Rise and fall, and provisional rebirth of exercise stress testing at the dawn of the third millennium

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The use of electrocardiographic (ECG) changes recorded during exercise stress testing to diagnose ischemic heart disease has a long history. Feil and Siegel in 1928 described changes in ST-segment and T-wave in patients with known angina pectoris during chest pain induced by after repeatedly sitting and standing up, and its regression after cessation of the activity or the administration of nitroglycerine medication.¹ Subsequently, several authors^{2–4} demonstrated the usefulness of analyzing ECG changes before and after exertion for the detection of myocardial ischemia. In 1956 Robert Bruce⁵ implemented an exercise protocol useful to functionally classify subjects according to New York Heart Association criteria. This protocol initiated the contemporary era of exercise testing, and many of the stress test protocols currently utilized for diagnostic, as well prognostic purpose are based on modifications of those described by Bruce. From the late 1970s, the application of Bayesian Analysis to exercise stress test contributed significantly to improving the accuracy of the test and now many guidelines rely on pre-test likelihood of coronary artery disease (CAD) to select the more appropriate diagnostic test.^{6–8} With the development of radionuclide techniques that permit imaging the myocardium or the left ventricular (LV) blood pool at rest and, most importantly, during exercise, exercise

stress test entered a new era, but significantly increased cost and introduced a radiation burden.⁹

GUIDELINES AND ECG STRESS TESTING FOR ASSESSMENT OF CAD

Starting from the second half of the 1960s, the ECG stress testing was increasingly used as a non-invasive, cost-effective method to evaluate CAD. However, something has recently changed in the experts' consensus. In fact, the 2013 European Society of Cardiology (ESC) guidelines on stable CAD recommended exercise ECG as the initial test to establish a diagnosis of stable CAD in patients with symptoms of angina and intermediate pre-test likelihood of CAD (15% to 65%), free of anti-ischaemic drugs, unless they cannot exercise or display ECG changes that make the ECG non-evaluable.¹⁰ Similarly, the 2012 American College of Cardiology/American Heart Association guidelines recommended with a Level of Evidence A exercise ECG testing for patients with an intermediate pre-test probability of CAD who have an interpretable ECG and at least moderate physical functioning or no disabling comorbidity.¹¹ However, the recent ESC 2019 guidelines downgraded the role of exercise stress test alone and state that “exercise ECG may be considered as an alternative test to rule-in or rule-out CAD only when other non-invasive or invasive imaging are not available,” and “exercise ECG is recommended for the assessment of exercise tolerance, symptoms, arrhythmias, BP response, and event risk only in selected patients.”¹² The 2019 ESC guidelines also state that it may be beneficial to assess non-invasively for silent ischemia asymptomatic patient every 3 to 5 years, preferably applying stress imaging, while coronary computed tomography angiography should not be used for follow-up of patients with established CAD given the lack of functional information related to ischemia but only for evaluation of CABG patency.¹² The recent NICE guidelines state that exercise ECG may be used

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instead of functional imaging for subjects with confirmed CAD but not for people without known CAD.¹³

DIAGNOSTIC AND PROGNOSTIC VALUE OF EXERCISE LEVEL

Beyond ST-segment depression, exercise stress test provides other valuable diagnostic and prognostic information. They include exercise capacity, chronotropic response, heart rate recovery, blood pressure response, and scores such as the Athens QRS score and the Duke Treadmill Score. However, among the various parameters one of the most important is the functional capacity assessed as metabolic equivalents (METs).¹⁴ A MET is defined as the resting metabolic rate, is ~ 3.5 mL O₂/kg/min (1.2 kcal/minutes for a subject of 70 kg). Despite the reliability of this parameter for assessing the functional capacity has been questioned,¹⁵ in particular in CAD patients,¹⁶ the MET concept is a practical, and easily understood procedure for expressing the energy cost of physical activities, to be included in the final report of an exercise stress test.

Previous studies evaluated the added prognostic value of myocardial perfusion imaging (MPI) over exercise ECG stress testing alone in individuals reaching a workload of ≥ 10 METs.^{17–21} In a first study, Bourque et al.¹⁷ found that the achievement of ≥ 10 METs was associated with a very low prevalence of $\geq 10\%$ LV ischemia on MPI. No patient (31% of overall study population) achieving $\geq 85\%$ of maximal predict heart rate and ≥ 10 METs without exercise ST-segment depression had this degree of ischemia by SPECT. The Authors concluded a strategy avoiding that further risk stratification with MPI in subjects achieving $\geq 85\%$ of their maximum age-predicted heart rate and ≥ 10 METs without ischemic ST-segment depression would be appropriate and cost savings. In a subsequent study,¹⁸ the same group aimed to prospectively evaluate mortality and non-fatal cardiac events in patients at either intermediate pre-test risk for CAD or patients with known CAD, achieving ≥ 10 METs regardless of peak exercise heart rate. These patients had very low rates of cardiac mortality, non-fatal MI, and late revascularization, irrespective of heart rate achieved. Cardiac events did not correlate with abnormalities on the index MPI study. The results suggest that patients who attain ≥ 10 METS during exercise stress have an excellent prognosis over an intermediate term of follow-up, regardless of peak exercise heart rate achieved, questioning the added value of MPI to standard exercise ECG testing in these subjects.¹⁸ In diabetic patients, Bourque et al.¹⁹ found that only 1.8% of patients able to reach 10 METs of exercise workload had a $\geq 10\%$ LV ischemia. It should be considered that In this study, only 197 of 570 patients

(34.6%) underwent exercise stress, and during a median 4.4 years follow-up there were only 8 events in the exercise subgroup versus 49 events in the pharmacological stress patients. Thus, exercise variables were not considered in the Cox model. In a further investigation, using two different METs cut-off, Padala et al.²⁰ found that, despite significant perfusion defects, diabetic patients who achieve ≥ 5 METs during stress MPI have a low risk of cardiac events with an annual event rate of 1.1% person-years and those reaching ≥ 10 METs have an annualized event rate as low as 0.9% person-years, respectively. The Authors concluded that exercise level reached during stress MPI is a surrogate for outcomes in diabetic patients undergoing nuclear stress imaging testing.²⁰ In this study, non diabetic patients achieving ≥ 5 METs during stress MPI have a risk of cardiac events of 0.4% person-years. Interestingly, it has been reported that a substantial proportion of adults ≥ 65 who undergo exercise SPECT MPI can achieve ≥ 10 METS and these subjects have low rates of significant LV ischemia and subsequent cardiac events.²¹ However, it should be noted that 5 METs are reached at the first stage and 10 METs at the third stage of a treadmill test with the Bruce protocol, while using a bicycle ergometer 10 METs are difficult to reach for subjects > 80 kg. In fact, considering the relation between METs and watts when exercising on a bicycle ergometer: METs = $((1.8 \times \text{watts} \times 6)/\text{kg} + 7)/3.5$, subjects of 90 kg need to exercise to at least 240 watts to reach 10 METs.¹⁴

Overall, these results^{17–21} suggest that subjects who achieve ≥ 10 METs on exercise testing in the absence of signs of stress-induced myocardial ischemia have a good prognosis and that the value and cost-effectiveness of MPI over standard exercise ECG testing in these patients is questionable. Thus a “provisional tracer injection protocol” has been proposed in which a patient would not have the tracer administered intravenously if ≥ 10 METs was achieved without symptoms and with a negative stress ECG response,²² a protocol that warrants further consideration and prospective assessment.²³

METS AND MPI IN PATIENTS WITH KNOWN CAD

The incremental prognostic value over ECG stress testing alone specifically in patients with known CAD who achieved ≥ 10 METs has not been previously investigated. To overcome this shortcoming, in a retrospective study Peclat et al.²⁴ evaluated the prognostic value of myocardial perfusion imaging (MPI) in 926 patients with known CAD and high exercise capacity. After the index test, patients were followed for a mean of 32.4 ± 9.7 months for the occurrence of a combined

end-point of all-cause death or non-fatal myocardial infarction (MI). Cardiac workload < 10 METs and abnormal MPI scan were independent predictors of hard events. The patients achieving ≥ 10 METs were younger, predominantly male, and had lower prevalence of cardiovascular risk factors and had a lower event rate compared to those achieving < 10 METs (1.13%/year vs 3.95%/year, $P < .001$). Interestingly, among patients who achieved ≥ 10 METs, those with normal scans had a very low rate (0.57%/year), lower than those with abnormal scans (3.37%/year, $P = .023$). From this study it appears that MPI is able to stratify patients with known CAD achieving ≥ 10 METs for the occurrence of all-cause death and non-fatal MI. If the results of this study can be generalized to all patients with known CAD it remains to be determined. In fact, the study population investigated by Peclat et al.²⁴ seems rather unique, perhaps not representative of all patients with CAD known as a whole, due to the a high prevalence of previous coronary revascularization and, nevertheless, a low incidence of events during follow-up. From Table 1 of Peclat et al.²⁴ study it appears that almost all patients (356/384, 93%) achieving ≥ 10 METs had previous percutaneous coronary intervention (PCI) vs 253/542 (47%) of those achieving < 10 METs (χ^2 211, $P < .001$). Moreover many of PCI patients also underwent coronary artery bypass graft (CABG). The Authors did not include previous revascularization as a potential predictor of hard events, thus we cannot exclude that this covariate is significantly associate with the clinical outcome. It is also a pity that the authors did not report how much time has elapsed since the last PCI or CABG before performing the stress MPI, in particular in the large subgroup of asymptomatic patients. In fact, it has been demonstrated that, after PCI, MPI results are useful to quantify the event risk and its temporal variation.²⁵ On the other hand, MPI screening in the initial post-CABG period is not routinely recommended and current guidelines do not support the use of routine imaging with either exercise or pharmacologic stress testing in asymptomatic patients within 5 years post-CABG.¹¹ Also the appropriate use criteria define stress testing early after coronary revascularization as either “rarely appropriate” or “uncertain benefit” while stress MPI performed 5 years after CABG is considered useful to stratify patients at higher risk of cardiac events.^{26,27}

An aspect of this study that deserves consideration is the low prevalence of inducible ischemia and of chest pain during the stress test. Accordingly, not only the presence of ST-segment depression but also the summed difference score were not predictive of events. For the ECG stress test data, this result is in line with the prospective study of the second Medical, Angioplasty, or Surgery Study (MASS II), a randomized clinical trial

designed to compare the long term effects of optimal medical therapy, PCI, or CABG in patients with stable multivessel CAD and preserved systolic ventricular function.²⁸ In this study, the presence of exertional angina or ST segment depression at 0.08 seconds after the J point were not associated with the occurrence of cardiovascular events during a 10-year follow-up. However, in the Acampa et al. study²⁵ at parametric Weibull survival analysis the presence of inducible ischemia on stress MPI performed 12 to 18 months after the index PCI was associated with an increased, accelerating risk of cardiac events.

In the study of Peclat et al.²⁴ the prognostic value of MPI appears to be driven mostly by the presence and, perhaps, extension of scar, despite the lack of predictive value of LV ejection fraction. The Authors do not mention how many patient had an implantable cardioverter defibrillator or a sudden death, thus it is not known whether the presence of necrosis was in any way related to arrhythmic events. Also the impact of early or late coronary revascularization after the index MPI study was not evaluated, and it has been demonstrated, considering revascularization as a time-dependent covariate, that both the degree of stress-induced ischemia and LV ejection fraction predict the effect of revascularization on outcome in patients with suspected or known CAD.²⁹ Finally, the Authors do not clarify if stress MPI was able to further stratify patients achieving < 10 METs. On the other hand, it is conceivable that other parameters obtainable from stress MPI can provide incremental prognostic information.^{30–32}

CONCLUSIONS

In conclusion, despite its limitations, the study of Peclat et al.²⁴ contrasts the hypothesis that an ECG exercise test can be performed alone in patients with good functional capacity and seems to confirm the recommendations of recent guidelines^{12,13} to always associate an imaging test to exercise ECG, even in patients with known CAD.

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