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EXERCISE STRESS TESTING IN THE 21st CENTURY

PROVA DE ESFORÇO NO SÉCULO XXI

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Resumo

Até às últimas décadas, a prova de esforço com monitorização eletrocardiográfica (PE) era um teste fundamental para avaliar indivíduos com suspeita ou doença cardiovascular (DCV) conhecida. No entanto, o cenário da DCV mudou profundamente, com indicações clássicas como o diagnóstico de doença coronária a serem progressivamente substituídas por outras indicações. Apesar disso, a PE pode ainda fornecer dados amplamente relevantes em todo o espectro da DCV. Neste artigo focado em duas partes, avaliamos o papel da PE em cenários contemporâneos: a parte I fornece uma visão geral dos principais parâmetros, enquanto a parte II aborda áreas principais de interesse selecionadas.

Palavras-chave: Prova de Esforço; Capacidade Funcional; Doença Cardíaca Isquémica; Eletrocardiograma.

Abstract

Until recent decades, exercise testing with electrocardiographic monitoring (ET) was a fundamental test to evaluate individuals with suspected or known cardiovascular disease (CVD). Since its inception, the landscape of CVD has profoundly changed; classical indications such as the diagnosis of ischemic heart disease have been progressively superseded by other modalities. ET can still, however, provide valuable data across the cardiovascular continuum. In this focused two-part article, we appraise the role of ET in contemporary settings: part I provides an overview of core parameters, while part II addresses select main areas of interest.

Keywords: Exercise testing; Functional Capacity; Indications; Ischemic heart disease; Electrocardiogram.

PART I: UNDERSTANDING THE PHYSIOLOGYCAL CARDIOVASCULAR RESPONSE TO EXERCISE

Functional capacity

Functional or exercise capacity reflects the ability to perform activities requiring sustained aerobic metabolism, resulting from integrated actions of the cardiovascular, musculoskeletal, and respiratory systems. [1,2] This core dimension provides important information across various clinical settings and can be expressed in metabolic equivalents of task (METs), which represent multiples of the rate of resting oxygen consumption (VO2), with 1 MET being *circa* 3.5 mL O_2 uptake/kg/min.[1,2] Of note, estimating VO2 using exercise testing (ET) with electrocardiographic monitoring tends to overestimate its value when compared to direct assessments.[1,3] Other parameters that could be used to infer exercise capacity include exercise duration and maximal workload achieved.[1,2]

Exercise capacity can be affected by several factors, including cardiovascular and non-cardiovascular comorbidities, age, sex, patient familiarization with the equipment, physical conditioning, environmental and psychological conditions.[1,4]

Although cardiopulmonary exercise stress testing (CPET) is the preferred method to assess functional capacity, its analysis by ET (i.e. without gas analysis) can also be of major interest.[2,4] Indeed, each 1-MET increase has been associated with decreases in cardiovascular and all-cause mortality.[2] This prognostic value has been predominantly validated using the Bruce protocol.[5] Although caution should be exercised when comparing achieved METs between different ET protocols, as the same achieved METs can have variable prognostic value, higher estimated METs are associated with lower mortality regardless of the protocol used.[5] Beyond the protocols chosen, the mode of exercise, typically performed on a treadmill or cycle ergometer, can also influence assessments.[4] Peak VO2 is, for example, 10% to 20% lower in cycle ergometers when compared to treadmill, mainly due to quadriceps fatigue.[6]

The higher the METs, the better the functional capacity, while achieving <5 METs in those who have cardiovascular disease (CVD) is considered poor tolerance.[2,3] Beyond absolute values, exercise capacity should also be described according to age and sex (normal if ≥85% of predicted values).[6,7]

Critically, clinical status and signs of exhaustion must be monitored throughout ET, with particular emphasis on the development of symptoms (such as dyspnea, palpitations, chest or limb pain, etc.).[6] In this regard, including subjective ratings of perceived exertion (namely the Borg scale) can also provide data in terms of fatigue incurred during the test.[6] Furthermore, it should be noted that integrating prior clinical information (encompassing the reason for referral to the test) with a focused patient assessment (including ongoing medication and the baseline electrocardiogram) is relevant to assess possible contraindications to ET, while also ensuring adequate protocol selection.[3,6]

Blood pressure

Arterial blood pressure (BP) provides insights into the cardiovascular response to exercise and is dependent on peripheral arterial resistance and cardiac output (CO), as well as their interplay.[6,8] The autonomic nervous system has a marked role in modulating these responses, which can also be influenced by factors such as age, sex, functional capacity, and medication.[3,6,8] BP should be measured at rest (in both arms, to assess potential discrepancies), during exercise in the last minute of each stage and at peak, and in the recovery phase, as its kinetics provide useful information.[3,6] Adequate cuff application and operator training are key steps to ensure optimal assessment.[3,8] Manual, semi-automatic or automatic methods have been described to assess BP non-invasively, although it should be noted that, at high levels of exercise, artifacts (including

those due to motion) may limit the latter. In these cases, the manual method is often the best choice.[3,6]

In healthy individuals, increases in CO during exercise are coupled with changes in vascular tone (Figure 1).[8,9] This leads to progressive increments in systolic BP (SBP), reflecting CO, typically *circa* 10 mmHg *per* MET, while these may be lower when progressing beyond 10 METs.[6,8] For diastolic BP, values are typically maintained (reflecting the vascular response), with variations around 10 mmHg within the normal range.[6,8] During recovery, SBP returns to baseline (or lower) levels, typically within six minutes.[6,10]

Abnormal findings may encompass exaggerated or hypertensive responses to exercise (HRE), and hypotensive responses.[3,6,8] A HRE may be defined as SBP >210 mmHg in males or >190 mmHg in females.[6] Notably, variations in cut-offs should be acknowledged.[11] Furthermore, achieving high workloads during the test (as in athletes) may be associated with higher BP levels.[8,11] In this context, cut-offs >220 or >200 mmHg (males and females, respectively), as well as adjustments to workload, have also been reported.[11]

Hypotensive responses should be considered pathological (until proven otherwise) as they have been associated with adverse events.[4,6,8] Also, suboptimal increases in SBP should be noted (as discussed in part II).

Heart rate

Heart rate (HR) is expected to increase during exercise, being a key component of CO.[3,6,9] HR variations are deeply intertwined with the autonomic nervous system.[3,6] Additionally, factors such as age, sex, and medications can influence HR, while comorbidities may also affect its kinetics.[3,6,12]

In healthy individuals, increases of approximately ten beats per minute per MET are expected.[3,6] During recovery, HR decreases, typically with a more rapid course during the early phase followed by a slower pace.[6] HR should be monitored throughout ET.[3,6] Several methodologies can be applied to assess the theoretical maximal HR (TMHR), which aim to overcome some of the limitations associated with this framework (especially given the multiple factors affecting HR responses).[13] Of note, assessment of chronotropism based on the TMHR is limited in those with arrythmias such as atrial fibrillation or atrial flutter.[10]

Failure to achieve ≥85% of TMHR or a delayed recovery are among potentially abnormal findings.[4] Importantly, solely achieving ≥85% of TMHR should not lead to test interruption, especially given the high interindividual variability and limited ability to define sufficient effort using this approach. This could compromise measurement of functional capacity, which is one of the most important parameters furnished by ET.[3,6] While the percentage of TMHR may provide some insights in terms of VO2 and exercise intensity (with ≥85% TMHR theoretically within the spectrum of high intensity exercise), data show that this metric may not adequately estimate effort levels.[12,14-6] As such, while assessing the percentage of TMHR should be incorporated in test interpretation (including in terms of possible chronotropic incompetence, and as one of the measures of effort), utilizing a specific cut-off for which test interruption should not be applied.[6,15]

Among the indications for terminating an ET are (as detailed in Fletcher et al.): a ST-segment elevation >1 mm in leads without prior Q waves, a drop in SBP >10 mmHg despite increasing workload when associated with ischemia, moderate-to-severe angina, central nervous system symptoms (such as ataxia, dizziness, near syncope), signs of poor perfusion (cyanosis or pallor), sustained arrhythmias affecting CO such as ventricular tachycardia and second or third-degree atrioventricular block, technical difficulties in monitoring the patient, patient's request to stop the test.[3,6,10] Others such as claudication may be considered as a relative indication for test termination, further emphasizing the importance of adequate monitoring throughout the exam and integration of prior clinical information.[6]

Electrocardiographic monitoring

Continuous electrocardiographic monitoring is pivotal and adequate skin preparation and signal acquisition are paramount to ensure proper analysis.[3,6] Beyond possible abnormal electrocardiographic findings during ET, there are also several exercise-induced physiological changes.[6,7,9]

In normal individuals, the P-wave magnitude increases during exercise, whereas its duration is in general unchanged or minimally increased.[3,6] As for the PR segment, there is a shortening and downward sloping in inferior leads. This should be acknowledged as it can cause apparent ST-segment depression if the negative wave persists into the early part of ventricular repolarization.[3,6]

The duration of the QRS complex generally decreases at higher exercise workloads, as HR is increasing. The magnitude of septal Q waves in the lateral leads tends to increase, while R waves tend to decrease, and S waves in inferior leads to an increase during exercise.[3,6,10]

A depression of the J-point may be present at maximal exercise, gradually returning to baseline in the recovery phase. A normalization of the ST-segment during exercise may occur in those with resting J-point elevation (early repolarization), although this should not be interpreted as a depression equivalent (when analyzed in the context of the baseline pattern).[6] The T wave decreases in amplitude in early exercise, rising to baseline values at higher workloads and above in the early recovery phase.[6,7] No substantial changes are evident in the U wave, though it should be acknowledged that evaluation is limited due to the approximation between T and P waves at a higher HR.[6,7]

The absolute QT interval shortens with exercise, but in some individuals (especially in women) a paradoxical prolongation in the early stages of ET may occur. However, the corrected QT interval using the Bazett formula increases in the early stages of exercise and decreases at higher exercise workloads.[3,6]

PART II: CLINICAL SCENARIOS WHERE IT CAN STILL MAKE THE DIFFERENCE

In part II of this article, we describe some of the main applications of ET in contemporary clinical settings.

Ischemic heart disease

The refinement of imaging modalities has substantially superseded ET in the diagnosis of ischemic heart disease (IHD).[17] While ET may still be considered in select clinical settings, guidelines have increasingly emphasized the preference for imaging techniques to enhance diagnostic accuracy.[17,18] In this context, inputs from exams such as exercise stress echocardiography may offer incremental value by providing additional data on different aspects of the cardiovascular response to stress.[17,19] Despite this, ET can still provide valuable data on functional capacity (for prognostic assessment and risk stratification), BP and HR, rhythm changes and symptoms appraisal.[17,18] The combination of several variables as exemplified in the Duke treadmill score including ST-segment depression, angina (with different scoring according to characteristics, namely if absent, non-limiting or limiting exercise), and exercise duration.[3,7]

Although limitations in its application should be noted, this has shown both diagnostic and prognostic relevance, once more illustrating the importance of an integrative approach to ET.[3,6]

Exercise testing can be a key element for those undergoing cardiac rehabilitation, and also before participating in sport, even when not coupled with respiratory gas assessment (CPET).[16] Moreover, functional capacity has shown robust prognostic capabilities, reinforcing the potential of its objective assessment.[6,16,18] Interestingly, data also reported that ET may provide information concerning other facets of IHD such as microvascular disease, underscoring its adaptability.[20]

Arrythmias and conduction disturbances

Assessing exercise-induced arrythmias is part of the work-up of those with IHD prior to participating in sport; this is also the case for diseases such as hypertrophic cardiomyopathy (HCM).[16] The behavior of premature ventricular complexes during ET is also relevant, as an increase in frequency during the exercise phase should be considered a potential red flag, leading to further assessment.[16] At the extreme of this spectrum, multiple morphologies and increase during exercise could be related to catecholaminergic polymorphic ventricular tachycardia.[16]

Exercise testing can also be useful in those with symptoms suggestive of bradycardia during exertion, to help unveil underlying mechanisms.[18,21] Indeed, as referred to in guidelines on this subject, whereas symptoms after exercise are often related to reflex mechanisms, those during exercise should raise suspicion of possible cardiac causes.[21] Among entities in this context, the development of advanced atrioventricular blocks, as well as chronotropic incompetence, may be uncovered.[21]

Beyond these, as for diagnostic assessments, it should be recalled that analyzing the electrocardiogram at the four-minute mark during the recovery period can also be incorporated when addressing long QT syndrome.[16] On the other hand, the use of ET in preexcitation syndrome assessment is presently considered as limited.[16,22]

Finally, ET can play a role in those with cardiac implantable electronic devices.[18,23,24] From a technical standpoint, the filter applied to the electrocardiogram should be considered, as to allow adequate visualization of pacemaker spikes.[3] In addition, the assessment of the ST-segment is limited in the presence of ventricular pacing.[3,6,16] Although CPET provides additional ancillary data, assessing the electrocardiogram during exercise may allow, among others, the

assessment of the chronotropic response, arrythmias, and tracking rate.[23] In terms of potential applications, some include programming optimization in the setting of ventricular arrythmias to prevent inappropriate shocks due to sinus tachycardia (particularly in younger patients) or arrythmias such as atrial fibrillation, or preventing desynchrony due to loss of biventricular stimulation at higher HR.[25] Furthermore, ET is also useful in athletes with a pacemaker in the setting of sinus node dysfunction, to assess parameters such as rate-response.[26] Finally, ET may also optimize subcutaneous implantable cardioverter-defibrillator candidate selection, especially in Brugada syndrome.[24]

Cardiomyopathies

In this setting some applications of ET could include risk stratification, assessment of symptoms or disability level, assessment of treatment strategies and prognostic evaluation.[4,6,16,27,28] While CPET has gained growing relevance among different diseases in this spectrum by providing powerful inputs across several domains, ET (both in isolation or when coupled with other methods) can also form an important part of the noninvasive evaluation of patients with cardiomyopathies.[6,16,27,28] From the information provided, functional capacity, rhythm, and BP responses to exercise are important parameters to consider.[6,16]

Although in the setting of HCM, and particularly in those with resting left ventricular outflow tract gradients, the use of ET should be carefully considered and performed by experienced operators, as it can be an important tool in this area.[6,16] This test is part of the comprehensive clinical evaluation of HCM, aiding in refining the assessment of these patients and in the identification of high-risk profiles.[16,27] Among these, features such as an abnormal BP response (usually defined as a fall in SBP during exercise, or in failure to increase it by at least 20 mmHg at peak when compared to baseline) and arrhythmias, or (when coupled with echocardiography) provocable left ventricular outflow tract obstruction and distinct levels of mitral regurgitation, can aid in a more individualized therapeutic decision-making process.[6,16,27]

Finally, ET forms a core part of methodologies such as CPET and exercise stress echocardiography, and a detailed knowledge of its interpretation (see part I) is key to improving these applications. Importantly, in HCM but also in several other CVDs, exercise-based methodologies are key for diagnostic, prognostic, and therapeutic purposes; h ET, whether in isolation or coupled to ancillary frameworks as described above, is central to optimizing its application while minimizing the risk of adverse events.[29]

Exercise prescription

Although CPET is the gold standard for exercise prescription, ET may also be useful for this purpose.[6,16,30] Briefly, ET prescription should, among others, take into consideration the FITT (frequency, intensity, time, and type of exercise) principle, while also accounting for the mode of exercise performed.[16,30] ET can be particularly relevant in this context, in terms of aerobic exercise components. Among the indexes and targets used for ET prescription in this setting, some of the most common are those encompassing the percentage of maximal HR (HRmax), HR reserve (HRR), peak exercise HR achieved, percentage of peak workload achieved, and rate of perceived exertion.[16,30] HRR results as a function of HRmax and resting HR, with the theoretical HRmax being determined by formulas, among which are those such as 220-age or the Tanaka formula [208−(0.7xage)].[6] Using the Karvonen method, multiplying the HRR by the targeted percentage of exercise intensity, plus resting HR, it is possible to define the target HR during exercise.[16] Notably, and although the several pitfalls, such as the use of beta-blocker therapy or atrial fibrillation, should be acknowledged, these concepts are relevant for exercise prescription in both athletes and patients with CVD (i.e. being incorporated in defining zones of low intensity <40%, moderate intensity 40-69%, high intensity 70-85%, and very high intensity >85%).[16,30]

Exercise prescription based on ET is also important in specific clinical settings, especially in terms of defining the myocardial ischemia threshold (often defined as the HR or work rate where a ST-segment depression of 1 mm, horizontal or down-sloping, develops during exercise).[6,30] Furthermore, determining the HR at the development of angina or arrythmias is also pivotal in optimizing training prescriptions on a case-by-case basis.[6,23]

Other indications

Given the depiction of an integrated representation of different components of the cardiovascular response, ET has garnered interest across other areas (Figure 2). In asymptomatic severe aortic stenosis (AS), it can be useful to assess symptom status and BP response. Both may, in the case of pathological responses, influence decisions concerning intervention timing (class I and IIa recommendations, respectively).[31] Importantly, although ET can be of major relevance in asymptomatic severe AS, it is contraindicated in those with symptomatic severe AS.[18]

In athletes, ET can be used to improve comprehensive cardiovascular assessment, particularly in master athletes undergoing high intensity activities.[16] ET may also assist when evaluating individuals with vasculogenic erectile dysfunction and CVD, as exercise capacity coupled with a multiparametric assessment during the test is a key component of risk stratification, as

highlighted in the most recent update of the Princeton consensus.[32] Finally, assessing functional capacity (see part I) can be highly useful to aid in the prognostic assessment across several moments of the cardiovascular continuum.[6]

Future perspectives

In this article we presented some core concepts and selected the main indications concerning ET. This pragmatic overview may be regarded as a starting point for those using ET in their clinical practice, while managing the challenging cardiovascular patient. In an era of growing personalization and tailored management, reappraising ET should be a focused and continued endeavor, to further explore the extensive potential of this dynamic and comprehensive framework.

Ética de la publicación

1. ¿Su trabajo ha comportado experimentación en animales?:

No

2. ¿En su trabajo intervienen pacientes o sujetos humanos?:

No

3. ¿Su trabajo incluye un ensayo clínico?:

No

4. ¿Todos los datos mostrados en las figuras y tablas incluidas en el manuscrito se recogen en el apartado de resultados y las conclusiones?:

Sí

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Figure legends

Figure 1. Overview of some of the physiological cardiovascular responses to exercise testing.

bpm = beats per minute; DBP = diastolic blood pressure; ET = exercise stress testing with electrocardiographic monitoring; HR = heart rate; METs = metabolic equivalents of task; SBP = systolic blood pressure; TMHR = theoretical maximal heart rate

[1] Should not be used in isolation for test interruption (see main text for details).

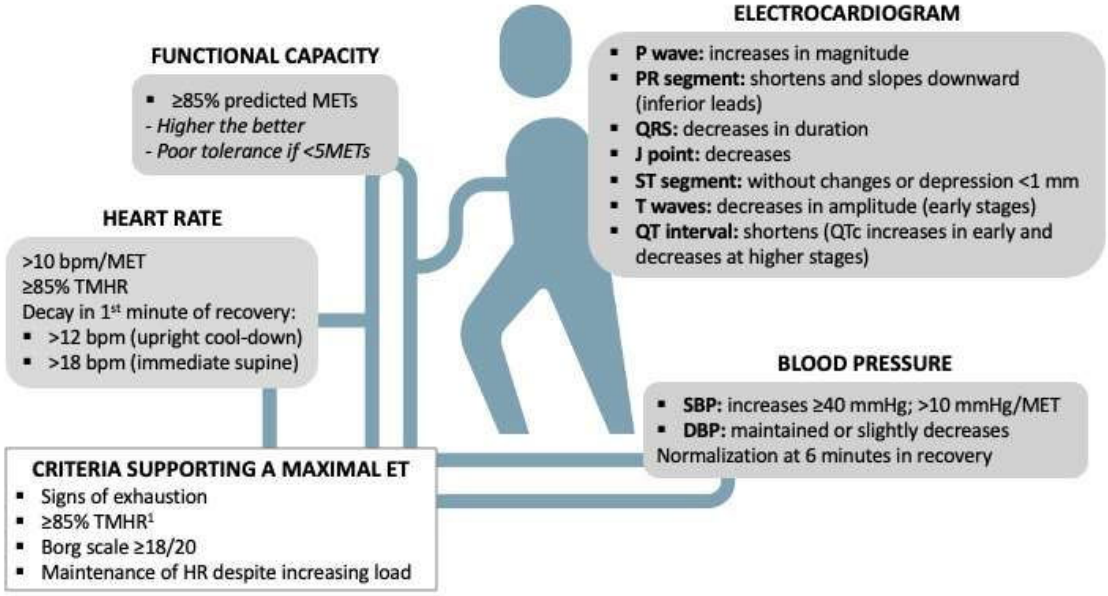

Figure 2. Some of the main contemporary indications for exercise stress testing with electrocardiographic monitoring.

ET = exercise stress testing with electrocardiographic monitoring.