural epicardial coronary vasculature abnormalities with INOCA. The etiology of INOCA, which is more common in women, is thought to be due to CMD or coronary artery spasm [96]. MCG may better at detecting CMD than the other NCI modalities including stress testing [64].

12. Conclusion

MCG has comparable sensitivity and specificity when compared with other SOC NCI. Moreover, MCG has many advantages over other SOC NCI including patient safety, comfort, ease of testing, patient experience, and time. MCG is a painless and rapid test. MCG can be obtained without dietary or medication restrictions, and patient preparation or cooperation. MCG avoids radiation exposure, contrast administration, and a needlestick with all their associated risks and dangers. There may be a cost saving in terms of time and personnel for obtaining an MCG versus other SOC NCI. Improved TAT and decreased LOS may help alleviate ED crowding and increase bed availability. Unlike hsTn which detects myocardial injury but not ischemia, MCG has the ability to detect ischemia.

Initial studies of MCG show promise, suggesting it may play a more significant role in the future as an additional tool for evaluating patients presenting with chest pain and in the diagnosis, prognosis, and treatment evaluation of various cardiovascular diseases. However, more robust clinical trials are necessary to confirm these initial findings. In its early stages of adoption, MCG may prove to be a valuable adjunct when used in combination with existing modalities. As more research is conducted and real-world experience accumulates, the potential applications of MCG as an NCI technique will be better validated, and additional clinical uses may be identified.

CRediT authorship contribution statement

Sharon E. Mace: Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Christopher Baugh:** Writing – review & editing, Writing – original draft, Data curation. **Margarita E. Pena:** Writing – review & editing, Writing – original draft, Data curation. **Robert Takla:** Writing – review & editing, Writing – original draft, Data curation.

Ethical statement

There was no funding for this article. The article has not been

published previously. The article is not under consideration for publication in any other journal. There are no copyright restraints. SEM conceived the idea for the article. All of the authors contributed to writing and editing of the manuscript.

Declaration of competing interest

The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for *American Heart Journal Plus: Cardiology Research and Practice* and was not involved in the editorial review or the decision to publish this article.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

SEM received a research grant from Genetesis and participated in a Genetesis scientific advisory board.
MEP received a research grant from Genetesis and participated in a Genetesis scientific advisory board.
CWB is a paid speaker for Roche Diagnostics and has previously participated in Roche, Salix Pharmaceuticals, Pfizer, and AstraZeneca advisory boards, consults for Abbott Laboratories, and is an advisor to Lucia Health Guidelines.
RBT is a paid speaker for Janssen and AstraZeneca Pharmaceuticals and is employed by Genetesis as the chief medical officer. RBT is an editorial board member for the journal AHJO.
Robert Takla is an employee of Gentesis.
Robert Takla is a guest editor for American Heart Journal Plus but was not involved in the editorial review or the decision to publish this article.

Acknowledgements

Dr. Michael Granovsky, MD, FACEP, President, LogixHealth, 8 Oak Park Drive, Bedford, MA 01730, for his expertise confirming the data regarding CPT/HCPCS codes and costs in Table 1f.

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