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CURRENT OPINION

The Respiratory Compensation Point: Mechanisms and Relation to the Maximal Metabolic Steady State

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Abstract

At a point during the latter third of an incremental exercise protocol, ventilation begins to exceed the rate of clearance of carbon dioxide (CO_2) at the lungs ($\dot{V}CO_2$). The onset of this hyperventilation, which is confirmed by a fall from a period of stability in end-tidal and arterial CO_2 tensions (PCO_2), is referred to as the respiratory compensation point (RCP). The mechanisms that contribute to the RCP remain debated as does its surrogacy for the maximal metabolic steady state of constant-power exercise (i.e., the highest work rate associated with maintenance of physiological steady state). The objective of this current opinion is to summarize the original research contributions that support and refute the hypotheses that: (i) the RCP represents a rapid, peripheral chemoreceptor-mediated reflex response engaged when the metabolic rate at which the buffering systems can no longer constrain the rise in hydrogen ions ($[H^+]$) associated with rising lactate concentration and metabolic CO_2 production is surpassed; and (ii) the metabolic rate at which this occurs is equivalent to the maximal metabolic steady state of constant power exercise. In doing so, we will shed light on potential mechanisms contributing to the RCP, attempt to reconcile disparate findings, make a case for its adoption for exercise intensity stratification and propose strategies for the use of RCP in aerobic exercise prescription.

1 Introduction

The exercise intensity domain schema originally proposed by Whipp [1] recognizes three ranges of exercise intensity that are partitioned by two individual-specific metabolic boundaries. Exercise in relation to these boundaries elicits distinct and predictable physiological stress profiles. The highest intensity at which blood lactate remains near baseline concentrations (i.e., the lactate threshold; LT) demarcates the

Key Points

The respiratory compensation point (RCP) has been defined as the onset of hyperventilation during incremental exercise.

A prevailing theory is that the RCP marks the intensity at which the body's buffering mechanisms fail to constrain the metabolic (or lactic) acidosis.

In this opinion article, we argue that the RCP represents a rapid ventilatory reflex response engaged when the highest metabolic rate associated with acid–base stability (i.e., the maximal metabolic steady state; MMSS) is surpassed.

Evidence for and against a peripheral chemoreflex-mediated response underpinning the RCP and its surrogacy for MMSS is provided.

Additional mechanisms contributing to the RCP are also discussed to reconcile disparate findings.

Finally, we provide recommendations for the use and interpretation of RCP in exercise intensity stratification and aerobic exercise prescription.

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first boundary and separates the moderate- from the heavy-intensity domains. The second boundary, which partitions the heavy- from the severe-intensity exercise domains [2–4], is identified as the highest intensity associated with steady state lactate, gas exchange and acid–base conditions (i.e., maximal metabolic steady state; MMSS) [5, 6].

In recent years, the respiratory compensation point (RCP) of incremental exercise has garnered increasing attention as a surrogate identifier of MMSS [7–12]. However, there remains divisiveness amongst proponents of the exercise intensity domain schema regarding the validity of the RCP as an indicator of the boundary that stratifies the heavy- and severe-intensity domains [13–18], particularly because the mechanisms that contribute to the RCP are debated [19]. This current opinion will summarize the evidence in support of the hypothesis that the metabolic rate at the RCP can represent the boundary that identifies the MMSS. Evidence refuting this hypothesis will also be presented as well as discussion on how to reconcile disparate findings and on potential factors contributing to the manifestation of the RCP during incremental exercise. Discussion of the topic will focus exclusively on the initiation of respiratory compensation and not the factors contributing to the magnitude of hyperventilation thereafter, which are multifactorial [20, 21] as detailed in the commentary [19] to a recent viewpoint on the topic [22].

2 Overview of the RCP

During exercise, ventilation ($\dot{V}_E$) rises in proportion to the rate at which carbon dioxide (CO_2) is cleared from the lungs. This tight coupling represents a remarkable control system that can prevent CO_2 accumulation and maintain arterial CO_2 tension ($PaCO_2$) and pH relatively constant over a range of metabolic rates up to 16-fold greater than resting oxygen uptake ($\dot{V}O_2$). During a typical incremental exercise test, the relationship between $\dot{V}_E$ and the rate of CO_2 excretion at the lungs ($\dot{V}CO_2$) is linear up to approximately 70–90% of maximum oxygen uptake ($\dot{V}O_{2max}$); beyond this metabolic rate, the rate of increase in $\dot{V}_E$ begins to exceed that of $\dot{V}CO_2$. The onset of this hyperventilation relative to $\dot{V}CO_2$ coincides with a progressive fall in arterial CO_2 tension ($PaCO_2$) and is referred to as the RCP [23].

In healthy adults (age range: 18–83 years), the RCP has been shown to manifest at ~ 83 ± 6% of $\dot{V}O_{2max}$ [± standard deviation (SD)] [24], well above the LT which can be identified noninvasively as the intensity at which $\dot{V}CO_2$ rises disproportionately from $\dot{V}O_2$ [25]. The latter phenomenon is a consequence of bicarbonate (HCO_3^-)-mediated buffering of the protons associated with heightened lactate anions (La^-) in blood [2, 25], commonly referred to as the gas exchange threshold (GET), and occurs at ~ 60 ± 7% of $\dot{V}O_{2max}$ [24]. Figure 1 depicts gas exchange and ventilatory responses as well as arterialized venous blood samples of a representative individual during ramp-incremental cycling exercise. Between the LT (or GET) and RCP, $\dot{V}_E$ and $\dot{V}CO_2$ rise proportionately such that $PaCO_2$ remains stable. Within this isocapnic buffering region of the incremental test, [HCO_3^-] declines in a manner that is reciprocal to the rise in [La^-] [26, 27]; as a result, the acidification of the blood is largely prevented [28]. The RCP marks the end of the isocapnic buffering phase and the onset of additional respiratory drive (in excess of that required for $\dot{V}CO_2$), which provides compensatory support to the bicarbonate-buffering system to attenuate the decline in arterial pH through the exhalation of CO_2 and reduction in $PaCO_2$ (as dictated by the Henderson Hasselbalch equation).

3 RCP: A Rapid Peripheral Chemoreflex Response Linked to Metabolic Events?

Above the RCP, the metabolic acidosis that had been largely constrained during the isocapnic buffering phase rapidly worsens reflecting a sudden loss of the body's ability to maintain acid–base homeostasis (see the arterial pH profile above versus below the $\dot{V}O_2$ at RCP in Fig. 1). On this premise, we propose that: (i) the RCP represents a rapid peripheral chemoreceptor-mediated ventilatory reflex response engaged when the highest metabolic rate associated with acid–base stability is surpassed; and (ii) the metabolic rate associated with the RCP is equivalent to the MMSS of constant-work rate exercise.

On transition across the MMSS boundary, lactic acid production accelerates rapidly [29] and the rise in intramuscular [La^-] is reflected in blood with a similar time course [30]. In turn, the consequent accumulation causes an acceleration of proton production in muscle and blood that overwhelms the bicarbonate (and other) buffering systems that, at lower metabolic rates, had diminished the rise in arterial [H^+] above resting levels [28] (Fig. 1). The sudden rise in arterial [H^+] prompts type I cells in the carotid body to initiate a rapid respiratory reflex response to eliminate CO_2 and provide (partial) compensation for the developing metabolic acidosis (i.e., the RCP). This sequence of events would be expected to occur rapidly as all involved metabolic and chemical processes are nearly instantaneous [31], circulatory times between muscle and carotid body at such intensities are short (likely < 5 s [32]), transduction of pH changes from intravascular to extracellular spaces are rapid [33, 34] and neurally mediated reflex responses occur within seconds [35–38]. For example, two breaths of hypercapnic gas administered during steady-state exercise of increasing intensity elicit a robust increase in $\dot{V}_E$ within seconds ([39] and illustrated in Fig. 2 in [40]; although, transduction of metabolic rather than respiratory acidosis to a $\dot{V}_E$ response is likely slower [41] albeit evidence indicates that

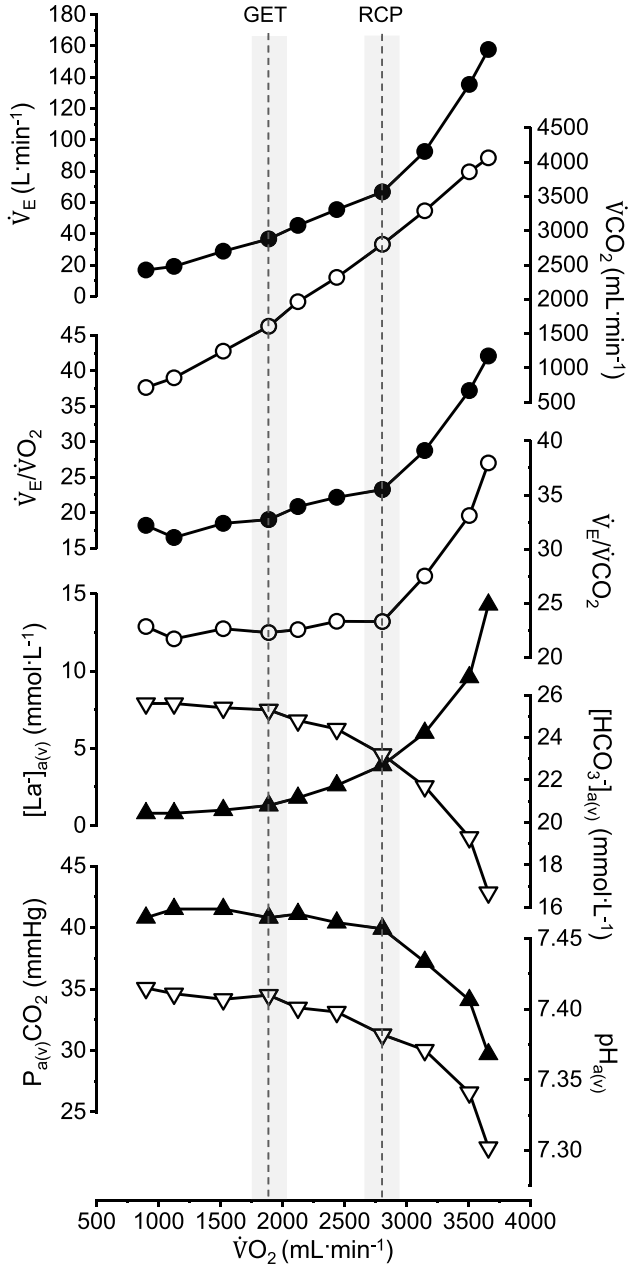

Fig. 1 Stack plot of gas exchange and ventilatory data (circles) as well as arterialized venous samples (triangles) of a 37-year-old male in response to 15 W min^{-1} ramp-incremental exercise performed on a cycle ergometer. Arterialized venous samples were drawn every ~ 30 W, from a catheter placed in the dorsal vein of a heated hand and immediately analysed using a blood gas analyzer (ABL90Flex, Radiometer). Vertical dash lines with shaded grey areas represent the approximate oxygen uptake ($\dot{V}O_2$) value of the gas exchange threshold (GET) and respiratory compensation point (RCP). Gas exchange and ventilatory variables include: oxygen uptake, carbon dioxide exhalation ($\dot{V}CO_2$), minute ventilation ($\dot{V}_E$) and ventilatory equivalents for $\dot{V}O_2$ ($\dot{V}_E/\dot{V}O_2$) and $\dot{V}CO_2$ ($\dot{V}_E/\dot{V}CO_2$). Arterialized venous (a(v))) blood chemistry variables include: lactate concentration ([La$^-$]), bicarbonate concentration ([HCO$_3^-$]), partial pressure of CO_2 ($PaCO_2$) and pH

the response to the former should be rapid enough to link RCP to MMSS [42, 43]). Importantly, this rapid reflex response occurs despite increased tonic contribution to total $\dot{V}_E$ from the peripheral chemoreceptors [44].

The following subsections will summarize the evidence in favour and opposed to the hypotheses that the RCP is a manifestation of a rapid ventilatory reflex that occurs when the metabolic rate associated with the MMSS is surpassed (Sect. 3.1) and thus is equivalent to MMSS (Sect. 3.2).

3.1 The RCP is a Rapid Peripheral Chemoreceptor-Mediated Reflex Response Engaged When the Highest Metabolic Rate Associated with Acid–Base Stability is Surpassed

3.1.1 Evidence for

An appropriate test of this hypothesis would be to examine conditions where the humoral stimulus to the peripheral chemoreflex or the peripheral chemoreceptors themselves are defective or removed. With respect to the latter, compared with healthy control participants who performed incremental exercise of 15 W min^{-1}, those with carotid body resection exhibited a blunted ventilatory response and a $\dot{V}_E$ versus $\dot{V}O_2$ relationship that maintained a more linear relationship above GET [45]. This occurred despite similar falls in arterial [HCO$_3^-$] and was attributed to an inability to develop respiratory compensation for the metabolic acidosis. The fact that those without carotid bodies exhibit a GET but not an RCP [45] provides support that the GET and the RCP reflect separate metabolic/physiological events and that the peripheral chemoreflex is involved mainly in the latter. Similarly, those with congenital central hypoventilation syndrome—a condition characterized by near absence of respiratory chemoreflexes—do not hyperventilate between GET and $\dot{V}O_{2max}$ [46]. These findings not only support peripheral chemoreflex involvement but also suggest that other feedback sensory mechanisms including, for example, the group III/IV muscle afferents, although involved in the control of breathing [47], do not contribute meaningfully to the RCP (see Sect. 3.3 below).

During incremental exercise, up to the RCP, the [H$^+$] of arterial blood rises approximately linearly above resting levels (Fig. 1). It is at the RCP that the rise in [H$^+$] begins to accelerate [28], providing a stimulus for a rapid respiratory peripheral chemoreflex response (superimposed upon its increasing tonic contribution [44]). In agreement with this view, at high intensities during ramp-incremental cycling exercise, when the acceleration of [H$^+$] is prevented by sodium bicarbonate infusion, the onset of hyperventilation is delayed [48, 49]. In this condition, despite the maintenance of arterial pH, a dampened hyperventilatory response

eventually ensues, albeit at a greater $\dot{V}O_2$ compared with normal conditions (near $\dot{V}O_{2max}$). At such intensities, other factors unrelated to an acceleration in arterial $[H^+]$ at MMSS including hyperthermia, catecholamines, osmolarity, hypoxemia (in some), central chemoreception and feedforward mechanisms are also likely to contribute. Notably, an inevitable effect of sodium bicarbonate infusion is a rise in $PaCO_2$ relative to control conditions (see Fig. 1 in [48]). With the blood–brain barrier impermeable to sodium bicarbonate, this rise in $PaCO_2$ would be expected to contribute to an elevated brain $[H^+]$ including in the brainstem where activated central chemoreceptors would initiate a compensatory ventilatory response [50], independent of carotid body involvement. This consideration suggests that the frank hyperventilation during ramp-incremental exercise in control conditions is mediated by the stimulation of peripheral chemoreceptors; however, in bicarbonate infusion conditions it may primarily be mediated by respiratory drivers that are independent of arterial $[H^+]$.

3.1.2 Evidence Against

Rather than a rapid chemoreflex response, an alternative hypothesis is that the RCP represents a delayed expression of the peripheral chemoreflex that is activated when arterial $[La^-]$ associated $[H^+]$ rises (i.e. after the metabolic rate associated with the LT (or GET) is surpassed during incremental exercise) [51, 52]. Based on this interpretation, the period of isocapnia that precedes the onset of hyperventilation would reflect slow kinetics of the compensatory ventilatory reflex response [53]. On this premise, the RCP should be considered a ventilatory construct secondary to LT (or GET) and not a metabolic construct [51] that is suitable to identify MMSS.

Comparisons of extremes ramp slopes lend support to this view. For example, on the high end of the spectrum, applying a ramp rate of 65 W min^{-1}, Scheuermann and Kowalchuk [54] observed that respiratory compensation for developing lactic acidosis, as evidenced by a fall in arterialized venous PCO_2 ($Pa(v)CO_2$), was absent. Similar findings were also documented by other groups applying ramp rates > 50 W min^{-1} [55]. In contrast, for very slow ramps ($\leq$ 8 W min^{-1}), evidence of isocapnia beyond GET is not always observed as both $Pa(v)CO_2$ and $P_{ET}CO_2$ may decline before frank hyperventilation is observed. Both extremes in ramp-incremental exercise slope indicate that time may be a factor per se in the expression of RCP. If too little time is provided, respiratory compensation will not be observed; whereas if sufficient time is provided, PCO_2 may begin to slowly decline shortly after the LT is surpassed. Although, in these conditions, a rapid fall in PCO_2 is still typically observed at a $\dot{V}O_2$ well above GET [54]. In addition, the peripheral chemoreflex response has been shown to occur within seconds of stimulation both at rest [56, 57] and during exercise [37, 39] making the hypothesis of a delayed expression of the peripheral chemoreflex response difficult to justify.

In addition, during constant-power exercise within the heavy-intensity domain, following a transient rise, the profile of $PaCO_2$ has been shown to fall below pre-transition pressures by ~ 2–3 mmHg and ~ 6–7 mmHg following 24 min of exercise at 20% of the difference between the GET and CP [58] and at estimated CP [59], respectively. Thus, at least in the constant-work rate paradigm, hyperventilation occurs at intensities below MMSS. Whether this reflects "respiratory compensation for lactic acidosis" or the emergence of some other respiratory drive induced by thermal [60], mechanical [61], humoral or feedforward mechanisms [22] to breathe is not clear (see Sect. 4 for further discussion).

Factors unrelated to humoral stimuli have also been implicated in the manifestation of the RCP including mechanical changes related to work of breathing, muscle afferent feedback, and feed forward mechanisms. Prior to the RCP, the increase in $\dot{V}_E$ is achieved by rises in both tidal volume and breathing frequency, but around the RCP [62], rises in breathing frequency predominate to limit work of breathing associated with achieving high lung volumes [63]. These changes are associated with a rise in $\dot{V}_E$ relative to $\dot{V}CO_2$ and a fall in $P_{ET}CO_2$ (the rising phase of expired CO_2 is truncated causing widening of the arterial-end-tidal gradient) [23]. Intrathecal injections of group III/IV muscle afferent suppressing fentanyl during exercise in humans have revealed their involvement in the hyperpneic response [47]. These local sensors of mechanical strain and metabolism would seem a prime candidate to initiate a compensatory response when the MMSS is surpassed. Although not tested directly, a sudden rise in $\dot{V}_E/\dot{V}CO_2$ appears to occur during incremental-type exercise with or without opioid-induced blockade of afferent signals [47]; although the relationship is displaced downward in the former. The RCP has also been related to a volitional response initiated, not reflexively, but from central regions involved in the generation of motorneuronal drive [22, 64, 65]. Disentangling feed-forward from feedback mechanisms as they relate to the initiation of hyperventilation (and not total ventilatory drive, e.g. [66]) remains an investigative challenge.

3.2 The Metabolic Rate Associated with the RCP is Equivalent to the MMSS of Constant-Work Rate Exercise

3.2.1 Evidence For

For the RCP to satisfy the definition of a distinct metabolic boundary, the $\dot{V}O_2$ at which it is identified in an individual should be invariably independent of the characteristics of the incremental protocol. Several studies have demonstrated that an RCP is identifiable in slow, moderate and fast-incrementing ramp protocols and that the $\dot{V}O_2$ associated with the identified RCP is constant and independent of ramp slope [16, 67, 68]. For example, in participants who performed in random order each of a 5, 10, 15, 25 and 30 W min^{-1} ramp-incremental cycling protocols to exhaustion, we observed that the $\dot{V}O_2$ associated with RCP (and GET) was not different and exhibited high inter-test uniformity within each of the eleven participants [68]. With the $\dot{V}O_2$ at GET and RCP both fixed, the key difference between ramp slope conditions was the rate at which $\dot{V}O_2$ rose between these indices. On average, the $\dot{V}O_2$ increased linearly with time at a rate of 55, 104, 127, 196 and 207 mL min^{-1} per minute of exercise for the 5, 10, 15, 25 and 30 W min^{-1} ramp protocols, respectively. As a consequence, compared with the slowest ramp protocol (i.e. 5 W min^{-1}), the time interval for the isocapnic buffering phase was reduced from 13 min to 7, 6, 4 and 4 min in the faster ramp tests. From a mechanistic perspective, this observation is incompatible with the hypothesis that the RCP reflects a delayed carotid body reflex response to a metabolic acidosis imposed by the elevation in arterial [La^-] above the LT. Were this to be true, one would expect the temporal response to occur at a relatively fixed interval above LT such that the isocapnic buffering phase interval is constant.

Unlike the $\dot{V}O_2$ at RCP, the work rate at RCP connection is affected by the dynamics of $\dot{V}O_2$ (i.e. the $\dot{V}O_2$ kinetics) that modify the $\dot{V}O_2$ versus work rate relationship in different exercise paradigms [8, 69, 70]. As a result, the work rate corresponding to RCP appears to differ between constant-power versus ramp-exercise and among ramps of variable slope unless the difference in the $\dot{V}O_2$ versus work rate relationship among paradigms is accounted for [9, 67]. To this aim, we developed a cycling-based exercise protocol named the step-ramp-step (SRS), which corrects for ramp- versus constant-power exercise discrepancies and identifies the constant-power output to elicit the $\dot{V}O_2$ at RCP [9]. Thereafter, we tested the hypothesis that exercise at versus above this intensity exhibits characteristics of the heavy-severe intensity boundary. In most individuals, exercise at the RCP exhibited physiological features consistent with the heavy-intensity domain (i.e. the ability to attain steady states in $\dot{V}O_2$ and blood [La^-]), whereas in 8 of 10 participants exercise just above the RCP did not [9]. Notably, in those two participants in whom the SRS protocol underestimated the correct PO, the $\dot{V}O_2$ at RCP and at MMSS were found, nonetheless, to be practically the same (i.e. within ~ 100 mL min^{-1}). Similar findings were also obtained using a treadmill-adapted version of the SRS protocol [71], using ramps of differing slope [72] and with the application of a different method of correcting ramp versus constant work rate responses [67]. Collectively, these findings demonstrate that the $\dot{V}O_2$ at which the RCP occurs can accurately approximate MMSS.

Within the literature, the asymptote of the severe intensity-derived power versus time relationship or critical power (CP) is largely (but not universally [73]) accepted as a key index of MMSS [6]. To explore the hypothesis that the RCP relates to the MMSS, we independently measured the steady-state $\dot{V}O_2$ associated with CP and compared these to the $\dot{V}O_2$ at RCP [74]. The $\dot{V}O_2$ associated with RCP was similar to and displayed high intra-individual agreement with the $\dot{V}O_2$ values at CP [74]. Since publishing this study in 2015, we and others have corroborated the surrogacy between these indices in several follow-up studies [67, 68, 75, 76]. In addition, in amateur cyclists, we explored the long-term association between RCP and maximal lactate steady-state (MLSS, another commonly used index of MMSS) and found that changes in both direction and magnitude between the $\dot{V}O_2$ associated with RCP and MLSS over a 6-month period of training and racing strongly correlated [77].

More recently, we surmised that if the RCP and CP are surrogates of each other, then the SRS-predicted PO at RCP and peak power output achieved during an exhaustive incremental exercise test could be used to calculate total work capacity above CP (i.e. W′ in kJ) [78]. Fourteen healthy participants completed an SRS protocol and four severe intensity trials at power outputs predicted to elicit exhaustion in 2.5, 5, 10 and 13 min. These bouts were also used to determine CP and W′ by conventional methods. On average, both CP and W′ parameters derived from the SRS protocol versus power–time series data were not different (192 ± 53 W versus 193 ± 53 W, respectively) and, as a corollary, time-to-exhaustion predictions from the SRS-predicted CP and W′ were highly accurate (varying on average by ~ 11 ± 9%) [78].

3.2.2 Evidence Against

By far, most of the cited evidence against an equivalence between RCP and MMSS stems from reports of significant differences between the ramp work rate at which RCP is observed and CP [16, 74, 79–83]. However, as highlighted in Sect. 3.2.1,

a direct equivalence between RCP and MMSS should not be expected unless a correction strategy is applied that accounts for the difference in the $\dot{V}O_2$ versus work rate relationship from ramp-incremental (used to identify RCP) versus the constant-work rate paradigm (used to determine MMSS). With respect to the former, the $\dot{V}O_2$ essentially "chases" the rise in work rate from ramp onset and thus requires correction. Within a given individual, the degree by which work rate is "ahead of" $\dot{V}O_2$ depends largely on how rapidly the work rate increases (i.e., the steepness of the ramp slope) [84]; the gap widens with faster ramps and narrows with slower protocols [16, 67, 68]. For example, in our study comparing multiple ramp slopes [68], the RCP was observed uniformly at 2.8 L min^{-1}, but the corresponding, uncorrected ramp power output rose from 213 W (which was not different from the measured MMSS) for the 5 W min^{-1} protocol to 223, 236, 252 and 262 W for 10, 15, 25 and 30 W min^{-1} protocols, respectively. Importantly, except for the 5 W min^{-1} slope, the power outputs identified at the RCP for the other protocols increasingly overestimated the constant power output that would elicit the $\dot{V}O_2$ at RCP. Furthermore, similar adjustments for $\dot{V}_E$ kinetics are unneccessary when identifying the $\dot{V}O_2$ at RCP. Although $\dot{V}_E$ kinetics are different from those of $\dot{V}O_2$ [85], if it is the rapid reflex response that signifies the crossing of the metabolic rate associated with accelerated arterial $[H^+]$, then this would be superimposed upon the overall $\dot{V}_E$ response to ramp-incremental exercise.

Work rate comparisons and $\dot{V}_E$ kinetics notwithstanding, there are other lines of argument that refute the RCP as a metabolic construct that is connected to MMSS.

First, individuals who lack glycogen phosphorylase and do not produce lactate (i.e., McCardle's syndrome) exhibit a hyperventilatory response during incremental exercise despite an absence of lactate-induced acidosis [86]. Compared with the mean response of 26 healthy controls, 4 individuals with McCardle's syndrome, exhibited a more robust fall in $P_{ET}CO_2$ near ~ 75% of $\dot{V}O_{2max}$ despite no change in blood lactate concentration compared to resting baseline values. However, the validity of this interpretation as evidence against $[H^+]$ and peripheral chemoreflex involvement in the hyperventilatory response has been criticized [87].

Second, in conditions of respiratory dysfunction, such as humans with chronic obstructive pulmonary disorder (COPD) [88] or horses with severe flow limitations of the upper airway during high-intensity exercise [89], $PaCO_2$ rises during severe-intensity exercise. Despite this, CP has been measured in COPD [90–92] and horses [93], indicating, perhaps, that both express an MMSS that should be surpassed during incremental exercise. In addition, the power–time relationship, but not RCP, has been demonstrated in numerous species and different modes of exercise (including those of small muscle mass) [14]. This would suggest that CP, and thus MMSS, is a ubiquitous feature of muscle metabolic responses to exercise, but the RCP is not.

Third, although many studies have demonstrated that, on average, the $\dot{V}O_2$ at RCP and CP are not different [74, 79, 80, 94], correlations range from strong to weak with some reporting a high degree of intra-participant variability between indices. In addition, interventions designed to alter the position of RCP and CP (e.g., pedal cadence [94] and exercise training [81]) have reported weak and statistically non-significant relationships between pre- versus post-intervention changes in RCP and CP (in terms of both $\dot{V}O_2$ and work rate). Such uncoupling would suggest that different mechanistic underpinnings between the two metrics.

4 Considerations for Reconciling Differences

We and others have generated evidence to support that the RCP is a metabolic construct initiated upon crossing MMSS during incremental exercise; however, there also exists considerable evidence against this assertion. How do we reconcile this?

One possibility is that the equivalence between RCP and MMSS is circumstantial. Although gas exchange and ventilatory variables and their changes during incremental exercise provide a non-invasive view to changes in muscle metabolism, this insight can only be valid under well-controlled circumstances [95]. In this regard a parallel could be made to the association between GET and LT. It is well accepted that these are surrogates [25, 95–99] and that GET may be used to identify the moderate-heavy intensity domain boundary [7, 98], but we also know that the two can be dissociated in certain conditions. For example, they may be dissociated by manipulation in substrate utilization by prior glycogen depletion [100] and in CO_2 storage by prior hyperventilation [101]. Presumably any condition that alters CO_2 storage/excretion (e.g. substrate alteration, anxiety) or $\dot{V}_E$ (e.g. mechanical constraint, flow limitation, chemoreflex control, physiological dead space) will make the RCP difficult, or even impossible, to detect. The flow-limited moderate-to-severe patient with COPD with high deadspace and low inspiratory reserve exemplifies these issues. At low intensities of exercise, these patients can become hypoxemic [102, 103] providing an atypical stimulus for the peripheral chemoreflex early during exercise and (potentially) a hyperventilatory response that is unrelated to lactic acidosis. Others with this condition may be unable to mount a hyperventilatory peripheral chemoreflex response despite metabolic acidosis due to mechanical constraint and high work of breathing [104, 105]. Thus, like GET from LT, the RCP, which under certain circumstances can be dissociated from MMSS, may not mean that these are not mechanistically related and that RCP cannot be a surrogate of MMSS.

In addition to CO_2 production and $[H^+]$-induced stimulation of breathing via peripheral chemoreceptors, other factors

impart additional drives to breathe during exercise including heat, hydration and changes in circulating concentrations of catecholamines, hormones and metabolites [20, 28, 49]. These variables have been shown to increase ventilation and induce hypocapnia; particularly during prolonged exercise. For example, Gonzalez-Alonso et al. [60] observed that $\dot{V}_E$ and $PaCO_2$ remain relatively stable during > 2 h of cycling exercise at ~ 60% of $\dot{V}O_{2max}$, during which progressive hyperthermia and dehydration were prevented. However, with similar exercise that permitted hyperthermia and dehydration (and hyperthermia plus euhydration), $\dot{V}_E$ rose progressively causing $PaCO_2$ to decline further from resting tensions as exercise continued. In that same study, adrenaline infusion also increased $\dot{V}_E$ at all points during prolonged exercise compared with a saline infusion control. The above reasons could explain the dissociation between $\dot{V}_E$ and $\dot{V}CO_2$ with associated hypocapnia observed during either prolonged constant-work rate below MMSS or slow-incrementing ramps, in the absence of accelerating metabolic acidosis. With respect to the latter, although $PaCO_2$ may begin to fall before MMSS, a rapid peripheral chemoreflex-mediated response with frank decline in $PaCO_2$ may still be observed when transitioning across the $\dot{V}O_2$ at MMSS.

With regard to the connection between RCP and MMSS, the use of CP as a surrogate of MMSS for comparisons to RCP may be, in itself, a source of limitation. Although CP is a helpful tool to identify the heavy-severe-intensity boundary, it too is an estimate of the MMSS that is subject to error in a range that is similar to RCP (~ 3–8%; [106, 107] or as much as ~ 100 mL min^{-1} or ~ 10 W). Determination of each candidate marker of the heavy-to-severe intensity boundary (e.g., MLSS, lactate turnpoint, etc.) carries its own inherent limitations, inaccuracies and imprecisions in predicting MMSS. Methods to identify the RCP are no exception. Potential sources of error stem from the signal-to-noise ratio of the data, the subjectivity associated with collectively interpreting the eight different profiles of gas exchange and ventilation data to estimate the $\dot{V}O_2$ at which the RCP occurs [97] and the translation of that ramp-identified $\dot{V}O_2$ into a work rate [8]. These factors must be considered when interpreting direct comparisons between any proposed index of MMSS.

Therefore, we suggest that in scenarios where a functional carotid body capable of raising $\dot{V}_E$ is present, the onset of this reflex response should coincide with the crossing of MMSS and this reflex response should coincide with a change in the rate of rise of arterial $[H^+]$. Importantly, other respiratory factors initiated before or after the MMSS can contribute to hypocapnia, but these do not refute the underlying MMSS-induced acidosis linkage with the peripheral chemoreflex. Based on this mechanistic definition of the RCP, there appear to be many conditions, activities and environments where the RCP will coincide with MMSS. That said, we acknowledge and have presented conditions (e.g., COPD, carotid body resection, central hypoventilation syndrome, McCardle's disease, exercise-induced arterial hypoxaemia) and interventions (e.g., sodium bicarbonate infusion, hyperoxia, prior hyperventilation) where, as defined herein, the RCP cannot and should not be identified and used as a surrogate of MMSS. These factors should be considered in the design of future prospective studies that aim to aid in the understanding of the mechanisms contributing to the RCP or consider using the RCP for aerobic exercise prescription.

5 Practical Utility of the RCP for Aerobic Exercise Prescription

The need to revise traditional methods of prescribing exercise intensity has gained momentum in recent years [7, 24, 108]. We and others advocate that the exercise intensity domain schema should be preferred to the traditional percentage maximum-based approaches (e.g. $\%\dot{V}O_{2max}$, heart rate max or their reserves) to obtain an individually tailored exercise intensity. Application of this method will improve the evaluation of physiological adjustments and adaptations to acute and chronic exercise through enhanced control of exercise stress characteristics [7–9].

Widespread adoption of this framework requires consensus on the indices that demarcate, in particular, the second of the two metabolic boundaries. Traditionally, the CP is used to estimate the heavy-severe intensity domain border. Importantly, we are not advocating against this metric. Instead, considering this current opinion, we are proposing that, under circumstances where the RCP can be identified, it is also a valid means to establish MMSS. Acceptance of this concept offers the tremendous prospect of being able to estimate, using slight modifications to standard ramp-incremental protocols (e.g. Iannetta et al. [9] and Caen et al. [67]), the full range of work rates defining the moderate- and heavy- (and severe- [78]) intensity domains at the individual level.

A notable issue with the RCP is that a near-maximal incremental exercise effort is required. We and others have demonstrated that clinical exercise tests performed in those with chronic conditions (e.g., acute coronary syndrome, heart failure) who are unaccustomed to exhaustive exercise may not be optimal for RCP manifestation due to premature or submaximal test termination [10, 109, 110]. However, use of ramp versus step protocols (e.g., Bruce or modified Bruce) increases the probability of achieving $\dot{V}O_2$ values above the RCP [12]. From our experience, ramp-incremental protocols of moderate slope designed to exhaust participants in 10–16 min appear to provide optimal data to identify the RCP. With this protocol, the RCP should be identifiable around ~ 80% $\dot{V}O_{2max}$ (± 10%) in healthy adults of all ages

[24, 111] and ~ 85% $\dot{V}O_{2max}$ (± 10%) in those with cardiovascular disease [10, 11] and the interested reader is referred to our previous work for standardized strategies to identify RCP [97] and, in cycling, identify the work rate at which it occurs [9, 78].

6 Summary and Conclusion

There exists opposition to the notion that the RCP of incremental exercise reflects a crossing of MMSS or the heavy-severe intensity boundary in the whole-body exercise paradigm [14, 15, 18, 51, 112]. However, several lines of evidence generated by our research and others support the view that the RCP of incremental exercise is a ventilatory manifestation of the transition across the metabolic boundary associated with MMSS initiated by the peripheral chemoreflex. There appear to be many conditions, where this hypothesis holds true and where the use of the RCP can aid in the prescription of aerobic domain-specific exercise. Acceptance of this will enrich research in exercise science and physiology and will increase the chances of performing successful and safe exercise training interventions and investigations.

Data availability Data displayed in this article will be made available upon reasonable request to the corresponding author.

Declarations

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Author contributions All authors contributed to the ideas and writing of the manuscript and have read and approved its final version.

Ethics approval and participant consent The study from which data for Fig. 1 were obtained was reviewed and approved by the University of Western Ontario Health Sciences Research Ethics Board (123924) and the individual depicted provided their written informed consent to participate in this study.

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