

Journal Pre-proof

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PII: S0914-5087(25)00134-0

DOI: <https://doi.org/10.1016/j.jjcc.2025.05.010>

Reference: JJCC 2921

To appear in:

Received date: 26 January 2025

Revised date: 12 May 2025

Accepted date: 21 May 2025

Please cite this article as: S. Kobal, Q. Ciampi, R. Arbucci, et al., Coronary anatomic, functional, and prognostic correlates of ischemic electrocardiographic changes during stress echocardiography, (2025), <https://doi.org/10.1016/j.jjcc.2025.05.010>

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Coronary anatomic, functional, and prognostic correlates of ischemic electrocardiographic changes during stress echocardiography

Sergio Kobal¹, MD, Quirino Ciampi², MD, PhD, Rosina Arbucci³, MD, Angela Zagatina⁴, MD, PhD, Elena Kalinina⁴ MD, Ratnasari Padang⁵ MD, Garvan C. Kane⁵ MD, Hector R. Villarraga⁵, MD, Adelaide M. Arruda-Olson⁵, MD, Jesus Peteiro Vazquez⁶ MD, Alla Boshchenko⁷ MD, Tamara Ryabova⁷ MD, Jelena Celutkiene⁸ MD, Ariel Saad⁹ MD, Francesca Bursi¹⁰ MD, Ana Djordjevic-Dikic¹¹ MD, PhD, Matteo Lisi¹² MD, PhD, Elisa Merli¹² MD, Fiore Manganeli¹³ MD, Clarissa Borguezan-Daros¹⁴ MD, PhD, Hugo Rodriguez-Zanella¹⁵ MD, PhD, Maria Grazia D'Alfonso¹⁶ MD, Fabio Mori¹⁶ MD, Nicola Gaibazzi¹⁷ MD, PhD, Jaroslaw D. Kasprzak¹⁸, MD, PhD, Aytan Safarova¹⁹ MD, PhD, Tatiana Timofeeva¹⁹ MD, PhD, Hugo Mosto²⁰ MD, Karina Wierzbowska-Drabik²¹ MD, PhD, Nithima Chaowalit Ratanasit²² MD, Marco Fabio Costantino²³ MD, Paolo Colonna²⁴ MD, PhD, Tamara Kovačević Preradović²⁵ MD, PhD, Miodrag Ostojic²⁵ MD, PhD, Lauro Cortigiani²⁶ MD, PhD, Albert Varga²⁷ MD, PhD, Aleksandra Nikolic²⁸ MD, PhD, Rosangela Cocchia²⁹ MD, Attila Palinkas³⁰ MD, PhD, Fausto Rigo³¹ MD, Giovanni Benfari³² MD, PhD, Filipa Xavier Valente³³ MD, Dimitrios Soulis³⁴ MD, Yi Wang³⁵ MD, Lixue Yin³⁵ MD, PhD, Jorge Lowenstein³ MD, Diego M. Lowenstein Haber³ MD, Sofia Marconi³ MD, Giovanni Tripepi³⁶, B Sc, PhD, Bruno Villari², MD, PhD, Mauro Pepi³⁷ MD, PhD, Scipione Carerj³⁸ MD, PhD, Patricia A. Pellikka⁵ MD, PhD, Eugenio Picano¹¹ MD, PhD, on behalf of the Stress echo 2030 study group

Affiliations for all co-authors:

1 Echocardiography Unit, Soroka University Medical Center, Beer Sheva, Israel

2 Division of Cardiology, Fatebenefratelli Hospital, Benevento, Italy

3 Cardiognosticos, Investigaciones Medicas, Buenos Aires, Argentina

4 Cardiology Department, Research Cardiology Center “Medika”, Saint Petersburg, Russian Federation

5 Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota, USA

6 CHUAC-Complejo Hospitalario Universitario A Coruna-University of A Coruna, La Coruna, Spain

7 Cardiology Research Institute, Tomsk National Research Medical Centre of the Russian Academy of Sciences, Tomsk, Russian Federation

8 Centre of Cardiology and Angiology, Clinic of Cardiac and Vascular Diseases, Faculty of Medicine, Institute of Clinical Medicine, Vilnius University, State Research Institute Center for Innovative Medicine, LT-03101 Vilnius, Lithuania

9 División de Cardiología, Hospital de Clínicas José de San Martín, Buenos Aires, Argentina

10 Department of Health Sciences, University of Milan, Cardiology Division, ASST Santi Paolo e Carlo, Milan, Italy

11 Cardiology Clinic, University Center Serbia, Medical School, University Clinical Center Serbia, University of Belgrade, Serbia

12 Cardiology Unit, Ospedale per gli Infermi, Faenza, Italy

13 Cardiology Division, Ospedale Moscati Avellino, Avellino, Italy

14 Cardiology Division, Hospital San José, Criciuma, Brazil

15 Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City, Mexico

16 Cardiology Department, Careggi University Hospital, Florence, Italy

17 University of Parma, Cardiology Department, Parma, Italy

18 Department of Cardiology, Bieganski Hospital, Medical University, Lodz, Poland

19 Department of Internal Medicine with a course in Cardiology and functional Diagnostics at the Medical Institute of the Peoples' Friendship University of Russia, Moscow, Russia

20 Hospital Echocardiography Laboratory, Ramos Mejia Hospital, Buenos Aires, Argentina

- 21 Department of Internal Diseases and Clinical Pharmacology, Medical University, Lodz, Poland
- 22 Division of Cardiology, Department of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand
- 23 Cardiology Division, San Carlo Hospital, Potenza, Italy
- 24 Cardiology Hospital, Policlinico University Hospital of Bari, Italy
- 25 Clinic of Cardiovascular Diseases, University of Banja Luka University Clinical Centre of the Republic of Srpska
- 26 Cardiology Department, San Luca Hospital, Lucca, Italy
- 27 Institute of Family Medicine, University of Szeged, Hungary
- 28 Department of Noninvasive Cardiology, Institute for Cardiovascular Diseases Dedinje, School of Medicine, Belgrade, Serbia
- 29 Azienda Ospedaliera Rilevanza Nazionale A. Cardarelli Hospital, Naples, Italy
- 30 Elisabeth Hospital, Internal Medicine Department, Hódmezővásárhely, Hungary
- 31 Villa Salus Foundation/IRCCS San Camillo Hospital, Venice Venezia, Italy
- 32 Department of Cardiology, University of Verona, Verona, Italy
- 33 Department of Cardiology, Hospital Universitario Vall d'Hebron, Institut de Recerca, Universitat Autònoma de Barcelona, Barcelona, Spain
- 34 Kosmoiatriki Medical Center, Athens, Greece
- 35 Department of Cardiovascular Ultrasound and Non-invasive Cardiology, Sichuan Provincial People's Hospital, Chengdu, China
- 36 CNR, Institute of Clinical Physiology, Reggio Calabria, Italy
- 37 Centro Cardiologico Monzino, IRCCS, Milano, Italy, Past-President SIECVI
- 38 Cardiology Division, University Hospital Policlinico G. Martino, University of Messina, Messina, Italy, President SIECVI

Corresponding author: Quirino Ciampi, MD, PhD,

Division of Cardiology, Ospedale Sacro Cuore di Gesù – Fatebenefratelli

Viale Principe di Napoli, 14/A - 82100 Benevento (BN)- Italy

Phone: + 39 0824 771 269 **Fax:** +39082447935

Authors' Email:

kobal@bgu.ac.il, qciampi@gmail.com, rosinaarbucci@hotmail.com, zag_angel@yahoo.com,
lennohka@mail.ru, Padang.Ratnasari@mayo.edu, kane.garvan@mayo.edu,
Villarraga.Hector@mayo.edu, ArrudaOlson.Adelaide@mayo.edu,
Jesus.Peteiro.Vazquez@sergas.es, allabosh@mail.ru, rtr@cardio-tomsk.ru,
Jelena.Celutkiene@santa.lt, arielsaad@gmail.com, francescabursi@gmail.com,
skali.ana7@gmail.com, matteo.lisi@hotmail.com, elisamerli@libero.it, fioreman@gmail.com,
clarissabdaros@cardiol.br, drzanella@gmail.com, mariagrazia.dalfonso@gmail.com,
fabiomori14@libero.it, ngaibazzi@gmail.com, kasprzak@ptkardio.pl, aytensaf@mail.ru,
timtan@bk.ru, hmosto@gmail.com, wierzbowska@ptkardio.pl, nithimac@hotmail.com,
marcofabiocostantino@tiscali.it, colonna@tiscali.it, tamara.kovacevic@medicolaser.info,
mostojic2011@gmail.com, lacortig@tin.it, , varga.albert@med.u-szeged.hu,
nikolicdrsasa@gmail.com, rosangelacocchia@hotmail.com, palinkasa@hotmail.com,
faustorigo@alice.it, giovanni.benfari@gmail.com, filipaxaviervalente@gmail.com, dsoulis@med.uoa.gr,
wangyihdl@126.com, yinlixue_cardiac@163.com, lowensteinjorge@hotmail.com,
lowediego@hotmail.com, sofi_1151@hotmail.com, giovanniluigi.tripepi@cnr.it,
Mauro.Pepi@cardiologicomonzino.it, scipione2@interfree.it, pellikka.patricia@mayo.edu,
eugeniopicano@gmail.com

Graphical abstract**Highlights**

ECG changes may occur during stress, usually as ST-segment depression.

ECG changes are more common with exercise than with pharmacologic stress.

ECG changes indicate greater functional impairment during stress.

Echo positivity is more malignant when ECG changes are present.

RESEARCH LETTER (n=992 words including references and legends)

Ischemic electrocardiographic (ECG) changes (ECG+) can appear during stress echocardiography (SE) with (Echo+) or without (Echo-) accompanying regional wall motion abnormality (RWMA); functional meaning of ECG+ remains unclear (1-2). The aim of this study was to assess the functional meaning of ECG+ (with Echo+ or Echo-) during SE. The 12-lead ECG response was analyzed in 4317 patients (age 64 ± 13 years; 2572 men, 59.6%), 922 patients (21.4%) with a prior myocardial infarction, undergoing SE for chronic coronary syndromes (CCS) prospectively recruited at 39 laboratories between March 2021 and February 2024. ECG response was considered abnormal in case of ST-segment shift >1.0 mm from baseline at 80 ms from the J point developed in ≥ 2 contiguous leads during exercise (n=3028, 70.1%), dobutamine (n = 768, 17.8%), or vasodilator (n=521, 12.1%, dipyridamole in 483 and adenosine in 38 patients) SE.

Wall motion score index (WMSI) was assessed in all patients and coronary flow velocity reserve (CFVR) in 1626. Survival analysis was performed in a subset of 1452 patients at 19 centers with follow-up information.

Results: ECG+ occurred in 641 patients (14.8%, Group 1), with ST-segment depression in 609 and ST-segment elevation in 32 patients. ECG+ showed a higher prevalence during exercise (505/3028, 16.7%) compared to dobutamine (74/768, 9.6%) or vasodilator (62/521, 11.9%) SE ($p < 0.001$; $p = ns$ between dobutamine and vasodilators).

Compared to patients with ECG- (Group 2, $n=3676$, 85.2%), patients with ECG+ showed higher values of peak WMSI (Group 1 = 1.22 ± 0.33 vs Group 2 = 1.12 ± 0.28 , $p < 0.001$) and higher prevalence of abnormal (≤ 2.0) CFVR ($n=1626$; Group 1 = $125/257$ vs Group 2 = $563/1369$; 49% vs 41%, $p=0.025$). There was a graded association between the presence and degree of ST segment changes and functional abnormalities. Particularly, patients with ECG+ and ST changes > 2 mm ($n=196$) compared to those with ECG+ and 1-2 mm ST changes ($n= 445$) showed a higher frequency of inducible RWMA (53% vs 49%) and abnormal CFVR (59% vs 46%, $p < 0.01$).

In the overall population, 3553 showed no RWMA (Echo-). In this subset, 392 (11%) showed ECG+, and 3161 (89%) showed ECG-. Compared to patients with ECG-, those with ECG+ showed more frequent CAD (73.4% vs 66.8%, $p=0.050$), the rest WMSI was similar (1.09 ± 0.24 vs 1.10 ± 0.24 , $p=0.365$), with similar values of peak WMSI (1.06 ± 0.19 vs 1.06 ± 0.18 , $p=0.885$).

During a median follow-up of 387 days (interquartile range 314-603 days), 87 events occurred in 80 patients: 31 all-cause deaths, 24 acute myocardial infarctions, and 32 acute heart failure hospitalizations. Echo+/ECG-, and Echo+/ECG+) was able to identify a pattern of risk progression which was statistically significant both at univariable and multivariable analysis (**Table 1**). The exposure-adjusted event rate was lowest in Echo-/ECG- [2.9 events per 100 person-years (p-yrs)], intermediate in Echo-/ECG+ (4.2 events per 100 p-yrs) and Echo+/ECG- (8.2 events per 100 p-yrs), and highest in Echo+/ECG+ (10.9 events per 100 p-yrs, $p < .001$ vs other groups) (**Figure 1**).

Revascularization was more frequent in patients with positive SE results (70.2% vs 29.8%, $p < 0.001$).

The stress to rest change WMSI was similar in patients with ST elevation compared to those with ST depression (0.16 ± 0.32 vs 0.12 ± 0.23 , $p=0.381$)

Conclusion: In all-comers with CCS, ECG+ during SE is associated with greater functional impairment and worse outcomes in patients with Echo abnormality. ECG and Echo provide complementary and additive clinical information (3). ECG is simple, quantitative, independent of imaging, and always accessible to cardiologists. ECG is interpretable in most patients, though a minority may present with conditions like left bundle branch block or paced rhythms that limit the use of ST-segment analysis (4). Observer dependence is further reduced by automatic readings available in most ECG devices. Therefore, ECG can effectively complement SE by providing additional useful information. However, its diagnostic sensitivity and specificity are limited when used as a stand-alone criterion. Echocardiography, on the other hand, is a bedside, relatively low-cost, and widely available tool. It is radiation-free with minimal environmental impact, though it is operator-dependent (5). Combining the two modalities (ECG and Echo) can provide additional clinical insights at no extra cost.

The study protocol did not alter routine practice, allowing sites to select the stress modality based on local protocols, patient contraindications, physician preferences, and drug availability and cost. All stress modalities provide comparable accuracy when performed with state-of-the-art protocols. However, exercise is the most physiological, dobutamine is preferred for concomitant viability testing, and vasodilators are favored for coronary flow reserve assessment (2).

References

1. Pellikka PA, Arruda-Olson A, Chaudhry FA, Chen MH, Marshall JE, Porter TR, et al. Guidelines for Performance, Interpretation, and Application of Stress Echocardiography in Ischemic Heart Disease: From the American Society of Echocardiography. *J Am Soc Echocardiogr.* 2020; 33:1-41.

2. Picano E, Pierard L, Peteiro J, Djordjevic-Dikic A, Sade LE, Cortigiani L, et al: The clinical use of stress echocardiography in chronic coronary syndromes and beyond coronary artery disease: a clinical consensus statement from the European Association of Cardiovascular Imaging of the ESC. *Eur Heart J Cardiovasc Imaging*. 2024; 25: e65-e90.
3. Daubert MA, Sivak J, Dunning A, Douglas P S, Coyne B, Wang T Y, et al. Implications of Abnormal Exercise Electrocardiography With Normal Stress Echocardiography. *JAMA internal medicine*, 2020; 180: 494–502. <https://doi.org/10.1001/jamainternmed.2019.6958>
4. Cerracchio E, Campagnano E, Villari B, Ciampi Q. The revival of the electrocardiogram in the stress imaging era: what European Society of Cardiology 2024 guidelines say (and don't say). *Explor Cardiol*. 2025;3:101256. <https://doi.org/10.37349/ec.2025.101256>
5. Picano E, Ciampi Q, Arbucci R, Cortigiani L, Zagatina A, Celutkiene J, et al. Stress Echo 2030: the new ABCDE protocol defining the future of cardiac imaging. *Eur Heart J Suppl*. 2023; 26;25(Suppl C): C63-C67.

FIGURE LEGEND

Figure 1: Exposure-adjusted event rates (events per 100 persons-year) in the 4 groups: Echo-/ ECG-; Echo-/ ECG+; Echo+/ ECG-; Echo+/ ECG+

Table 1. Univariable and multivariable Cox regression analyses of hard events.

Variables	Univariable		Multivariable	
	HR (95%CI)	<i>P</i>	HR (95%CI)	<i>P</i>
Age (<i>years</i>)	1.041 (1.018-1.064)	<.001	1.036 (1.013-1.061)	.001
Sex (<i>male</i>)	1.601 (0.983-2.707)	.058		
Hypertension (%)	1.547 (0.855-3.005)	.142		
Beta-blockers therapy (%)	1.326 (0.840-2.091)	.226		
Diabetes mellitus (%)	1.540 (0.944-2.512)	.084		
Prior MI	1.893 (1.206-2.972)	.006		
LV EF at rest	0.959 (0.940-0.979)	<.001	0.954 (0.931-0.977)	<.001
Echo-/ECG-	1		1	
Echo-/ECG+	1.560 (0.648-3.757)	.321	1.864 (0.766-4.536)	.170
Echo+/ECG-	2.611 (1.555-4.395)	<.001	2.267 (1.292-3.977)	.004
Echo+/ECG+	5.438 (2.352-12.573)	<.001	3.287 (1.743-6.201)	<.001

ECG+, electrocardiographic changes present; ECG-, electrocardiographic changes absent; LV EF, left ventricular ejection fraction; MI, myocardial infarction

Running title: The value of ECG in the stress echo era

Disclosures: The Authors have no conflicts of interest to disclose

Funding: Unrestricted funding from Società Italiana di Ecocardiografia e Cardiovascular Imaging (SIECVI).

Word count (n= 992 words, including references, figure legends, and tables)

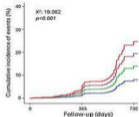
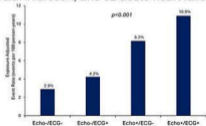
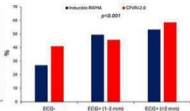
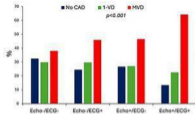
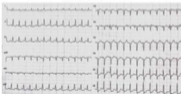
N=4317 patients
 SE for chronic coronary syndromes
 prospectively recruited by 39 laboratories
 ECG+= 647 patients (14.8%)

Median follow-up time: 387 days
 End points: 87 spontaneous hard events in 80
 patients: 31 all-cause deaths, 24 acute
 myocardial infarction, and 32 acute heart failure.

Rest



Stress



ECG Status	0	365	730
Echo-/ECG-	917	594	128
Echo-/ECG+	119	65	12
Echo+/ECG-	378	224	21
Echo+/ECG+	138	101	9

Graphical Abstract

Graphics Abstract

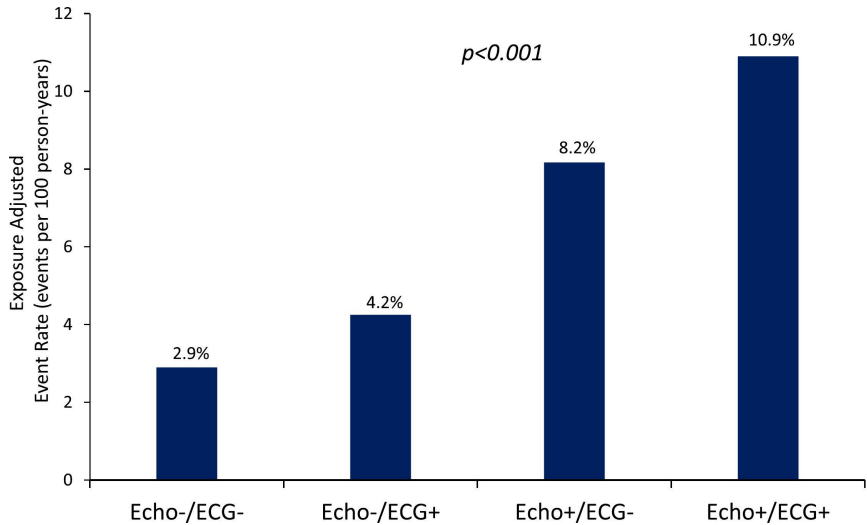


Figure 1