Original Article

Exercise Stress Echocardiography in the Identification of Coronary Artery Disease in the Elderly with Chronotropic Incompetence

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Summary

Background: **Chronotropic incompetence (CTI) is frequent in elderly patients and may limit the role of the exercise test in the identification of coronary artery disease (CAD) in this population.**

Objective: **To assess the value of CTI in an elderly population in the diagnosis of CAD.**

Methods: **A total of 3,308 patients were studied, 804 were elderly individuals (age ≥ 65 years) who underwent exercise stress echocardiography (ESE). Based on the heart rate (HR) reached during the exercise test, were divided into two groups: G1 150 patients who did not reach 85% of the age-predicted HR, and G2 654 patients who did. The groups were compared to clinical characteristics, segmental left ventricular contractility rate (WMSI) and coronary angiography (CAG).**

Results: **Clinical characteristics were similar between the groups. WMSI was higher in G1 than in G2, both at rest (1.09 ± 0.21 *versus* 1.04 ± 0.15) and after exercise (1.15 ± 0.29 *versus* 1.08 ± 0.2) (p < 0.001). Abnormalities in wall contractility were more frequent in G1 than in G2 (55% *versus* 37%; p < 0.05), thus suggesting that elderly with CTI have a higher frequency of CAD. CAG was performed in 69% ESE positive for myocardial ischemia. In the G1 group, 91% of the ESE were true positive *versus* 84.5% in G2, that is, presence of obstructive coronary artery disease (> 50%).**

Conclusion: **CTI is associated with a higher frequency of contractile alterations in the elderly population and adds a positive predictive value to ESE in the identification of patients with obstructive CAD. (Arq Bras Cardiol 2007;89(2):100-106)**

Key words: **Echocardiography, stress; aged; coronary disease.**

Introduction

Individuals with age higher than or equal to 65 years comprise the fastest growing segment of the population. In Brazil, an elderly population greater than 27 million persons is estimated by 2025[1]; currently, coronary artery disease (CAD) is the leading cause of death in the third age.

A high prevalence of structural disease is known to occur (70% according to autopsy studies[2]); however, only 20% to 30% of the elderly have clinical manifestations of CAD. Certain peculiarities of the ischemic disease in the elderly may be attributed to this discrepancy: the presence of "anginal equivalents" (shortness of breath, fatigue, syncope)[3]. Typical effort angina is usually less severe or absent because of the common presence of a sedentary life style and physical and cognitive disabilities and occurs only in half of the coronary disease patients[4]. Silent ischemia is also highly prevalent[5].

Exercise test (ET) is the most frequently used noninvasive test for diagnostic and prognostic assessment of CAD[6]. However, a potential limitation of this method in the elderly population is that chronotropic incompetence (CTI) is highly prevalent in this age bracket and may limit the appearance of ST-segment abnormalities correlated with myocardial ischemia[7]. Nonetheless, CTI, which is defined as a failure to reach 85% of the maximum age-predicted HR[8], is an independent predictor of mortality and incidence of CAD[9-10]. The reasons for this association are not properly explained, although several mechanisms have been proposed, such as: severity of CAD, left ventricular (LV) dilatation, parasympathetic hyperactivity, sinus node dysfunction and ischemia, and advanced age[11-12].

Exercise stress echocardiography (ESE) is a noninvasive method established for the diagnosis and risk stratification of CAD, especially when complete left bundle branch block, left ventricular overload, and preexcitation syndrome are present[13]. The unbalance between oxygen supply and demand leads to myocardial changes that are caused by ischemia, and these alterations occur in a time sequence of pathophysiological phenomena described by Heyndrickx et al[14] and called "ischemic cascade", which is temporally characterized by heterogeneous perfusion, metabolic changes, diastolic dysfunction, regional dyskinesia, electrocardiographic changes, and angina[14]. Therefore, ESE is

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able to detect ischemic alterations earlier than ET. However, the role of ESE in patients who are unable to reach the submaximal HR remains not fully explained. We hypothesize that ESE may bring a significant contribution to this subgroup of patients, since it is more sensitive than conventional ET and able to detect resting segmental LV changes.

The objective of the present investigation is to assess the value of CTI in an elderly population in the diagnosis of CAD using ESE, considering coronary angiography (CAG) as the gold standard for comparative purposes.

Methods

From December, 2000 to October, 2005, 3,308 consecutive patients with known or suspected coronary artery disease were referred to the Laboratory of Echocardiography of *Clínica e Hospital São Lucas* (city of Aracaju, State of Sergipe, Brazil) to undergo ESE. The ethical principles that guide human experimentation were carefully observed, and informed consent was obtained from all patients. The study was approved by the Ethics and Research Committee of *Universidade Federal de Sergipe*.

Patients with unfavorable echocardiographic windows at rest remained in the study, because a considerable number of them showed a significant improvement of this quality parameter in the immediate post-exercise period. If no improvement in the echocardiographic window was observed even in the post-exercise period, the patient was then excluded from the analysis. A total of 66 patients were excluded. Of the 3,308 patients, 804 (24.3%) with age > 65 years and favorable echocardiographic windows were evaluated (elderly group).

For the analysis, the elderly patients were divided into two groups: G1 group – elderly patients who did not reach 85% of the age-predicted HR, and G2 group – elderly patients who reached 85% of the age-predicted HR or above during exercise in an exercise treadmill (Bruce protocol).

In the cardiologic history, the presence or absence of symptoms such as typical or atypical angina, past medical history of CAD, use of medications, and risk factors for CAD were recorded. Hypercholesterolemia was defined as serum total cholesterol levels higher than 200 mg/dl (after a 12-hour fasting), and hypertriglyceridemia as serum triglyceride levels higher than 150 mg/dl (after a 12-hour fasting), or use of lipid-lowering agents (vastatins and/or fibrates). Systemic hypertension was considered when pressure levels taken in the upper limb, at rest, were ≥ 140 x 90 mmHg or when the patient referred the use of antihypertensive medication.

Diabetes mellitus was defined by the presence of fasting glucose levels above 126 mg/dl, or by the use of insulin or oral hypoglycemic agents. Previous myocardial infarction was defined by the past medical history and/or laboratory tests such as electrocardiogram, echocardiogram, and coronary angiography performed earlier.

Single or combined indications for the test were: assessment of chest pain (561 patients), preoperative assessment of noncardiac surgery (23 patients), presence of a positive ET with no clinical characteristics of CAD (293 patients), negative ET with clinical characteristics of CAD (191 patients), stratification of an already established CAD (148 patients), and risk stratification after myocardial infarction (59 patients).

All patients were examined after having a light meal. On the day the patients underwent the test, they avoided any excessive physical activity, and beta-blocker was discontinued four days prior to the test. All the investigation was conducted with the individual breathing spontaneously in room air, at a constant room temperature of approximately 20°C to 24°C.

The study consisted of the performance of a complete clinical investigation (history taking and physical examination) followed by a 12-lead electrocardiogram (ECG) and resting echocardiogram. Next, patients underwent physical exertion on a treadmill and, right after, another echocardiogram was obtained. CAG was indicated for the patients who presented an ESE positive for myocardial ischemia.

Exercise test - All patients underwent ET according to the Bruce protocol, and the exercise was interrupted whenever the maximum age-predicted HR was exceeded, or in the presence of the following signs and/or symptoms: chest pain, shortness of breath, muscle fatigue, hypertension (systolic blood pressure > 220 mmHg), hypotension, presyncope, and severe arrhythmias. During the test, the individuals were continuously monitored with a three-lead ECG.

ET was considered positive for myocardial ischemia when we observed a horizontal or downsloping ST-segment depression, or higher than 1 mm for men and 1.5 mm for women, 80 ms after the J point. In the presence of electrocardiographic changes suggestive of CLBBB, left ventricular hypertrophy, preexcitation syndrome, and use of medication (digitalis), the test was considered nondiagnostic[15].

Exercise stress echocardiography - Echocardiographic study was performed in all participants of this investigation, according to the technical aspects classically described by Schiller et al[16]. Initially, the study was performed using a two-dimensional echocardiography system, with the volunteer at rest, in the absence of any medication, in the left lateral position at 45°, or at an inclination appropriate to obtain satisfactory echocardiographic images in the parasternal (long axis and short axis) and apical (two and four chambers) acoustic windows. This technique was also used for image acquisition right after the exercise, when the HR was still elevated, and in the recovery period.

All images thus obtained were selected and displayed side by side in a quadruple format, to be analyzed comparatively at different HR levels by two skilled echocardiographers from our service, both with level III training, as recommended by the American Society of Echocardiography[17]. Segmental LV wall thickening was quantitatively assessed with a 16-segment model, and rated as: 1 (normal), 2 (hypokinetic), 3 (akynetic), and 4 (dyskinetic).

The wall motion score index, in turn, was obtained by summing up the score of each segment visualized and dividing the amount found by 16, which is the number of LV segments. Individuals were considered normal if all the segments with preserved mobility at rest had a hyperdynamic response after exercise. As regards the type of ischemic response, the ESE was classified as follows: a) ischemic, when an abnormal exercise-induced segmental LV wall motion was present; b) fixed ischemic, when abnormal segmental wall motion was observed at rest, and remained unchanged after exercise and c) fixed and induced ischemic, when exercise worsened the preexisting segmental abnormality or caused the appearance of abnormality in additional LV areas[17].

Echocardiographic records obtained during the experimental session were performed with Hewlett-Packard/ Phillips SONOS 5500 systems equipped with Hewlett-Packard/Phillips 2.5-mHz transducers, and recorded in Sony and Display Video Digital videocassettes.

Coronary angiography (CAG) - CAG was performed in the patients who had an ESE positive for myocardial ischemia, using the Judkins technique, preferably via the right femoral vein[18]. The angiograms thus obtained were analyzed by a skilled hemodynamicist from our service, using a quantitative score system. After undergoing the procedure, these patients were divided into five subgroups: a) normal coronary arteries; b) narrow, tortuous coronary arteries; c) myocardial bridge or coronary spasm; d) coronary stenosis between 30%-50%; and e) coronary stenosis greater than 50%. Therefore, the test was considered positive when an epicardial coronary artery stenosis greater than 50% was detected.

The positive predictive value for each type of positive ESE (ischemic, fixed ischemic, or fixed and induced ischemic) was calculated in comparison to the result of CAG[19].

Statistical analyses were performed using the SPSS 11.5 software program. Quantitative variables were expressed as means and standard deviation, and categorical variables were expressed as number of cases and percentages. The chi-square (χ^2) test was performed for the comparison of positive ESE modalities with the results of CAG, and the odds ratio was used for the associations between variables of HR behavior (G1 and G2 groups) and ESE results. P values < 0.05 were considered significant.

Results

Clinical characteristics - A total of 331 men (41%) and 473 women (59%), with a mean age of 71.04 ± 5.07 years (ranging from 65 to 89 years) was studied. The G1 group was comprised of 150 (18.6%) elderly individuals and the G2 group of 654 (81.4%).

As regards the indications for ESE, a significant difference was only observed when a positive exercise test was performed without clinical characteristics of CAD (p = 0.0001), and a negative exercise test was performed with clinical characteristics of CAD (p = 0.041), and these were more prevalent in the G2 group.

G1 and G2 groups had similar anthropometric measurements (Table 1). Associated or isolated risk factors for CAD were: dyslipidemia, systemic hypertension, diabetes mellitus, tobacco smoking, and a positive family history. No difference

Table 1 - Comparison of the clinical findings in the elderly. G1 = patients who did not reach the submaximal HR; and G2 = patients who reached the submaximal HR ≥ 85% of the age-predicted HR

Clinical findings	G1 (n = 150)	G2 (n = 654)	p
Age	70.6 ± 4.7	72.0 ± 5.6	0.703
Gender (M/F)	69 (46.0%)/81 (54.0%)	262 (40.0%)/392 (60.0%)	0.183
BMI (kg/m²)	27.2 ± 4.5	27.0 ± 4.6	0.675
Asymptomatic	37 (24.6%)	206 (31.5%)	0.101
Typical angina	24 (16.0%)	73 (11.2%)	0.101
Atypical angina	89 (59.3%)	375 (57.3%)	0.656
Hypertension	107 (71.3%)	417 (63.7%)	0.079
Dyslipidemia	117 (78.0%)	484 (74.0%)	0.310
Tobacco smoking	5 (3.3%)	18(2.75%)	0.700
Diabetes mellitus	19 (12.6%)	94 (14.4%)	0.588
Family history	89 (59.3%)	355 (54.3%)	0.262
Previous MI	15 (10.0%)	44 (6.7%)	0.156
Revascularization (MR)	20 (13.3%)	52 (7.9%)	0.037
Angioplasty	17(11.3%)	59(9.0%)	0.383
Use of betablocker	49 (32.7%)	108 (16.5%)	0.001
Use of calcium antagonist	21 (14.0%)	69 (10.5%)	0.227
Use of nitrates	18 (12.0%)	47 (7.2%)	0.051
LBBB	7 (4.6%)	36 (5.5%)	0.681

BMI - body mass index; MI - myocardial infarction; MR - myocardial revascularization; LBBB - left bundle branch block.

was observed in relation to these factors when G1 and G2 were compared.

No significant differences were found between the asymptomatic group, the group with atypical angina, and that with typical angina.

In relation to previous events - myocardial revascularization, percutaneous transluminal coronary angioplasty, previous myocardial infarction, and LBBB, the groups were similar except for myocardial revascularization, which was more prevalent in the G1 group (p = 0.037). The use of beta-adrenergic blockers was more prevalent in the G1 group (p = 0.001) (Table 1).

Exercise test - The mean exercise test duration was 3.9 ± 2.2 minutes in the G1 group, and 5.7 ± 3.34 minutes in the G2 group (p = 0.001). At peak exercise, there was a significant difference in the level of systolic blood pressure achieved (Table 2).

Typical angina was more frequent in the G1 group (p = 0.001). Electrocardiographic changes defined as upsloping, downsloping and horizontal ST-segment depression were more frequently observed in the G2 group (p = 0.001). The frequency of severe arrhythmias (sustained ventricular tachycardia) and simple arrhythmias (supraventricular and ventricular extrasystoles, and nonsustained supraventricular tachycardia) were similar in the two groups, as well as the need for test interruption due to high blood pressure (BP > 220 x 120 mmHg)[20] (Table 3).

The reasons for test interruption were: nonsustained ventricular tachycardia (34 patients), typical chest pain (53 patients), systemic hypertension (111 patients), and shortness of breath (10 patients).

No patients presented complications such as myocardial infarction and/or death.

Exercise stress echocardiography - The G1 group had 45% of normal results and 55% were considered ischemic. The G2 group had 63% of normal results and 37% were considered ischemic (p = 0.001) (Figure 1).

SLVCR was significantly higher in the G1 group both at rest (p = 0.001) and during exercise (p = 0.001) (Table 2).

Among the ischemic responses in the G1 group, 34 (41.0%) were transient ischemic, 28 (33.7%) were fixed ischemic, and 21 (25.3%) were fixed + induced ischemic responses. In the G2 group, 126 (51.4%) were transient ischemic, 79 (32.2%) were fixed ischemic, and 39 (15.9%) were fixed + induced ischemic responses (Figure 2).

The odds ratio for the G1 group was 1.798 (CI =1.346-2.402), and 0.869 for the G2 group (CI = 0.808-0.935). Therefore, in our study, the G1 group elderly had a 2.06 risk of having CAD (CI = 1.44-2.96).

Coronary angiography (CAG) - CAG was performed in patients who had an ESE positive for myocardial ischemia. In

Table 2 - Hemodynamic changes during exercise stress echocardiography (ESE) in the elderly from G1 *versus* G2

	G1	G2	p
Resting heart rate	68.09 ± 14.3	75.6 ± 13.5	0.001
Peak heart rate	107.8 ± 14.0	142.9 ± 15.03	0.001
Baseline systolic blood pressure	129.4 ± 12.25	133.6 ± 41.3	0.018
Peak systolic blood preassure	170.95 ± 19.72	185.01 ± 20.22	0.001
Baseline diastolic blood pressure	81.51 ± 6.62	86.3 ± 13.6	0.199
Peak diastolic blood pressure	84.93 ± 8.04	86.6 ± 9.01	0.020
Resting ejection fraction	0.63 ± 0.085	0.65 ± 0.065	0.253
Resting WMSI	1.09 ± 0.21	1.03 ± 0.12	0.001
Exercise WMSI	1.15 ± 0.29	1.06 ± 0.17	0.001

G1 - Patients who did not reach the submaximal HR and G2 = HR ≥ 85% of the age-predicted HR; WMSI - wall motion score index.

Table 3 - Comparison of clinical and electrocardiographic findings during exercise stress echocardiography in elderly individuals from G1 *versus* G2

	G1	G2	p
Angina	19 (12.6%)	34 (5.2%)	0.001
Hypertension (BP ≥ 220 X 120 mmHg)	15(10%)	96 (14.7%)	0.133
Simple arrhythmia	38 (25.33%)	204 (31.2%)	0.158
Severe arrhythmia	8 (5.33%)	26 (4%)	0.456
ECG Changes	39 (26%)	321 (49%)	0.001

G1 - Patients who did not reach the submaximal HR, and G2 = HR ≥ 85% of the age-predicted HR; BP - blood pressure; ECG - electrocardiogram.

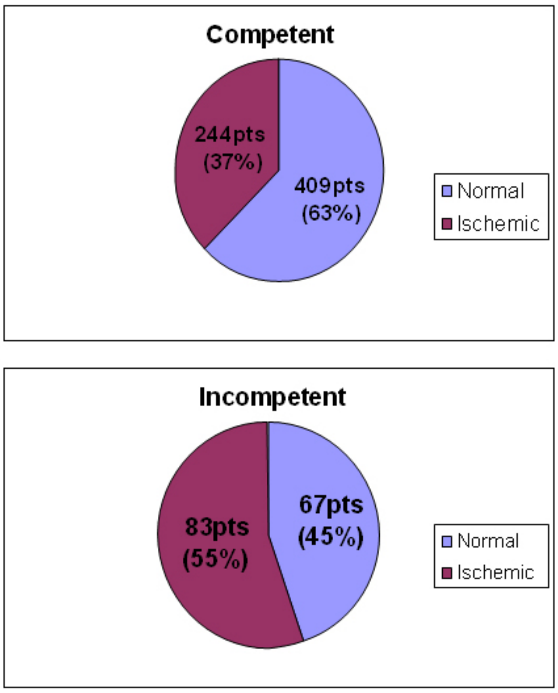

***Fig. 1 -** Prevalence of abnormal test (ischemic) on exercise stress echocardiography in individuals with and without chronotropic competence (p = 0.0001).*

the G1 group, of the 83 patients with an abnormal ESE, 57 (68.7%) underwent CAG; in the G2 group, of the 244 patients with an abnormal ESE, 168 (68.8%) underwent CAG.

In the G1 and G2 groups, 91% and 84.5% of the patients with a positive ESE were considered true positives for myocardial ischemia, respectively (Table 4).

Discussion

CTI is a common finding during exercise tests, especially in the elderly population. Although a recent study[21] had suggested that CTI is an independent predictor of cardiovascular risk, it has not yet been systematically used as a cardiovascular risk marker, and the investigation of CAD is frequently interrupted after this type of finding.

The chronotropic response during exercise reflects a very complex regulation that is correlated with age, functional capacity, resting heart rate, autonomic balance, and severity of coronary stenoses. Several mechanisms are proposed to explain the inability to reach 85.0% of the maximal HR or more during isotonic exercises. In our study, we investigated the hypothesis of the association between CTI and segmental contractility changes at rest and/or during exercise, in addition to assessing its value in the diagnosis of CAD using ESE, in comparison with CAG. We evaluated 804 patients with age equal to or higher than 65 years, and found the following results: a) CTI was associated with a higher prevalence of the three types of ischemic response: transitory ischemic, fixed, and fixed + induced (Figure 2); and b) a lower prevalence of normal echocardiograms in the G1 group (45.0% versus 63.0%; p = 0.001) (Figure 1). These finding have two potential implications: mechanistic and clinical implications.

The first one suggests that, by means of not fully understood mechanisms, the transitory and/or fixed ischemia is associated with a chronotropic deficit during physical activity. The CTI phenomenon was more significantly observed in patients who also presented segmental contractility alterations on resting echocardiography. Some authors suggest that this phenomenon may result from a protective mechanism to avoid an increased MVO_2. This explanation is corroborated by the finding that the blood pressure response is also depressed in this subgroup, that is, the double product (indirect MVO_2 parameter) is reduced.

The second potential implication of our study is that it confirms that ESE is a very useful method to be used in patients who do not reach the submaximal HR. In our case series, 55% of the elderly individuals who did not reach the predicted HR had an abnormal ESE. We should point out that the positive

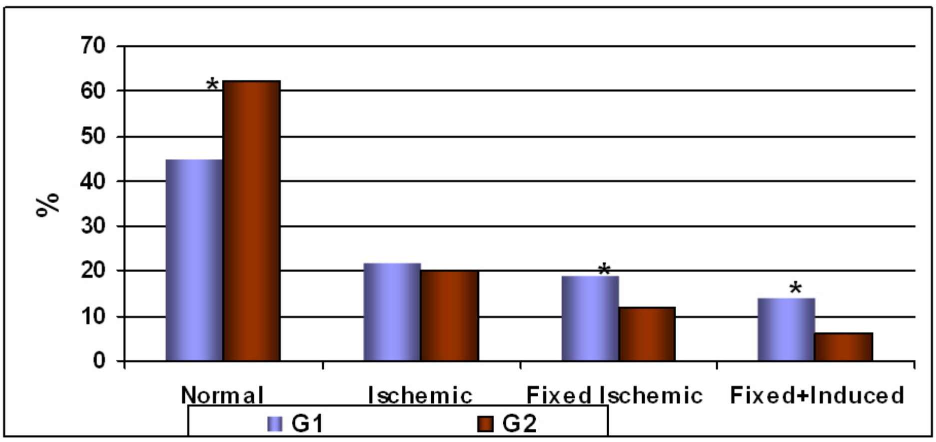

***Fig. 2 -** Exercise stress echocardiography results. Note: *Statistically significant; G1 - patients who did not reach the submaximal HR; G2 = HR ≥ 85% of the age - predicted HR.*

Table 4 - Comparison between coronary angiography (CAG) results of patients with exercise stress echocardiography positive for ischemia in the elderly individuals of G1 *versus* G2

CAG	G1	G2	Total
Normal	1 (1.8%)	6 (3.6%)	7
Tortuous, narrow coronary arteries, or with wall lesions	0 (0.0%)	2 (1.2%)	2
Myocardial bridge or coronary spasm	2 (3.5%)	3 (1.8%)	5
Lesion of 30% – 50%	2 (3.5%)	15 (9.0%)	17
Lesion > 50%	52 (91.0%)	142 (84.5%)	194
Total	57 (100%)	168 (100%)	225

G1 - Patients who did not reach the submaximal HR, and G2 = HR ≥ 85% of the age-predicted HR.

predictive value of ESE in this subgroup was 91%. Therefore, in light of this result, it is important to continue the diagnostic investigation for CAD in elderly individuals who do not reach the submaximal HR on the exercise test.

An interesting point that corroborates our findings on the predictive value of CTI is that we did not find significant differences between clinical variables such as age, baseline heart rate, and prevalence of diabetes mellitus between the two groups. Therefore, in our case series these were not potential confounding factors.

Elhendy et al[22] demonstrated that CTI in patients undergoing ESE is predictive of death and nonfatal myocardial infarction and is associated with the severity of left ventricular dysfunction and extension of myocardial ischemia. This study is consistent with our findings as regards the methodology used and the values obtained in this group of patients.

Azarbal et al[23] demonstrated that the chronotropic response to exercise was a more important marker predictive of cardiac death than the myocardial ischemia observed on positron emission tomography scan for the study of myocardial perfusion. Our findings also demonstrated that patients with more severe CAD were in the G1 group.

A recent study demonstrated that mechanisms such as endothelial dysfunction, increased inflammation markers, and increased natriuretic peptides may suggest why CTI is predictive of cardiovascular risk and increased death[24]. Another study analyzed the chronotropic response to exercise and concluded that it is associated with carotid artery atherosclerosis, regardless of risk factors established for healthy males, and this could contribute to a high incidence of cardiovascular disease in individuals with CTI[25].

A limitation of the present study was the fact that the use of betablockers was more prevalent in the G1 than in the G2 group. Although the agent had been discontinued four days earlier, its residual effect cannot be excluded.

Conclusion

In the assessment of patients with ≥ 65 years of age by using ESE, we suggest that: 1) ESE is a safe and very useful method to assess elderly patients who are not able to reach the submaximal heart rate; 2) CTI frequently observed in the elderly should not be underestimated or deemed physiological; our data suggest that CTI is associated with a higher prevalence of segmental LV alterations, that is, ischemic heart disease; 3) CTI adds a positive predictive value to ESE by identifying patients with obstructive CAD.

These findings should encourage further studies to evaluate whether CTI in other age brackets has the same meaning as that observed in the elderly. In addition, pathophysiological mechanisms involved in this process still remain unclear.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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