Studies using pharmacological blockade of muscle afferents provide new insights into the neurophysiology of perceived exertion

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Muscle contractions produce mechanical and chemical stimulation of both thinly myelinated (group III) and unmyelinated (group IV) muscle afferents, increasing their discharge towards the central nervous system. This afferent feedback is a key determinant in the regulation of human endurance performance as it stimulates cardiovascular responses to the exercise (i.e. "exercise pressor reflex"). While the role of group III-IV muscle afferents in the regulation of cardiovascular responses to the exercise in healthy subjects is well known, its role in the regulation of cardiovascular responses to the exercise in pathological population remains poorly understood. In a recent article in The Journal of Physiology, Barbosa *et al.* (2016) demonstrated that feedback from group III-IV muscle afferents contributes to the exaggerated blood pressure response to cycling exercise in hypertensive men. To do so, the authors attenuated the "exercise pressor reflex" by pharmacological blockade of muscle afferent feedback. The spinal blockade of feedback from group III-IV muscle afferents in hypertensive men induced a reduction in blood pressure during cycling, bringing blood pressure values to a similar level to that of normotensive men. Interestingly, by monitoring rating of perceived exertion (RPE) during cycling exercise with or without feedback from group III-IV muscle afferents, the authors also significantly contributed to increase the knowledge on the neurophysiology of perceived exertion. Namely, the authors reported that RPE was similar in hypertensive subjects with or without pharmacological blockade of muscle afferents (see p.719, paragraph "Responses to cycling").

Perceived exertion, also known as perception of effort or sense of effort, is defined as "*the conscious sensation of how hard, heavy and strenuous a physical task is*" (de Morree & Marcora, 2015). This perception: i) provides information on the intensity of the exercise, ii) is well used by clinicians to prescribe and monitor exercise during a rehabilitation program, iii) strongly influences the self-regulation of human behaviour and iv) is one of the main features of fatigue experienced by pathological populations. Despite its importance for researchers and clinicians, to date, no consensus exists on the sensory signal(s) generating perceived exertion. It is well accepted that the corollary discharge associated with the central motor command constitutes, in part at least, the sensory signal producing the perception of effort. However, there is an existing debate on the possibility that group III-IV muscle afferents could also contribute to the sensory signal involved in the generation of perception of effort.

As performed in the recent study of Barbosa *et al.* (2016), one of the strongest experimental manipulations that can be used to test the causal relation between group III-IV muscle afferents and perceived effort is the pharmacological blockade of muscle afferent feedback. Indeed, pharmacologically reducing the amount of muscle afferent feedback integrated by the central nervous system, while monitoring RPE during a physical task, provides a unique opportunity for testing the hypothesis that feedback from group III-IV muscle afferents generates perception of effort. Such experimental manipulation has previously been performed during static (Mitchell *et al.*, 1989; Smith *et al.*, 2003) and dynamic (Fernandes *et al.*, 1990; Smith *et al.*, 2003) exercises. However, as RPE was not the main outcome of these studies, the RPE results have not been thoroughly discussed. This Journal Club aims at putting the results of Barbosa *et al.* (2016) in perspective with those of other similar studies published in The Journal of Physiology (Mitchell *et al.*, 1989; Fernandes *et al.*, 1990; Smith *et al.*, 2003) to get a better insight into the neurophysiology of perceived exertion. Since perception of effort differs from perception of discomfort, pain and other exercise-related sensations, we discuss the RPE results of studies that did not explicitly associate discomfort and effort. In the studies cited below, authors used the 6-20 Borg scale to quantify "*the intensity of effort*" exerted during dynamic and static exercise.

Dynamic exercise. Similarly to Barbosa *et al.* (2016), other studies reported no effect of pharmacological blockade of muscle afferents on perceived exertion during dynamic exercises. Of particular interest is the study of Fernandes *et al.* (1990) demonstrating that epidural anaesthesia (i.e. using lidocaine) does not reduce perceived exertion during submaximal cycling at a fixed workload corresponding to 57% of maximum oxygen uptake, but in contrast increased it (due to lidocaine-induced muscle weakness and compensatory increase in central motor command). Another key finding of this study is that at a given oxygen uptake, RPE was similar with or without epidural anaesthesia (see Fig.1A). The lack of effect of pharmacological blockade of muscle afferents on RPE during dynamic exercise has also been shown by Smith *et al.* (2003). In this study, the authors demonstrated that cycling during 7 min at 30% of maximal work rate with or without epidural anaesthesia does not influence perception of effort. Therefore, the aforementioned studies provide strong experimental evidence suggesting that removing feedback from group III-IV muscle afferents does not reduce perceived exertion during dynamic exercise.

Static exercise. In 1989, Mitchell *et al.* (1989) performed one-leg static contractions of the knee extensors with or without epidural anaesthesia (i.e. using lidocaine). Due to lidocaine-induced muscle weakness, the effort required to produce the same absolute force was higher after epidural anaesthesia. As explained by the authors, muscle weakness induced by lidocaine injection leads the subjects to produce a greater central motor command to maintain the same absolute force, consequently increasing perceived exertion. Interestingly, when the reduction in force production capacity was taken into account and subjects were asked to produce the same relative force (i.e. same central motor command), subjects perceived the same effort with or without feedback from group III-IV muscle afferents. In 2003, Smith *et al.* (2003) also found that subjects reported the same RPE during static contraction of the dominant leg performed with or without epidural anaesthesia (Fig 1B). Similarly to dynamic exercises, it seems that removing feedback from group III-IV muscle afferents does not reduce perceived exertion during static exercise.

PLEASE INSERT FIGURE 1 HERE

By integrating experimental evidence gathered during dynamic and static exercises, the present Journal Club highlights that pharmacological blockade of muscle afferents does not alter perceived exertion. Therefore, these results support the hypothesis that perceived exertion is generated by central processing of the corollary discharge (associated to the central motor command), and not by feedback from group III-IV muscle afferents. However, it is important to note that even if feedback from group III-IV muscle afferents does not generate perceived exertion (i.e. is not the sensory signal), this feedback may still indirectly impact perceived exertion via its complex interaction with motor control and cardiovascular responses to the exercise. This is indeed supported by the contrasted results of two experimental studies investigating the impact of epidural anaesthesia (i.e. using fentanyl) on endurance performance in competitive cyclists (Amann *et al.*, 2009; Amann *et al.*, 2011). In these studies, pharmacological blockade of muscle afferent feedback led to increased central motor drive (measured with EMG) that induced an exacerbated power output that would otherwise be chosen by the subject (when performance was measured during self-paced exercise; Amann *et al.*, 2009), itself leading to a faster O_2 consumption by the working muscles and to a 21% performance decrement (time to exhaustion at 80% of peak power output; Amann *et al.*, 2011) or no change in performance (5 Km time trial; Amann *et al.*, 2009).

Current theories in motor control propose that afferent feedback is continuously monitored and integrated by the central nervous system so as to optimize the planning and control of voluntary movements. Notably, echoing humans' well-known laziness, computational studies emphasize the importance of effort-related optimization processes as a guiding principle tailoring the production of motor patterns (Selinger *et al.*, 2015). For example, by perturbing legs biomechanics of walking subjects, Selinger *et al.* (2015) recently showed that humans continuously adjust stepping frequency in such a way that some effort-related criterion is minimized. Also, not only the tailoring of motor patterns but also whether or not one would engage in physical exercise is thought to be under the influence of effort-related central processes. As voluntary movements are inherently costly, it has been proposed that decision-making (i.e. the process of choosing between different options) relies on a cost-benefit comparison from which the option that entails the best trade-off is chosen over the others. A newly published study suggests that obese people, compared to lean people, may be characterized by an abnormal cost-benefit decision-making that under-values the reward obtained from the engagement in physical exercise (Mathar *et al.*, 2016). Unexpectedly, Mathar *et al.* (2016) demonstrated that obese individuals, compared to lean individuals, are less willing to engage in physical effort to obtain high caloric sweet snack food rewards.

Given the outstanding societal challenge of inciting people to engage in physical activity (for primary to tertiary disease prevention), the important role of effort-related central processes in human volition warrants the absolute need for a fine understanding of the complex neurophysiological mechanisms underlying perception of effort. Studies using pharmacological blockade of muscle afferent feedback present strong interests for this matter.

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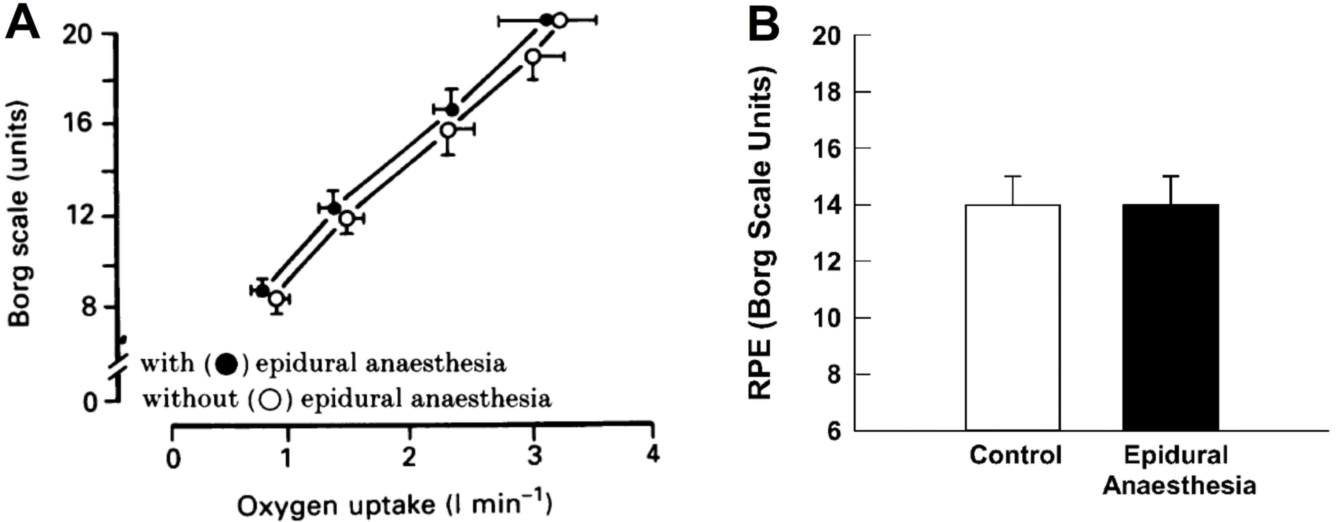
FIGURE

Effect of pharmacological blockade of muscle afferents on rating of perceived exertion (RPE) during dynamic (panel A, adapted from Fernandes *et al.*, 1990) and static (panel B, adapted from Smith *et al.*, 2003) exercise.


A
Borg scale (units)
20
16
12
8
0
with (●) epidural anaesthesia
without (○) epidural anaesthesia
0
1
2
3
4
Oxygen uptake (l min−1)
B
RPE (Borg Scale Units)
20
18
16
14
12
10
8
6
Control
Epidural
Anaesthesia