Review Article

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# Sixty years of the Bruce protocol: reappraising the contemporary role of exercise stress testing with electrocardiographic monitoring

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**Abstract** The cardiovascular response to exercise has long been a focus of interest. Over a century ago, the first descriptions of electrocardiographic changes occurring during exercise highlighted the possible relevance of this dynamic assessment. In this background, the inception of the Bruce protocol circa 60 years ago allowed for a major leap in this field by providing a standardized framework with which to address this issue, by means of an integrated and structured methodology. Since then, exercise stress testing with electrocardiographic monitoring (ExECG) has become one of the most widely appraised tests in cardiovascular medicine. Notably, past few decades have been profoundly marked by substantial advances in the approach to cardiovascular disease, challenging prior notions concerning both its physiopathology and overall management. Among these, the ever-evolving presentations of cardiovascular disease coupled with the development and implementation of several novel diagnostic modalities (both invasive and noninvasive) has led to a shifting paradigm in the application of ExECG. This technique, however, has continuously shown to be of added value across various momentums of the cardiovascular continuum, as depicted in several contemporary guidelines. This review provides a pragmatical reflexion on the development of ExECG, presenting a comprehensive overview concerning the current role of this modality, its challenges, and its future perspectives.

**Keywords:** cardiovascular prevention, electrocardiography, exercise testing

## Introduction

Throughout the decades, substantial improvements have been made in the management of cardiovascular disease (CVD), stemming from advances from a wide range of areas encompassing preventive, diagnostic, and therapeutic modalities.[1-4] Although these have continuously changed the landscape in cardiovascular medicine, these pathologies, nonetheless, still comprise a major cause of morbidity and mortality worldwide.[1,5] As such, the quest for strategies to address CVD remains an area of great interest.[3,6,7] While, as stated above, the contribution from diverse fields should be highlighted as being central to current concepts regarding CVD (across its various presentations), the advent of different diagnostic modalities has been instrumental for both enhancements on the understanding of its physiopathology and in overall improvements in patient care.[7-10]

A major milestone in cardiovascular medicine pertains to the introduction of the electrocardiogram (ECG).[3,11,12] Building on previous studies, this technology, providing a graphical representation of cardiac electrical activity, was first introduced more than a century ago.[11,12] Since then subsequent improvements have rendered it fundamental across several CVDs, from ischemic heart disease (IHD) to rhythm and conduction disorders.[12-16] This concept has since been incorporated in other methodologies such as heart rhythm monitoring and the assessment of the cardiac response to exercise, with technological developments allowing for novel insights.[15,17,18] Notably, already in the early days of its use, the electrocardiographic response to exercise was a focus of interest.[19-21] Since these first descriptions, different protocols were applied to provide a dynamic overview of the cardiovascular system during exercise.[19,20] Among these, the Bruce protocol, first introduced 60 years ago, was to be particularly important.[22,23]

This review provides an overview on the development of exercise stress testing with electrocardiographic monitoring (ExECG) with the background of the Bruce protocol while discussing the contemporary role of this test, its challenges, and future perspectives.

## Exercise and CVD

Exercise has a major impact on the cardiovascular system, both acutely and chronically.[24-28] Albeit a detailed account of the myriad cardiovascular adaptations to exercise is beyond the scope of this review, a brief discussion of its acute effects should be recalled when exploring exercise stress testing.[29-32]

During acute (aerobic) exercise, there is a progressive increase in cardiac output (CO) in the background of a diverse and integrated physiological response, encompassing changes in the heart and vessels per se as well as those in the respiratory (such as

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increases in ventilation), musculoskeletal (with increases in muscle contraction), and autonomic nervous systems.[24,30,33] These are reflected in increases in both heart rate (HR) and stroke volume (determinants of CO).[30,33] Given these phenomena, systolic blood pressure (BP) is expected to increase during exercise, whereas diastolic BP is predominantly maintained (with slight changes being considered within the range of normality).[31,34] Importantly, these responses to exercise can vary in their magnitude because of several factors (among which age and genetic background).[35,36] Furthermore, these can also be modulated by the effects of training and be disrupted by pathological processes or medications.[17,26,33,37,38] During ExECG, these responses may be monitored, providing insights into the cardiovascular response and being of relevance (as detailed below) in various clinical settings.[15-17,26,39-41] For example, for HR monitoring, its response can be of use when considering chronotropic incompetence as a cause of effort intolerance.[15] As for BP, an inability of systolic BP to increase (or a decrease during exercise) may be a harbinger of increased risk in entities ranging from aortic valve disease to hypertrophic cardiomyopathy.[26,37,42] On the other hand, although not recommended for the routine assessment of arterial hypertension (because of limitations such as lack of standardized definitions and methodology and the possible influence of cardiorespiratory fitness [CRF] levels), an exaggerated BP response to exercise can suggest an increased risk for the development of hypertension and thus lead to further monitoring.[33,43-45]

Of note, the incorporation of ventilation and gas exchange data into ExECG (i.e., cardiopulmonary exercise stress testing [CPET]) provides a plethora of information, allowing a detailed objective analysis of functional capacity and of factors leading to potential exercise intolerance, being a pivotal test in settings ranging from exercise prescription to the assessment of heart failure.[34,46-50] While CPET continues to evolve and encompass applications across a range of areas, the use of ExECG (i.e., without gas exchange parameters) may still provide crucial information in the assessment of CVD (Fig. 1).

## Exercise stress testing with electrocardiographic monitoring: contemporary paradigm

### *Overview*

The interaction between exercise and CVD has long been a focus of interest.[20,23,51-53] Over a century ago, observations were made that patients with CVD could present ST segment changes in the ECG, namely during physical effort, thus creating a base on which further study would ensue.[20,21,23,53] Although pioneering works attempted to provide a framework for this assessment, a breakthrough occurred with the development of what would go on to become one of the most widely appraised tests in cardiovascular medicine, the use of ExECG with the Bruce protocol.[20,22,23] First presented by the late Robert Arthur Bruce (who, among other achievements, was to be the first chief of Cardiology at the University of Washington School of Medicine, now sometimes being recalled as the Father of Exercise Cardiology) and colleagues, this protocol provided a standardized rigorous methodology for the dynamic assessment of CVD.[22,23,52,54,55] Among some of its strengths, the presence of multiple stages (in comparison with a single-stage approach), the assessment of various participants (to develop standards for subsequent findings), and the multiparametric approach should be recalled.[23,54] Although possible pitfalls in subgroups such as the elderly, obese, and pediatric populations coupled with limitations such as the concept that relatively large increments between stages might lead to difficulties in estimating functional capacity and the fact that other protocols have since been introduced, this was, nevertheless, instrumental in this field.[23,52]

Since the introduction of what would mature into the "Bruce protocol," many changes in CVD, including its presentations and assessment, have elapsed.[1,2,5,56] While the central role of the twelve-lead ECG (without an associated exercise component) in settings such as acute chest pain or when considering rhythm disturbances and interventions (such as cardiac resynchronization therapy) are consensual, the utility of ExECG has undergone substantial changes.[4,13,15,16,39,57,58] These resonate deeply with current recommendations regarding chronic coronary syndromes where the utility of ExECG in the diagnosis of IHD has progressively been superseded by imaging modalities because of issues related to both sensitivity and specificity.[4,16,59,60] Interestingly, while data reinforce the limitations of this examination in the assessment of suspected IHD (a hitherto classical indication), contemporary guidelines also acknowledge the potential of ExECG in several scenarios (Fig. 1).[4,15,16,26,39,40,42,57,61,62]

### *IHD*

Although the diagnostic assessment of IHD is a classical indication of ExECG, as detailed above, there are increasing data attesting to its limitations.[4,16,52,63,64] In this regard, a seminal meta-analysis showed a better performance of imaging modalities when compared with ExECG, with the latter having a limited ability in diagnosing or ruling out anatomically significant coronary artery disease (CAD).[65] These are illustrated in the guidelines of the European Society of Cardiology (ESC), which have downgraded ExECG for diagnostic purposes (presenting a class IIb, level B recommendation) when compared with its

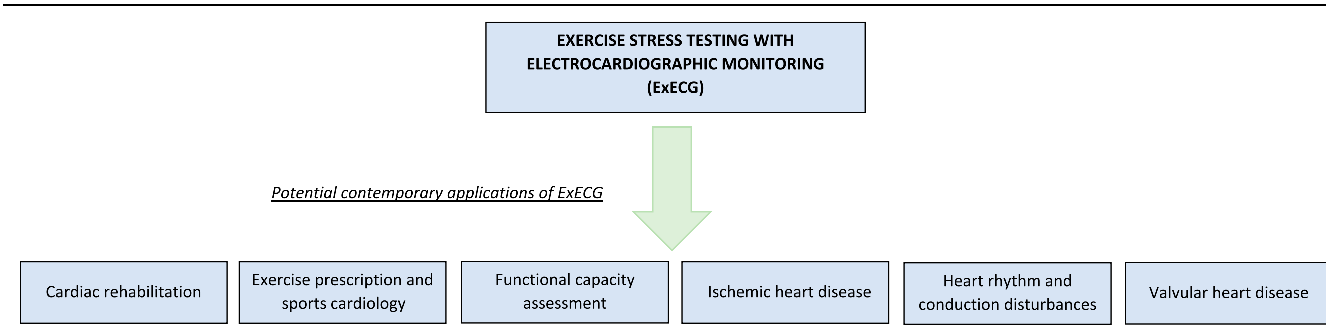


**Figure 1.** Overview of some of the potential applications of exercise stress testing with electrocardiographic monitoring.

previous iteration.[16,58] Similarly, British recommendations also underscore the use of imaging (notably computed tomography) in the diagnosis of CAD.[66] Albeit this, the ESC guidelines showcase the role of ExECG in those with suspected CAD to assess parameters such as arrhythmias, BP response, exercise tolerance, and symptoms while also considering that it could be of use for risk assessment in selected patients (as a class I, level C recommendation).[16]

American guidelines on chest pain, on the other hand, while also highlighting the role of imaging modalities, nonetheless, present a relatively broader applicability of ExECG in the diagnosis of CAD.[57] In the setting of stable chest pain in intermediate-high risk patients without prior CAD diagnosis, ExECG may be used in those able to exercise and with an interpretable ECG (class IIa, level B-R recommendation), although imaging modalities are still preferred (class I, levels of evidence A to B-R).[57] For those at low risk, ExECG may also be considered (class IIa, level B-NR recommendation).[57] Recently, a report on multimodality appropriate use criteria in the setting of chronic coronary syndromes has also detailed some possible uses of ExECG.[4] These also detail some of the possible uses of ExECG in chest pain assessment while highlighting its utility in scenarios such as arrhythmia and exercise assessment.[4] Notably, this possible ancillary role of ExECG is also echoed in American guidelines for patients with chronic coronary syndromes.[67]

Some hindrances should be acknowledged when considering the use of ExECG in the assessment of suspected CAD.[16,57,63,68,69] First, technical issues such as ECG quality or baseline abnormalities (including left bundle branch block or ventricular pacing, both of which could affect interpretation) should be considered.[26,52,57] Second, the use of medications (namely anti-ischemic agents) as well as pathologies such as anemia and valvular heart disease may influence repolarization findings.[70] Moreover, workload levels performed and ensuing HR should also be taken into consideration.[17,70,71] Third, there are still some questions regarding the overall use of ExECG in different subgroups.[68,69,71] Although different studies support the added value of imaging in the face of ExECG, two randomized controlled trials showed that in women at low and moderate risk (respectively), an ExECG-based strategy provided similar efficacy to one based on imaging (with nuclear and echocardiographic assessments, respectively).[63-65,68,69] Finally, data have emerged showing that ECG abnormalities may be associated with an increased risk of events in those with normal imaging findings.[72,73] Although further data are needed to fully clarify these findings, and the fact that factors such as functional capacity and BP should also be equated, these, however, show that there are still unmet issues relating to this technique.[72-75]

As shown above, ExECG may still be of use in the diagnostic process of selected patients with suspected CAD.[4,16,57] Albeit this, in this setting, its role has progressively focused on providing a comprehensive assessment able to detail relevant ancillary data regarding several facets of the cardiovascular response to physical effort.[16,59,60]

### Cardiac rehabilitation and exercise prescription

Given its integrative nature, ExECG may be particularly relevant in the evaluation of the exercise response in patients with CVD.[4,16,26,76,77] This encompasses the detection of possible cardiovascular abnormalities (for symptoms, but also arrhythmias and the BP response) while also allowing for an objective measure of the individual's functional capacity.[26,78,79] In addition, an exercise test is also paramount for exercise prescription.[26,48,76,77] While, for this latter point, it has been well-explored that CPET can be of major value for a physiological approach to prescription (by allowing, among others, assessment of the ventilatory thresholds), ExECG may still be relevant (namely in contexts without access to CPET).[48,76] Though with its limitations (as expertly detailed in a recent statement by the European Association of Preventive Cardiology [EAPC]), the use of parameters such as HR and peak workload may still allow insights into exercise prescription (being part of the minimal standards for aerobic exercise prescription).[48,76]

The role of a functional assessment in exercise prescription among those with CVD is depicted in current guidelines.[26,48] The guidelines of the ESC recommend a risk-stratification approach (encompassing an exercise test) for patients with CAD while this concept is also echoed in those of the American College of Cardiology (ACC)/American Heart Association (AHA).[26,76,78,80] These latter societies also endorse ExECG as an appropriate indication in asymptomatic patients before cardiac rehabilitation and before initiation of an unsupervised exercise programme.[4] Of note, reassessment of functional capacity during (namely after) the cardiac rehabilitation programme should also be structured to analyze patient gains while also keeping in consideration the quality indicators proposed by the EAPC.[76,77]

Exercise stress testing should be undertaken in patients with heart failure or hypertrophic cardiomyopathy before exercise.[26,37] In these, CPET also takes a prime place because of its ability to provide extensive data which could be used for both prognostic purposes and exercise prescription.[26,37] Nonetheless, ExECG may also be of interest as the presence of symptoms, arrhythmias, and reductions in systolic BP has been used in stratifying risk.[26,37]

### Valvular heart disease

In valvular heart disease, exercise testing may be used to objectively assess symptom status (in patients who refer being asymptomatic) and to assist in exercise counseling.[26,42,62] For the former, ExECG is particularly helpful in aortic stenosis.[42,62,81] It should be recalled that in aortic stenosis, mortality is substantially related to the development of symptoms.[82] These may, however, sometimes be challenging to ascertain.[81,82] In this setting, exercise testing can be useful in those with asymptomatic severe aortic stenosis.[42,62,81,83] This concept has been incorporated in guidelines from both the ESC and the ACC/AHA.[42,62] In the former, intervention is recommended in asymptomatic patients with severe aortic stenosis who develop symptoms (class I, level C recommendation) while this should be considered in those with a sustained (above 20 mmHg) decrease in systolic BP during the test (class IIa, level C recommendation).[42] In the latter, exercise testing is deemed as reasonable to assess symptom status and physiological changes in those with asymptomatic severe aortic stenosis (class IIa, level B-NR recommendation).[62] While exercise testing may thus merit consideration when assessing severe asymptomatic aortic stenosis, it should be emphasized that it should be performed by experienced individuals and that this should not be undertaken in those with severe symptomatic aortic stenosis (being an absolute contraindication) given the risk of hemodynamic compromise.[52,62]

Though outside the scope of this report, combining exercise testing with imaging (namely echocardiography) may also provide useful insights into valvular heart disease, such as mitral valve disease.[42,84]

### *Conduction, HR, and rhythm monitoring*

The ECG is crucial in the management of rhythm disorders, and a dynamic approach (by means of exercise) may be of added value in several clinical contexts.[15,17,39,40,61] Among these, the assessment of the HR response, changes in heart rhythm, and derangements in the conduction of electrical signals are some of the possible targets of ExECG.[15,39,40,61]

As mentioned above, during exercise, HR is expected to progressively increase to allow for a continuous cardiovascular adaptation to shifting metabolic requirements.[17,30,34] An abnormal HR response may be a cause of cardiovascular limitation to effort, and ExECG can be pivotal in this setting.[15,85,86] In this regard, chronotropic incompetence comprises an inability to increase HR during exertion and may be defined as an inability to reach at least 80% of expected HR reserve.[15,61,85] The guidelines from both the ESC and the ACC/AHA (these in conjunction with the Heart Rhythm Society [HRS]) recommend the use of ExECG in those with suspected chronotropic incompetence to aid in diagnosis (both as a class IIa, level B recommendation).[15,61] Beyond its diagnostic role, the ExECG may also be of use in addressing prognosis.[61,85,87] It should be recalled, however, that these data need careful clinical correlation because there are several potential causes of chronotropic incompetence ranging from medications to comorbidities.[15,86,87]

ExECG can also be highly relevant in the study of heart rhythm and conduction disturbances.[15,39,61] When symptoms potentially attributable to these (such as syncope, dyspnea, or chest pain) develop during exertion, ExECG may help unveil the underlying cause.[15,39,61] An example of this can be illustrated in the reproduction of symptoms with the development of advanced heart block during exercise testing, thus providing a correlation between symptoms and conduction anomalies.[88] The ESC guidelines on cardiac pacing and cardiac resynchronization therapy recommend exercise testing in those presenting symptoms compatible with bradycardia during (or immediately after) exertion (class I, level C recommendation) while the ACC/AHA/HRS guidelines state that this is reasonable in this setting (class IIa, level C recommendation).[15,61] These notions are also echoed in the recommendations for those with syncope, which albeit recalling that exercise testing should not be performed in all cases, highlight that it should be considered in those with syncope during (or immediately after) exercise (class I, level C recommendation in the ESC guidelines on this subject).[39]

The analysis of the response of premature ventricular complexes (PVCs) to exercise is also a focus point of current ExECG applications.[26,40,89] Indeed, a decrease in frequency or a suppression of PVCs during exercise is suggestive (in conjunction with other ancillary findings) of a benign nature of these arrythmias while the induction of PVCs during ExECG should be considered as a "red flag" prompting further workup.[26,89,90] This is underscored in the ESC guidelines on sports cardiology and exercise in patients with CVD, which provide a class I (level C) recommendation for exercise testing in patients with frequent PVCs and nonsustained ventricular tachycardia.[26] While the specificities of the cardiovascular assessment of athletes are beyond the scope of this article, this examination may, nonetheless, be of interest in the workup of those who present frequent PVCs.[26,91,92] Recently, a study on athletes who underwent cardiac magnetic resonance imaging and repeat exercise testing for the study of ventricular arrythmias also showed that reproducibility of these could refine risk stratification by predicting the presence of an underlying nonischemic left ventricular scar.[93] On the other hand, although ExECG has been used as a noninvasive tool to analyze the presence of low-risk features in risk stratification of asymptomatic patients with pre-excitation (Wolff-Parkinson-White pattern), its overall place has progressively been challenged.[40,94-98] Contemporary guidance illustrates this notion by providing a stronger recommendation for invasive versus noninvasive assessment in those who are asymptomatic and do not have high-risk occupations or hobbies (IIa versus IIb, respectively; both level B recommendations).[96]

Finally, in those with primary electrical diseases such as the long QT syndrome and catecholaminergic polymorphic ventricular tachycardia, ExECG can provide key diagnostic findings.[40] In the case of the long QT syndrome, the 4-minute recovery (i.e., after exercise) QTc can be incorporated in diagnostic criteria, further reinforcing the notion that not only exercise but also recovery parameters of ExECG can be particularly relevant.[40,99] When assessing the Brugada pattern, a study on 74 patients who performed ExECG also showed that applying high precordial leads could improve diagnostic yield.[100] Interestingly, when considering interventions such as the implantation of a subcutaneous implantable cardioverter-defibrillator (namely in patients with Brugada syndrome), ExECG may also be useful in the screening process of potential candidates.[41,101,102] By analyzing ST-T segment changes during exercise, this framework may allow refinements in the approach to these patients as to avoid the occurrence of possible inappropriate therapies.[102,103]

### *Functional capacity*

Several studies have provided data on the interplay between functional capacity and the risk of events, across different populations.[17,71,104,105] While this concept in not novel, the recognition of CRF as a powerful variable in risk assessment has prompted a renewed interest.[105,106] Although there are several possible methodologies to infer CRF, the use of ExECG may be helpful to provide an objective measure of this important parameter.[105,107] While in this context, CPET can provide a highly precise estimate of CRF by means of the peak oxygen consumption (among other parameters), ExECG may also be of value by the assessment of metabolic equivalents of task (METs, wherein one MET equates to approximately 3.5 mL/kg/min of oxygen consumption).[105] Importantly, an inverse association between the level of METs obtained during stress testing and events has been described in different studies.[104,105,107]

In this context, ExECG may be useful in the workup of patients with cardiomyopathy (although, also in this setting, the added value of CPET should be pondered with).[108]

Importantly, the application of ExECG for functional assessment intersects deeply with several others, most notably those related to exercise prescription counseling and the integrated analysis of the cardiovascular system (whose physiological response is necessary for adequate CRF).

## Current challenges and future perspectives

Beyond the classical use of ExECG in the diagnostic process of IHD, there are several scenarios in which this examination can provide valuable data, with the potential to affect clinical care.[4,16,26,39,40,42,48,57,61,62] Although some issues remain regarding the optimal implementation of this methodology across different momentums of the cardiovascular continuum, namely in the face of the progressive evolution of novel diagnostic methods, current data, nevertheless, attest to its continuous utility.[17,40,42,89,93]

In an era where contributions from different areas progressively and rapidly lead to marked changes in the approach to CVD, ExECG has stood the test of time as a pivotal test in cardiovascular medicine.[4,17,26,40,57,109] Among some of the challenges to be faced, the incorporation of new technologies (such as those encompassing artificial intelligence) could further change the landscape by optimizing its assessment and scope.[23,110,111] Indeed, as digital tools become increasingly intertwined with several diagnostic modalities, so too may ExECG be affected by these applications.[11,110-112]

When considering ExECG in contemporary settings, an integrated assessment should be undertaken focusing not only on the ST segment but also on all the different and interlinked components that take part in the cardiovascular response to exercise and can be dynamically influenced by pathologic processes.[17,30,31,52] In this way, data derived from this complex examination can be streamlined as to improve its applicability and relevance while harnessing its full potential.[52] As elegantly stated approximately thirty years ago by Kliegfield and Okin[113] in a classical editorial concerning the (then) evolution of ExECG and commenting on different algorithms for improved test performance, "*first it must be perceived that the exercise tolerance test is capable of change*."

## Conclusion

ExECG has evolved substantially in parallel to the major improvements across cardiovascular care in general. Since the dawn of the Bruce protocol 60 years ago, this examination has continuously proven to be of substantial value across several pathologies. Albeit its many limitations, the ability to provide a dynamic assessment of different components of the cardiovascular response to exercise makes it particularly suitable in various clinical contexts. As medicine becomes increasingly personalized, with the focus on a comprehensive and integrative approach to CVD taking an ever more prominent center stage, ExECG is at present set to remain at the forefront of optimal cardiovascular care.

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