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PERSPECTIVE

Heart rate thresholds as integrative biomarkers: a systems approach to exercise physiology and cardiovascular regulation

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Abstract

Heart rate (HR) kinetics during exercise reflect complex interactions between cardiovascular, autonomic, and metabolic systems. Yet, traditional assessments, such as maximal HR or HR reserve, fail to capture HR adjustments to metabolic transitions and mechanical signals sent from skeletal muscle, respiratory muscles, and the vascular system. This perspective introduces a novel systems physiology framework for analyzing HR thresholds in synchronization with ventilatory and metabolic transitions. A biphasic regulation model is proposed where Phase 1 is governed by afferent reflex mechanisms (e.g., metaboreflex, baroreflex) driving an exponential HR increase (heart rate inflection point, HRIP), while Phase 2 reflects β_1-adrenergic receptor saturation, leading to a plateau or deflection in HR (heart rate deflection point, HRDP). Using this framework, we propose new analytical strategies to assess threshold agreement and physiological synchronization across bodily systems. Our approach has practical applications in tailored exercise prescriptions and clinical diagnostics. We argue that HR thresholds may reflect activation of the exercise pressor reflex and shifts in sympathetic activity. By moving beyond isolated biomarkers, this model promotes a more integrative and dynamic understanding of exercise physiology.

Keywords Cardiovascular diagnostic technique · Exercise testing and prescription · Integrative physiology

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Abbreviations

Dmax	Maximal distance approach
FATmax	Exercise intensity at which maximal fat oxidation occurs
HR	Heart rate
HRIP	Heart rate inflection point
HRDP	Heart rate deflection point
HRVT	Heart rate variability thresholds
LT1	First lactate threshold
LT2	Second lactate threshold
RCP	Respiratory compensation point
VT	Ventilatory threshold

Regulation of heart rate during aerobic exercise

During a graded exercise test, heart rate (HR) usually follows a sigmoidal or S-shaped curve in healthy individuals (Fig. 1a) (Birnbaumer et al. 2023). This pattern begins with a gradual increase in HR at low-to-moderate exercise intensities, transitions into a steeper rise as intensity increases, and eventually reaches a plateau or deflection at high intensities.

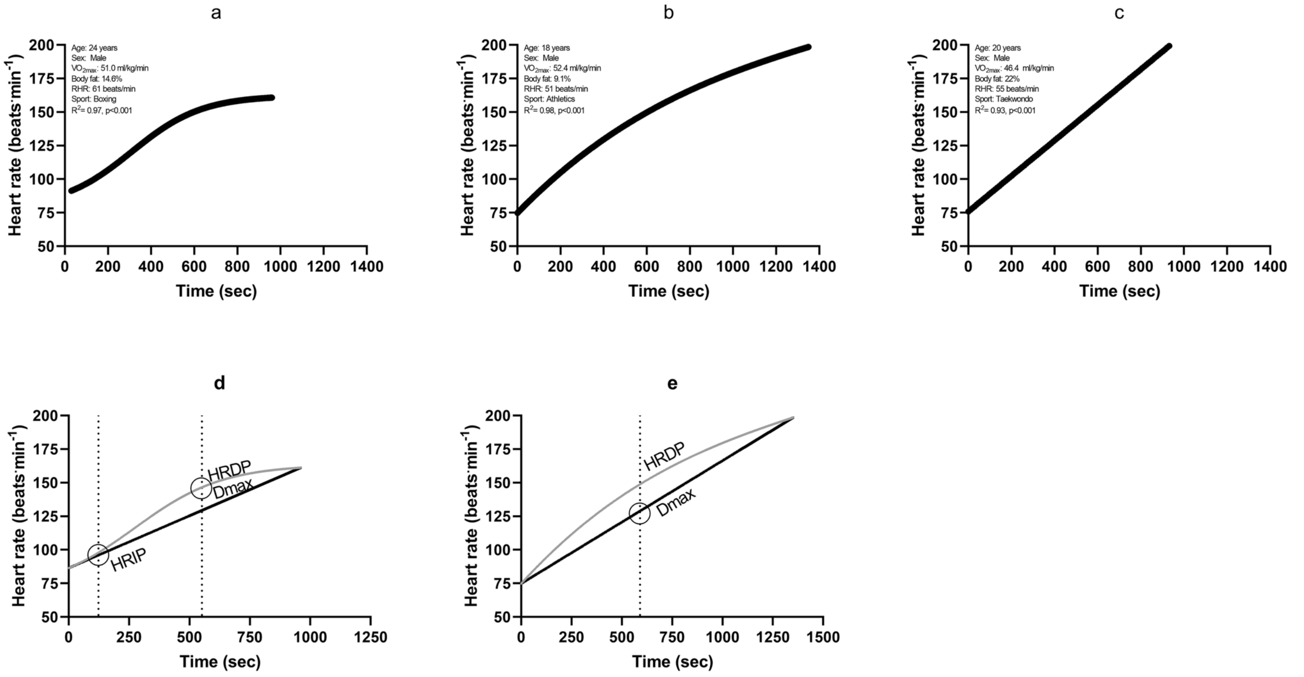


Fig. 1 Plausible heart rate kinetics during a graded exercise test. According to Birnbaumer et al., (2023), a sigmoidal heart rate pattern is evident in ~ 92% of healthy individuals, whereas linear (~ 2%) and curvilinear (~ 6%) patterns are less common. A heart rate inflection (HRIP) and deflection (HRDP) points can be automatically computed from a sigmoidal or curvilinear heart rate pattern, using the maximal distance approach (Dmax). For this, the difference between heart rate values computed throughout the polynomial or sigmoidal curve and the heart rate values retrieved from linear regression are obtained (solid black lines), and the time corresponding to the maximal difference between these values is identified. Once the HRDP is determined through this analysis, a modified Dmax can be then applied to identify the HRDP, computing the distance between heart rate values computed throughout the polynomial or sigmoidal curve and the heart rate values retrieved from a new linear regression up to the HRDP. For a detailed explanation of these procedures, the reader is referred to Cambri et al. (2016) and Kara et al. (1996), highlighting that HRIP or HRDP cannot be detected in linear heart rate kinetics. * Own data collected from young athletes during a graded exercise test. All the subjects signed informed consent before evaluations, and the protocol was approved by the Ethics Committee of the Faculty of Sports Ensenada (CEEIP0004-FDE). The test was performed on a treadmill (T170DE MED, Cosmed The Metabolic Company, IT), under fasting conditions (10–12 h), applying the same starting workload (4 km/h) and step progression (+ 1 km/h every 3 min) up to the athletes' maximal exertion. A wireless heart rate monitor (Polar H10, Polar, FN) was used to record beat-to-beat values in the VO2 Master Manager App (VO2 Master, CA). Raw heart rate data were subsequently modeled in GraphPad Prism v.8.1. by interpolating a linear, sigmoidal or polynomial regression analysis (Supplementary file 2). Athletes' characteristics and fitting of the computed models is provided on each panel. RHR, resting heart rate; R^2, determination coefficient; VO_{2max}, maximal oxygen uptake

Alternative HR responses (i.e., linear (2%) or curvilinear (6%) pattern with inverse deflections) occur less frequently and may vary with age, sex, and/or fitness level (Fig. 1b and c) (Birnbaumer et al. 2020). Understanding these behaviors is crucial to describe HR regulation during exercise, which is governed by intricate afferent and efferent mechanisms that eventually change across exercise intensity phases.

Phase 1: afferent regulation of heart rate during exercise

In the first phase, various afferent mechanisms—collectively known as the exercise pressor reflex—coordinate the rise of HR to meet the increased oxygen demand of working muscles (Supplementary file 1) (Texeira and Vianna, 2022). This exponential increment is often called the "heart rate inflection point" (HRIP) (Cambri et al. 2016). While multiple physiological pathways contribute to HR modulation, the skeletal muscle mechanoreflex and metaboreflex mechanisms are among the most extensively studied and characterized[3]. Additional reflexes including the arterial baroreflex, arterial chemoreflex, cardiac vagal mechanoreflex, and cardiac sympathetic afferent reflex all contribute to the complex regulation of HR during exercise (Herring et al. 2024).

Skeletal muscle mechanoreflex and metaboreflex

These reflexes are driven by Group III and IV afferent fibers located in the dorsal root ganglia, which detect mechanical and chemical changes in the skeletal muscle and convey signals to spinal and medullary centers to increase HR. Piezo-type mechanosensitive ion channel components 1 and 4 (Piezo1 and Piezo4) sense muscle stretch, while acid-sensing ion channels respond to acidosis resulting from lactate build-up. This activation triggers sympathetic output increasing HR to deliver oxygen and nutrients to active skeletal muscle tissue (Grotle et al. 2020; Herring et al. 2024).

Arterial baroreflex

During exercise, the baroreflex undergoes rapid resetting to a higher pressure setpoint, allowing for an elevation in arterial pressure without triggering vagal inhibition of HR. This is regulated by an inhibitory GABAergic mechanism within the nucleus tractus solitarius, driven by afferents activated during muscle contraction (Potts et al. 2003). This adaptation prevents a reduction in HR, thereby sustaining elevated blood flow to the muscles.

Arterial chemoreflex

Sensitive to blood gas levels, this reflex is mediated by glomus cells in the carotid and aortic bodies, which monitor oxygen, carbon dioxide, and pH levels. Activation due to hypoxia, hypercapnia, or acidosis enhances sympathetic activity and increases HR, especially during high-intensity or sustained exercise (Herring et al. 2024; Torres-Torrelo et al. 2021). This mechanism helps maintain oxygen delivery during prolonged and strenuous exercise when metabolic demand is elevated.

Cardiac vagal mechanoreflex

Atrial walls stretch, mainly caused by increased venous return, triggers this reflex. Afferent signals from the vagal nerve target the nucleus tractus solitarius temporarily reducing sympathetic drive and moderating HR. This negative feedback mechanism contributes with the adjustment of cardiac output dynamically in response to changing venous return and balancing both HR and stroke volume to meet moment-to-moment circulatory demands (Herring et al. 2024).

Cardiac sympathetic afferent reflex

This reflex is activated by both chemical and mechanical changes within the heart. Cardiac sympathetic afferents relay these signals via the dorsal root ganglia to the nucleus tractus solitarius and higher centers, enhancing sympathetic output and thus increasing HR. This mechanism supports HR increases, especially as exercise intensifies, contributing to the HR inflection point and reflecting a shift to sympathetic dominance in HR control (Herring et al. 2024; O'Leary et al. 2024).

Phase 2: sensitivity and saturation of β_1-adrenergic receptors

In the second phase, HR response is largely driven by β_1-adrenergic receptors in myocardial tissue, which are sensitive to catecholamines (Hofmann et al. 2005; Pokan et al. 1995). β_1-receptor activation accelerates sinoatrial node firing, increasing HR and promoting myocardial contractility through phosphorylation of the sarcoplasmic/endoplasmic reticulum calcium ATPases in the sarcoplasmic reticulum. This mechanism enhances calcium reuptake, bolstering muscle contraction. However, given saturation of β_1 receptors, the HR increments are limited, leading to a plateau or slight deflection in HR kinetics named the “heart rate deflection point” (HRDP). This saturation point corresponds with a curvilinear pattern in cardiac output and stroke volume, indicating that cardiovascular efficiency has reached its peak (Birnbaumer et al. 2020, 2023). In fact, the HRDP is a significant predictor of a curvilinear pattern of cardiac output, denoting that β_1-receptor saturation balances HR kinetics with maximal cardiovascular efficiency constraints during high-intensity endurance exercise (Beck et al. 2006).

Thus, this biphasic model reflects a balance between afferent-driven HR modulation in the early exercise stages and β_1-adrenergic receptor sensitivity and saturation at peak intensities, with individual variations influencing the specific HR pattern response.

Analysis of the heart rate thresholds

The analyses of HR thresholds can be broadly categorized into visual methods and computational methods, each providing unique perspectives on the interplay between sympathetic and parasympathetic nervous systems. Key thresholds include HRIP, HRDP, and heart rate variability thresholds (HRVT), as discussed in studies by Cambri et al. (2016), Birnbaumer et al. (2023), and Zimatore et al (2022).

Heart rate inflection point

The HRIP refers to the workload in which the linearity between HR and exercise intensity breaks down. This shift is typically marked by a sharp increase in HR as vagal withdrawal and peripheral input signals give way to sympathetic activation as earlier discussed. This threshold can be computed by using the maximal distance approach (Dmax). Concretely, this refers to the point of maximum negative difference between a polynomial curve fitted to HR data and a linear regression retrieved from the first and the last HR values recorded during the graded exercise test (Fig. 1d) (Cambri et al. 2016).

Heart rate deflection point

The HRDP represents a downward or upward deflection in the HR–performance curve at vigorous exercise intensity. Visual inspection remains a conventional method for HRDP identification but importantly relies on observer experience. Although it is practical and feasible (especially in field settings), it suffers from subjectivity and reduced accuracy at identifying subtle or irregular deflection points (Bodner and Rhodes 2000). Interpolation of the HR–workload or HR–time curve using a third-order polynomial regression or logistic functions offer greater objectivity and reproducibility. Indeed, the Dmax approach can be applied for a precise detection of the HRDP, calculating the maximum perpendicular distance between a regression curve and a straight line retrieved from the regression of the first and the last HR values recorded during the graded exercise test (Fig. 1e).

Birnbaumer et al. (2023) analyzed the HR performance curve (HRPC) using the Vienna CPX-Tool, which fits a second-degree polynomial function to the HR data segment recorded between the first ventilatory threshold (VT) and maximal exercise intensity. This tool calculates the deflection degree and direction (kHR) based on the slopes of two tangents, categorizing HRPCs as follows:

- Downward deflection (regular HRPC): $kHR < -0.1kHR <$ -0.1kHR < -0.1
- Inverse deflection (non-regular HRPC): $kHR > 0.1kHR > 0.1kHR > 0.1$
- Linear (non-regular HRPC): $-0.1 \leq kHR \leq 0.1$–0.1 \leq kHR \leq 0.1 $-0.1 \leq kHR \leq 0.1$

The above-described method offers a precise and reliable assessment of HRDP. However, it is computationally complex, requiring specialized software (Vienna CPX-Tool) and prior training to interpret kHR values correctly.

Heart rate variability thresholds

HRVT relies on the analysis of beat-to-beat HR variability (HRV) to detect shifts in autonomic control. Zimatore et al. (2022) highlight advanced non-linear methods (i.e., Poincaré plots and recurrence quantification analysis) to pinpoint transitions from parasympathetic to sympathetic dominance. These computational methods use reductions in SD1 (instantaneous variability) or complexity indices to determine thresholds:

- HRVT1: The first stage where SD1 < 3 ms, reflecting vagal withdrawal.
- HRVT2: A further decrease in SD1 with < 1 ms change between stages.
- * SD1: standard deviation of instantaneous beat-to-beat interval variability

The Dmax approach can be also applied to detect the HRVT1, determining the longest perpendicular distance between SD1 predicted by a third-order polynomial function over actual value and the linear regression calculated with the first and last values of the curve.

Interpretation of the heart rate pattern in the contexts of integrative physiology

The exercise pressor reflex theory proposes that HR transitions are well aligned with mechanical, respiratory, and metabolic adjustments during exercise. However, to test such hypotheses, applying an integrative physiology approach would be necessary. Below, key aspects of HR regulation and its implications for physiological systems are explored, examining the interplay between HR thresholds, ventilatory thresholds (VT), metabolic thresholds, and skeletal muscle deoxygenation.

Agreement between the heart rate thresholds and metabolic thresholds

As discussed in Sect. 1.1, an exponential inflection in HR kinetics can be observed during the initial phase of a graded exercise test, reflecting a vagal withdrawal and enhanced sympathetic activation promoted by multiple peripheral reflexes (e.g., exercise pressor reflex). In this regard, Kauffman et al. (2023) reported a small positive bias (2.7 beats/min) but wide limits of agreement (LoA: − 20.4 to 25.8 beats/min) between the HRVT1 and the first lactate threshold (LT1) among healthy, endurance-trained males. Similarly, LoA between workload parameters at the HRVT1 and LT1 were larger than power output or treadmill velocities progression commonly applied during a graded exercise test (power output: − 27.6 to 36.6 watts; running speed: − 3.2 to 3.7 km/h), implying that these thresholds occur at distinct phases during the graded exercise test. Considering that skeletal muscle lactate levels are usually higher than blood lactate levels—lactate accumulates first in the skeletal muscle, activating monocarboxylate transporter 1 and 4 for its subsequent efflux to capillaries (Goodwin et al. 2007; Poole et al. 2021)—it seems reasonable that HRVT1 or HRIP precedes the LT1 during a graded exercise test. Afterward, lactate accumulation in the blood will activate glomus cells, accelerating HR due to a sympathetic drift.

However, according to Kauffman et al. (2023) an analysis of sequential agreement between the HRVT1 and the LT1 has not been previously explored in these investigations. Besides, in that same meta-analysis, a large heterogeneity was found among studies results, with distinct methods applied to determine both the HRVT1 and LT1. Chávez-Guevara et al. (2023) reported that the correlation between the HRIP and LT1 varied among young men with obesity, depending on methods applied to determine the LT1 (i.e., higher correlation coefficients when LT1 was defined by the logarithmic transformation of oxygen uptake and lactate levels [log–log]). Thus, further studies are necessary to understand if the HRIP precedes the LT1, representing a synchronization between skeletal muscle lactate accumulation and sympathetic drift which accelerates HR during exercise, defining the best methods to explore the agreement between HR and lactate thresholds.

During graded exercise test, as an individual approaches maximal exertion, the HR starts to level off, showing a plateau or deflection that has been associated with (1) a saturation of cardiac β_1-adrenergic receptors, (2) a reduction of stroke volume reserve, and (3) maximal myocardial contractility (Beck et al. 2006; Birnbaumer et al. 2023). At this point, further increases in cardiac output are limited, and the efficiency of oxygen delivery now relies heavily on peripheral adaptations, such as capillary density and mitochondrial capacity (Beck et al. 2006).

Considering this physiological model, the plateau of cardiac output (represented by the HRDP) would limit oxygen availability to skeletal muscles, exacerbating the glycolytic flux and lactate production. Indeed, Bodner and Rhodes (2000) highlighted strong correlations between HRDP and the anaerobic threshold in some populations. Supporting the association between HR dynamics and metabolic thresholds, Kaufmann et al. (2023) reported a mean bias of 2.5 bpm and LoA of -12.1 to 17.1 beats/min between the HRVT2 and the LT2. This indicates a variable relationship between biomarkers, influenced by large heterogeneity in HRV methodologies and LT2 definitions. Interestingly, the sequential appearance of the HRDP/HRVT2 and the LT2 remains unexplored, although the wide LoA reported between biomarkers suggest that HRDP/HRVT2 does not always precede the LT2 as proposed in other physiological models.

Building on the physiological connections between HR thresholds and metabolic transitions, intramuscular lactate accumulation during exercise exerts a significant influence on substrate utilization. Specifically, lactate accumulation inhibits mitochondrial fat oxidation by reducing the activity of carnitine palmitoyl transferase 1, a key transporter for long-chain fatty acids into the mitochondria, and by disrupting β-oxidation pathways (Frangos et al. 2023). This metabolic shift forces a greater reliance on carbohydrate metabolism, aligning with the crossover concept described by Brooks and Mercier (1994), where carbohydrate becomes the predominant fuel source as exercise intensity increases and oxygen availability becomes constrained.

Intriguingly, Chávez-Guevara et al. (2023) observed that HRIP and the first lactate threshold (LT1) were strongly associated with the exercise intensity at which maximal fat oxidation occurs (FATmax) in young men with obesity. Similarly, Saéz-Olivares et al. (2019) demonstrated a significant correlation between HRVT1 and FATmax in physically active individuals ($r = 0.84$, $p < 0.01$), highlighting a regulatory loop between cardiorespiratory control and metabolic dynamics during submaximal exercise. These findings suggest that HR thresholds provide valuable insights into the coordination of autonomic and metabolic responses. However, the sequential or simultaneous appearance of HRIP/HRVT1, LT1, and FATmax has yet to be thoroughly investigated.

Whether the HRDP or HRVT2 aligns with the exercise intensity at which carbohydrate metabolism becomes dominant (the crossover point) remains another critical area of investigation. Such a connection would provide insight into whether impaired oxygen delivery to skeletal muscle at higher intensities accelerates glycolytic flux, exacerbating lactate production and inhibiting fat metabolism. This would ultimately lead to negligible fat oxidation, defined as the workload where fat oxidation declines to insignificant levels (Achten et al. 2002). Exploring these associations is essential for elucidating how cardiac, autonomic, and metabolic systems interact to regulate endurance performance.

Agreement between heart rate thresholds, ventilatory thresholds, and skeletal muscle deoxygenation breaking points

Interestingly, the above-mentioned agreement between HR and metabolic thresholds, the HRIP, and HRVT1 coincide with an exponential regulation of pulmonary ventilation during graded exercise. To be precise, Chávez-Guevara et al. (2023) reported a low systematic bias (2 beats/min) and a strong correlation ($r = 0.81$) between HRIP and VT in subjects with obesity. Similarly, Kaufmann et al. (2023) observed a small bias (0.6 beats/min) and narrow LoA (0.9–0.3 beats/min) between HRVT1 and VT in endurance-trained males, reflecting a tight coupling of HR and ventilatory transitions during dynamic exercise. The exercise pressor reflex seems to play a central role in this process, enhancing sympathetic activity and increasing the contractility of both cardiac and respiratory muscles (Grottle et al. 2020).

According to Kipp et al. (2024), ventilatory transitions during exercise increase the metabolic cost of respiration, leading to greater oxygen extraction by respiratory muscles. Concurrently, the exponential acceleration of HR increases myocardial oxygen consumption, as HR is the primary determinant of cardiac oxygen uptake. This heightened oxygen demand creates competition for oxygen between respiratory, cardiac, and limb muscles. In turn, this exacerbates glycolytic flux and lactate production, having a key impact on metabolic regulation by restricting oxygen delivery to skeletal muscles.

Fleitas-Paniagua et al. (2024) reported that HRVT2 and the skeletal muscle deoxygenation breakpoint, identified as the breakpoint in deoxygenated hemoglobin ([HHb] BP), are closely aligned with the respiratory compensation point (RCP). Additionally, Zurbuchen et al. (2020) observed that VT, [HHb]BP, and FATmax were located at a similar exercise intensity in healthy young men, with moderate to strong correlations between these biomarkers. Petelczyc et al. (2018) also noted simultaneous transitions in HRV and [HHb]BP during an incremental graded exercise test, proposing that acceleration of HR mediated by muscle metaboreflex influences blood flow to skeletal muscle during low intensity exercise. Additional mechanisms (e.g., baroreceptor and mechanoreceptor feedback or central command) that modulate cardiovascular control may override this coupling at higher intensities, redistributing blood flow to prioritize oxygen delivery to vital organs like the heart and respiratory muscles.

Contreras-Briseño et al. (2022) and Expinoza-Ramirez et al. (2021) clearly demonstrated this O_2 redistribution as O_2 saturation levels of *vastus lateralis* drastically diminish with the VT, while O_2 saturation levels of *intercostalis* muscle remain stable up to the RCP. At present, the order in which HR thresholds, ventilatory thresholds, muscle deoxygenation thresholds, and metabolic thresholds occur has not been investigated. Thus, a model to test such physiological synchronization from an integrative exercise physiology approach is proposed below.

Exploring heart rate dynamics and its synchronization with ventilatory and metabolic thresholds

Data preparation

Our proposal relies on determining the specific pattern that HR follows during a graded exercise test (Fig. 1). For this purpose, raw HR values are exported to GraphPad Prism (GraphPad, Boston, US), creating a time-series graph allowing a preliminary inspection of the HR curve through a visual analysis. Afterward, all possible patterns for HR dynamics are explored, computing (1) a sigmoidal regression analysis (fourth-degree polynomial regression), (2) a linear regression analysis, and (3) a third-degree polynomial regression analysis (Supplementary file 2). To select the best fitting model, goodness of fit indicators that allow comparison between models with different numbers of parameters (e.g., linear vs. polynomial), such as adjusted R^2, should be examined while ensuring that the Runs test analysis is not significant, which indicates no deviation from the original data.

Once the best fitting model has been identified, HR thresholds can be computed through the Dmax method (see Fig. 1). This decision depends on whether HR follows a sigmoidal or curvilinear pattern. If a sigmoidal pattern is identified, the agreement of the HRIP and HRDP with the other thresholds can be explored. However, if a curvilinear behavior with a single HRDP is noticed, only the agreement with the second exercise threshold could be assessed. Integrative thresholds analysis cannot be performed for patients showing a linear heart rate kinetic (Fig. 1).

Thresholds analysis

Assessing synchronization between different thresholds is a complex task due to the multiple indicators that could define their appearance, such as elapsed time, oxygen uptake (VO_2), HR, or power output, expressed in absolute terms or relative to maximal values recorded during the test. Additionally, defining a practically meaningful difference for each indicator while considering interindividual variability is crucial.

Keir et al. (2022) suggest using VO_2 as a reference for threshold alignment, proposing an acceptable variation of ± 100 mL/min to define synchronized transitions. This criterion accounts for the VO_2 variability registered during the steady-state exercise below the LT1 or VT. Nevertheless, other indicators should still be considered based on test design (e.g., stage duration, increment magnitude) and individual characteristics (e.g., fitness level, training background).

From a practical perspective, we propose that an acceptable delay between thresholds should not exceed 60 s, regardless of whether they occur within the same test stage or across adjacent stages. A delay within this range concurs with the fast component of HR registered at the moderate to heavy intensity domains (Zucarelli et al., 2018). Besides, Cruz et al., (2019) reported that 60 s at any workload was enough to capture the HRVT, while a 60 s delay accounts for systematic errors arising from differences in data collection intervals between measurement devices. This is particularly relevant for lactate sampling, which is typically obtained at discrete time points (e.g., 1 sample per stage), whereas gas exchange, heart rate, and muscle oxygen saturation (SmO_2) are continuously recorded multiple times per minute. However, if thresholds occur with delays exceeding 60 s, especially across multiple test stages, this may imply a desynchronization of bodily systems. Such desynchronization could result from (1) an impaired signaling to the central nervous system, potentially due to dysregulated activation of mechanoreceptors, metaboreceptors, or baroreceptors, or (2) a malfunctioning in central processing structures, such as the nucleus tractus solitarius, which integrates afferent inputs to regulate HR and pulmonary ventilation. Further interpretation of HR patterns and threshold synchronization is provided in Fig. 2.

For visualizing thresholds agreement at the individual level, four to five panels can be aligned vertically, depicting all thresholds available in conjunction with stage duration (Fig. 3). Using this approach, the delay between exercise thresholds can be easily identified, allowing us to explore if bodily systems are working in synchronization, responding to the exercise stimulus. Additionally, comparisons between individuals can be achieved by using radar charts, where the shape/symmetry of the charts may show if their thresholds are similarly aligned (i.e., a similar shape) or widely spread apart (Fig. 4).

Limitations and further directions

In this methodological paper, we describe some of the methods that can be applied to determine HR thresholds; however, several other approaches to computing ventilatory, metabolic, and muscle deoxygenation thresholds are currently available in literature. This implies a challenge for exercise physiologists and data analysts who need to select the most reliable methods, which requires knowledge on how these different approaches influence the agreement and correlation between exercise thresholds (Chávez-Guevara et al. 2024; Gronwald et al. 2024). This is particularly relevant to those that apply the computational modeling of raw HR, ventilation, or any other physiological variable since, depending on the model adjustment, the thresholds will be displaced to a higher or lower exercise intensity potentially leading to an interpretation bias on the synchronization of bodily systems.

Undoubtedly, as discussed by Chavez-Guevara et al. (2024), there should be a consensus or intention to move forward, consolidating laboratory analysis in exercise physiology. Besides, as recently highlighted by Westerblad and Lindinger (2025), interpretation of physiological data must go beyond mere computational models and automatic thresholds detection, requiring strong arguments and algorithms

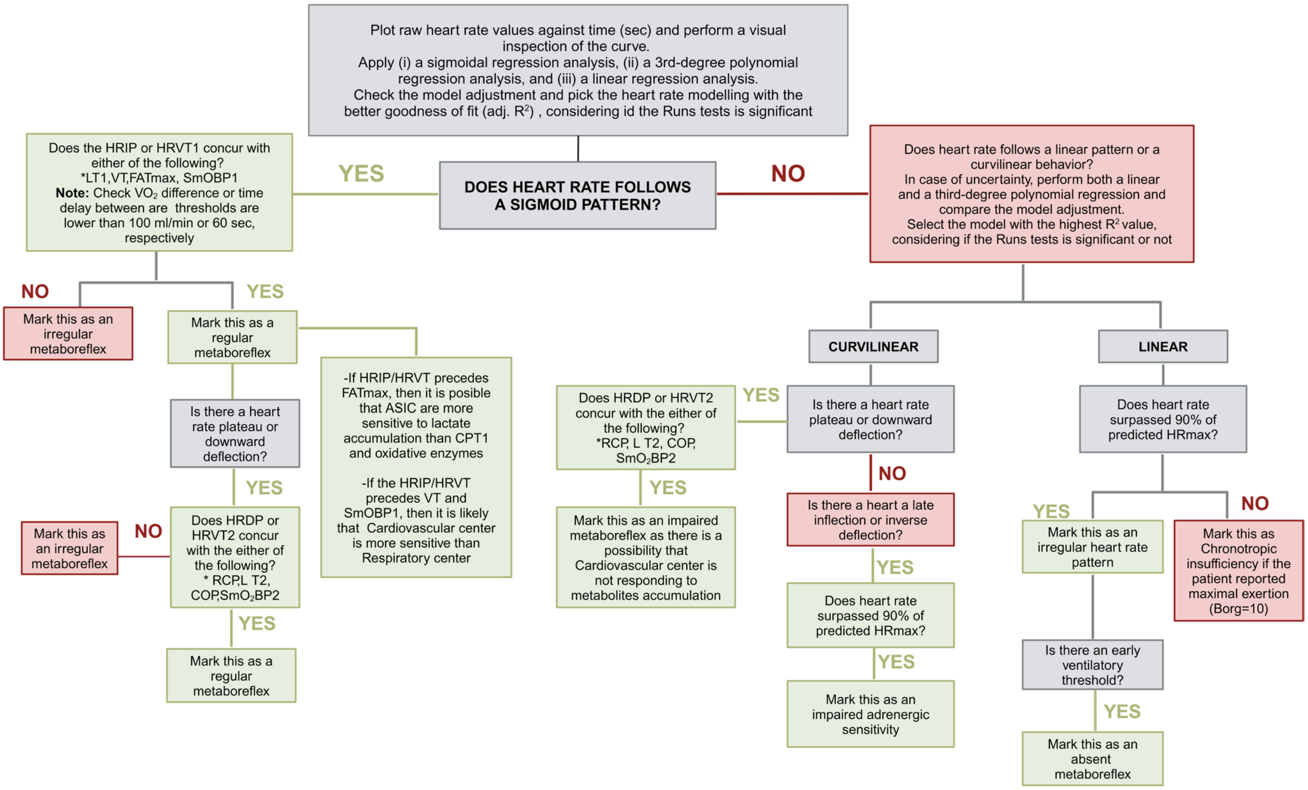
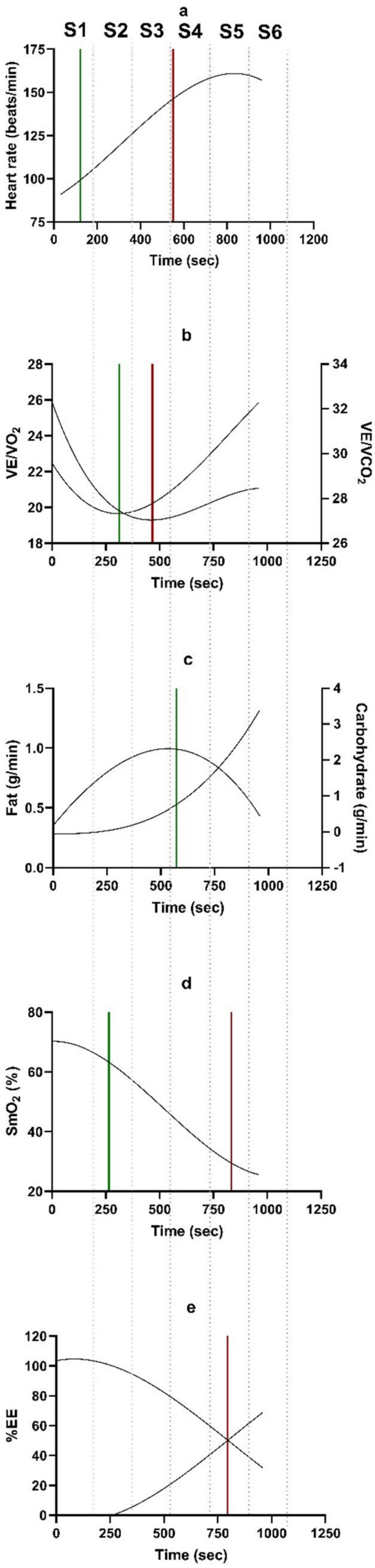


Fig. 2 A novel algorithm to explore heart rate kinetics during dynamic exercise and its synchronization with ventilatory and metabolic thresholds

Fig. 3 Agreement between physiological thresholds in a professional ▸ boxer during a graded exercise test. All transitions corresponding to the first exercise threshold are represented in green discontinuous lines, while all transitions corresponding to the second exercise threshold are represented in red discontinuous lines. The test stages (180 s) are demarcated in gray discontinuous lines to visualize if a significant delay between exercise thresholds is present. As can be seen in the graphs, the heart rate inflection points, the first ventilatory threshold, and the first breaking point in muscle deoxygenation kinetics preceded the stage at which fat oxidation began to decrease. From this analysis, it can be inferred that chemoreceptors are more sensitive to H^+ and lactate accumulation in comparison to enzymes regulating fatty acid oxidation. Particularly, an early activation of these chemoreceptors may have triggered an exponential rise in heart rate and pulmonary ventilation, leading to blood flow redistribution and higher oxygen uptake in cardiac and respiratory muscles. Consequently, this reduced muscle oxygen saturation levels in the limbs, affecting fat oxidation, which responded lately to muscle acidosis. *Note: This analysis corresponds to the professional boxer, also represented in Fig. 1a. For better visualization of the data, all curves were smoothed in GraphPad Prism v.8.1 using a third-degree polynomial regression analysis, verifying that the run test was not significant. In this illustration, the ventilatory threshold and respiratory compensation point were defined as the nadir of ventilatory equivalents of oxygen and carbon dioxide output, respectively (Binder et al. 2008). In addition, the FATmax was computed throughout a 3rd-degree polynomial regression analysis of the fat oxidation curve (Amaro-Gahete et al. 2019), with automatic detection of the area under the curve and its corresponding peak in GraphPad Prism v.8.1. The breaking points in skeletal muscle deoxygenation levels were computed through the Dmax method (Sendra-Pérez et al. 2023), while the crossover point was identified by the visual inspection of the relative contribution of fat and carbohydrates oxidation to energy expenditure (Brooks and Mercier 1994)



that can be easily applied in practice by non-experts outside the laboratory, just as we propose in our new algorithm. By addressing these considerations and fostering interdisciplinary collaboration, this article and the proposed algorithm aim to contribute to advancing an integrative approach in the field of exercise physiology by bridging the gap between laboratory research testing and practical applications in performance optimization and clinical care.

By assessing all possible thresholds, athletes can optimize performance through targeting specific energy systems (e.g., maximizing fat oxidation at FATmax or managing carbohydrate metabolism beyond the crossover point). Besides, in the clinical context, this model may help detect an impaired exercise pressor reflex or deficient oxygen delivery to skeletal muscle.

Of course, several limitations and considerations need to be addressed to refine its application and interpretation. To be precise, this model is a good starting point but has to be validated in future studies, including longitudinal trials where modification of exercise thresholds can be assessed. Additionally, less studied thresholds related to respiratory dynamics (e.g., tidal volume plateau or breathing rate thresholds) and cardiac efficiency (e.g., blood pressure, oxygen pulse, and double product) could be integrated into

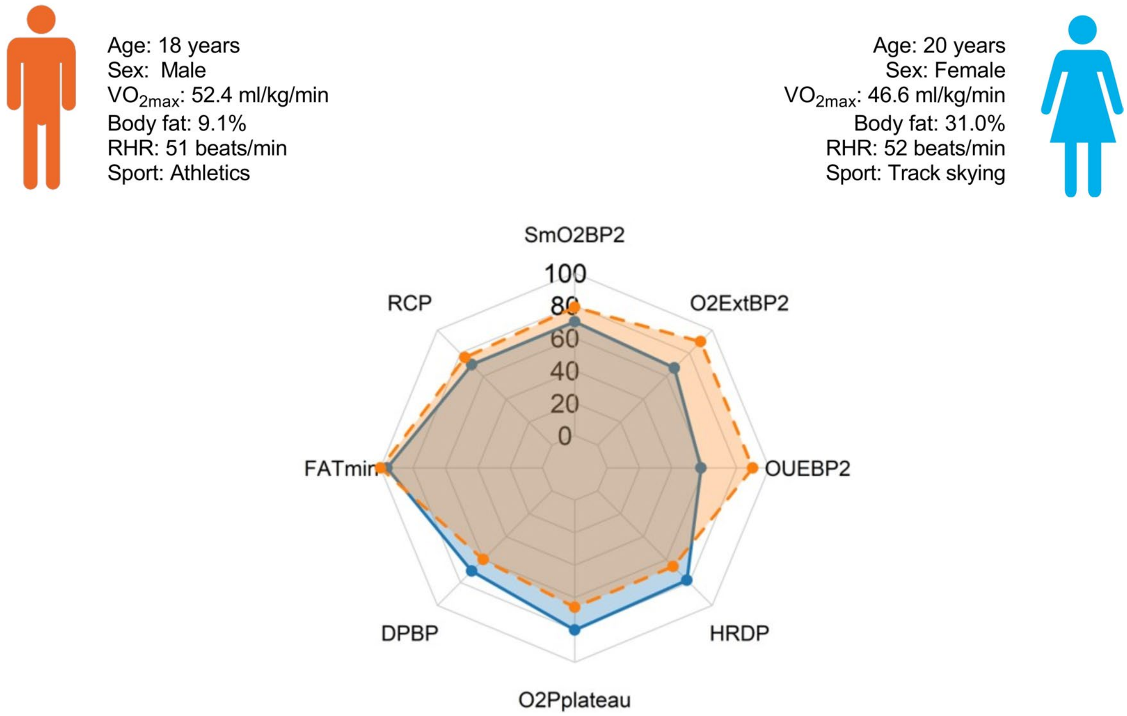


Fig. 4 Synchronization of exercise thresholds during a graded exercise test in a long-distance male runner (orange) and a female cross country track skier (blue). The graph represents the synchronization of cardiovascular, metabolic, and ventilatory transitions during a graded exercise test (second threshold represented in this figure). If the radar chart's data points for each threshold converge or are close to one another, it may suggest that the thresholds are well synchronized. For instance, when comparison among individuals is performed, the shape/symmetry of their radar charts may show if their thresholds are similarly aligned (i.e., a similar shape) or widely spread apart. In this graph, the subject represented in blue exhibits a better synchronization of physiological systems in comparison to the individual represented in orange. Subjects with better synchronization (better symmetry and tighter threshold alignment) might benefit from specific threshold training, while others may need targeted interventions (e.g., improving fat oxidation or ventilatory efficiency). Likewise, asynchrony could indicate underlying metabolic or cardiovascular issues that might need further investigation or customized interventions. *DPBP* double product breaking point, *FATmin* exercise intensity at which fat oxidation becomes negligible, *$O_2ExtBP2$* oxygen extraction breaking point 2, *OUEBP2* oxygen uptake efficiency breaking point 2, *RCP* respiratory compensation point, *RHR* resting heart rate, *SmO_2BP2* skeletal muscle oxygen saturation breaking point 2, *VO_{2max}* maximal oxygen uptake

this analysis, allowing a full characterization of physiological response to exercise for personalized medicine and exercise training (Supplementary file 3).

Complementing integrative threshold analysis with an isolated metaboreflex test would be also recommended to prevent biased interpretations of sympathetic response to metabolic stress (Gamma et al., 2021). Applying the protocol described by Teixeira et al., (2019), clinicians, athletic trainers, and researchers could verify if the cardiovascular center is not responding to lactate accumulation and muscle hypoxia, which may concur with a linear heart rate response during a graded exercise test. Adding assessments of gas exchange and muscle deoxygenation kinetics to that protocol would also be convenient to check if a dampened heart rate response concurs with an impaired muscle perfusion and ventilatory regulation (i.e., delayed SmO_2 recovery after muscle induced ischemia or blunted ventilatory modification).

Conclusion

This perspective introduces a novel systems physiology framework for analyzing heart rate (HR) thresholds in relation to ventilatory, metabolic, and muscular oxygenation transitions. By modeling HR inflection and deflection points as physiological biomarkers—driven, respectively, by afferent feedback mechanisms and β_1-adrenergic receptor saturation—our approach moves beyond traditional, reductionist interpretations of HR response during exercise.

We demonstrate that the expected physiological synchronization proposed by the exercise pressor reflex theory—suggesting tightly coupled responses between HR, ventilation, and metabolism—is not always observed in practice. Discrepancies in the timing and agreement of thresholds suggest that interindividual variability, altered reflex control, or localized impairments in oxygen delivery may disrupt this coordination. Our proposed method allows for the identification of such desynchronization and may help clinicians and performance specialists detect underlying physiological limitations.

Ultimately, this integrative analysis provides a conceptual and analytical foundation to reframe how we assess exercise thresholds in both research and applied settings. It encourages a shift toward multi-system assessment, enabling more personalized diagnostics, performance optimization, and therapeutic strategies in clinical, athletic, and aging populations. Future research is needed to validate this model in diverse populations and with complementary physiological tests, including isolated metaboreflex protocols.

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Declarations

Conflict of interest The authors declare no conflict of interests.

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