Aspects of Respiratory Muscle Fatigue in a Mountain Ultramarathon Race

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ABSTRACT

WÜTHRICH, T. U., J. MARTY, H. KERHERVE, G. Y. MILLET, S. VERGES, and C. M. SPENGLER. Aspects of Respiratory Muscle Fatigue in a Mountain Ultramarathon Race. *Med. Sci. Sports Exerc.*, Vol. 47, No. 3, pp. 519–527, 2015. **Purpose**: Ultramarathon running offers a unique possibility to investigate the mechanisms contributing to the limitation of endurance performance. Investigations of locomotor muscle fatigue show that central fatigue is a major contributor to the loss of strength in the lower limbs after an ultramarathon. In addition, respiratory muscle fatigue is known to limit exercise performance, but only limited data are available on changes in respiratory muscle function after ultramarathon running and it is not known whether the observed impairment is caused by peripheral and/or central fatigue. **Methods**: In 22 experienced ultra-trail runners, we assessed respiratory muscle strength, i.e., maximal voluntary inspiratory and expiratory pressures, mouth twitch pressure (n = 16), and voluntary activation (n = 16) using cervical magnetic stimulation, lung function, and maximal voluntary ventilation before and after a 110-km mountain ultramarathon with 5862 m of positive elevation gain. **Results**: Both maximal voluntary inspiratory (−16% ± 13%) and expiratory pressures (−21% ± 14%) were significantly reduced after the race. Fatigue of inspiratory muscles likely resulted from substantial peripheral fatigue (reduction in mouth twitch pressure, −19% ± 15%; $P < 0.01$), as voluntary activation (−3% ± 6%, $P = 0.09$) only tended to be decreased, suggesting negligible or only mild levels of central fatigue. Forced vital capacity remained unchanged, whereas forced expiratory volume in 1 s, peak inspiratory and expiratory flow rates, and maximal voluntary ventilation were significantly reduced ($P < 0.05$). **Conclusions**: Ultraendurance running reduces respiratory muscle strength for inspiratory muscles shown to result from significant peripheral muscle fatigue with only little contribution of central fatigue. This is in contrast to findings in locomotor muscles. Whether this difference between muscle groups results from inherent neuromuscular differences, their specific pattern of loading or other reasons remain to be clarified.
Key Words: MOUTH TWITCH PRESSURE, ULTRAENDURANCE, RUNNING, POSTURE, CERVICAL MAGNETIC STIMULATION

Since the 1970s, ultraendurance events have become increasingly popular in the Western world (15). Such events provide the unique possibility to study physiology when the human body is pushed toward its limits (25). Several studies have investigated different phenomena associated with ultraendurance-type competitions such as the occurrence of neuromuscular fatigue of the locomotor system (e.g., (27)). However, the pulmonary system and particularly the respiratory muscles have not yet been conclusively investigated in this type of competition. So far, only three studies assessed changes in either lung function (22,39) or respiratory muscle strength (19,39) after ultraendurance running ranging from 80 to 154 km, but results are conflicting. Warren et al. (39) reported no change in both forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) after a 24-h race, and Mahler and Loke (22) reported significant reductions in FVC (−12%) and FEV_1 (−10%) after an 81-km ultramarathon competition; neither of them found significant changes in maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) after these races. This may have two reasons, as follows: Warren et al. (39) reported large interindividual variability in the reduction of MIP and MEP pressure (0% to −37%) in a small number of subjects (n = 10), whereas Ker and Schultz (19) performed the after-race measurements not immediately but 3 d after the race. Interestingly, despite three days of recovery, these authors measured 27% reduction in time to exhaustion in a respiratory muscle endurance test. After marathon running (i.e., 42.2 km), MIP was significantly decreased by 15%–25% (6,21,31) whereas MEP was found to be decreased by 28% (21). Given the task-specific nature of fatigue (9), the extent to which respiratory muscle fatigue occurs during ultramarathon running remains to be clarified.

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Neuromuscular fatigue is defined as "… a condition in which there is a loss in the capacity for developing force and/or velocity of a muscle, resulting from muscle activity under load and which is reversible by rest" (28). Importantly, fatigue can occur at different levels, from the brain to the skeletal muscles (11). None of the existing studies in both ultraendurance events and marathon running performed measurements to distinguish between central and peripheral mechanisms of respiratory muscle fatigue, i.e., measurements of muscle contractility during nerve or muscle stimulation. Interestingly, assessments in exercise challenges of shorter duration showed that peripheral changes in respiratory muscle contractility are usually substantially greater than changes observed in voluntary maneuvers such as MIP and MEP (17), which are, in fact, similar to observations in locomotor muscles (26). Given that substantial levels of central fatigue have been reported for locomotor muscles after ultraendurance running (27), some of the reduction in maximal voluntary respiratory muscle strength assessed with voluntary maneuvers may also be attributed to central fatigue, i.e., reduction in maximal drive to the contracting muscles. In fact, peripheral respiratory muscle fatigue has traditionally been associated with high levels of ventilation observed during intense exercise (17). Additional loads are placed upon respiratory muscles in ultramarathon running apart from ventilation, which could impair respiratory muscle contractility as well, one of them being the postural demand (12). Moreover, it has been suggested that an increase in inflammatory mediators (e.g., tumor necrosis factor α) may also alter muscle contractility (40) and/or the capacity to produce maximal muscle force (27). Thus, the contribution of peripheral and central mechanisms to respiratory muscle fatigue after an ultraendurance run remains to be clarified.

To determine the development of respiratory muscle fatigue, both maximal inspiratory and expiratory muscle strength were assessed by volitional MIP and MEP maneuvers before and after a mountain ultramarathon (110 km). For inspiratory muscles, we also assessed mouth twitch pressure ($P_{m,tw}$) in response to cervical magnetic stimulation to better understand the origin of potential loss in volitional muscle strength after the race. In addition, we determined changes in lung function to account for potential changes in lung volume that would affect measures of respiratory muscle strength and to add to the sparse data available on the effect of ultramarathon running on pulmonary function. We hypothesized that inspiratory muscle fatigue would develop during the ultramarathon because of both central and peripheral mechanisms, measured by reductions in $P_{m,tw}$, in volitional respiratory muscle strength and activation and in flow-dependent variables of lung function measures.

METHODS

Participants and Ethical Statement

Thirty-five runners were initially recruited for the present study. Twelve runners either did not finish the race (n = 6) or could not perform post-race measurements (n = 6) for different reasons such as excessive coughing, dizziness, or general uneasiness. The remaining 23 participants (eight women) had normal lung function and respiratory muscle strength (Table 1). All participants were experienced ultramarathon runners, which was a requirement for participation in the competition supporting this study (North-Face® Ultra-Trail du Mont Blanc® 2012).

All participants were fully informed about the procedures and risks involved in this study and that they could withdraw from the study at will at any time. Each participant gave his/her written informed consent. The study was approved by the local ethics committee (Comité de Protection des Personnes Sud-Est 1, France) and was performed according to the Declaration of Helsinki.

Experimental Overview

Each participant visited the laboratory three times. During the first visit, which was scheduled 3–4 wk before the competition, participants performed an incremental test and were introduced to the experimental procedures (for details, see the following section). The second visit (before race) took place within the 3 d before the race and included baseline measurements of respiratory muscle strength and lung function (for details, see the following section). The third visit (after race) took place 1.4 ± 0.4 h after completion of the race, and procedures were identical to those of the pre-race assessment. The 2012 edition of the competition supporting this study was shortened to 110 km (instead of 167 km) because of bad weather conditions (rain and snow), and it included a total positive elevation gain of 5862 m. The maximal temperature during the race was 12°C in Chamonix (1459 m above sea level) and dropped below 0°C at altitudes above 1800 m.

First visit. After medical examination, participants performed an exhaustive incremental test on a treadmill (EF1800; HEF Tecmachine, Andrézieux-Bouthéon, France), with a 10% grade to determine maximal oxygen consumption. The protocol started at 4–6 $km \cdot h^{-1}$ depending on running ability of the participant and was then increased by 1 $km \cdot h^{-1}$ every 2.5 min. At the end of each stage, participants were stopped for 30 s for blood sampling to assess blood lactate concentration. Ventilation and gas exchange were obtained breath by breath using a metabolic cart (Ergocard; Medisoft, Sorinnes, Belgium) and were averaged over 30-s intervals. Maximal oxygen consumption was defined as the fulfillment of at least three of the four following criteria during the last 30 s before reaching exhaustion: 1) no further increase in oxygen uptake with increasing workload,

TABLE 1. Subjects characteristics.

Age (yr)	42.9 ± 9.4	MIP (%pred)	125 ± 26
Height (m)	1.72 ± 9.0	MEP (%pred)	161 ± 28
Body mass (kg)	67.0 ± 9.4	FVC (%pred)	92 ± 9
$\dot{V}O_{2max}$ ($mL \cdot min^{-1} \cdot kg^{-1}$)	57.2 ± 6.1	FEV_1 (%pred)	103 ± 11
MVV (%pred)	114 ± 32	PEF (%pred)	104 ± 12

Values are mean ± SD.
%pred, percent of predicted value; $\dot{V}O_{2max}$, maximal oxygen consumption.

2) RER > 1.1, 3) achievement of the age-predicted HR_{max} within 10 bpm, and 4) blood lactate concentration > 8 mM. All subjects met this requirement.

Second (before) and third (after) visit. The second and third visits were conducted at a laboratory near the finishing area of the race. On the second visit, all participants were first thoroughly familiarized with the assessment of respiratory muscle strength and lung function. Thereafter, participants performed all measurements in the following order: cervical magnetic stimulation protocol, assessment of MIP and MEP, and lung function (details are in the following section). On the third visit, measurements were repeated in the same order.

Assessment of Respiratory Muscle Contractility

Volitional respiratory muscle strength. MIP (from residual volume) and MEP (from total lung capacity) were measured using a handheld mouth pressure meter (Micro RPM; Micro Medical Ltd., Rochester, United Kingdom) to obtain volitional maximal inspiratory and expiratory strength. Participants performed a minimum of three maneuvers or until values did not improve anymore. The larger of the two maximal values that did not differ by more than 5% was selected as the maximum. Percent predicted values were calculated according to reference values (41).

Nonvolitional inspiratory muscle strength. Phrenic nerves were stimulated on the back of the flexed neck between the sixth and seventh cervical vertebra to induce muscle twitches. Cervical magnetic stimulation was performed using a MagStim 200 stimulator (max. 2 T, 1-ms rectangular pulses; MagStim, Whitland, United Kingdom) equipped with a 90-mm circular coil. During all stimulations, participants were comfortably seated on a chair, breathing through a mouthpiece connected to a heated pneumotachograph (MLT3813H-V; Hans Rudolph Inc., Shawnee, KS) that was attached to a differential pressure transducer (FE141; ADInstruments, Bella Vista, Australia) to measure respiratory flow. The measurement system also included a shutter for short airway occlusions during stimulations (Zan, Oberthulba, Germany). Before each stimulation, participants were instructed to passively expire to functional residual capacity (FRC). As soon as the point of zero flow was reached (i.e., FRC), the shutter closed and subjects were instructed to gently inspire until mouth pressure (P_m) reached -5 cm H_2O, which triggered the release of the stimulation (18). FRC was obtained during a 2-min resting period before the start of the cervical magnetic stimulation protocol. End-expiratory lung volume at FRC was placed within vital capacity maneuvers to compare between measurements before and after the race. The pressure response of each muscle twitch was obtained at the mouth (i.e., $P_{m,tw}$) using a calibrated pressure transducer (DPT-100; Utah Medical Products Ltd., Athlone, Republic of Ireland). Figure 1 shows pressure, flow, and volume traces for a single stimulation in a representative subject before and after the race.

The cervical magnetic stimulation protocol consisted of nine potentiated $P_{m,tw}$ responses at 100% of the stimulator output. Special care was taken to ensure that inspiratory muscles were in a fully potentiated state. Potentiated muscle twitches were evoked, as they are known to be more sensitive to changes occurring within a fatigued muscle (20). $P_{m,tw}$ responses were assessed after 3–4 submaximal and three maximal inspiratory efforts at FRC against a closed airway, maximal efforts lasting for 5 s. After the third and sixth stimulations, another 5-s maximal inspiratory effort followed to maintain the potentiated state. Moreover, during the third, fourth, and fifth maximal inspiratory effort, a single stimulation was superimposed onto the maximal inspiratory effort. The ratio between the superimposed twitch amplitude and that of the following $P_{m,tw}$ was used to calculate the maximal voluntary activation (VA) as follows:

$$\mathrm{VA}(\%) = 1 - A \times \frac{\text{superimposed twitch amplitude}}{\text{amplitude of } P_{m,tw}} \times 100$$

A correction term A was included to correct for superimposed stimulation, which was not delivered at the highest volitionally achieved P_m.

$$A = \frac{\text{volitional } P_m \text{ just before superimposed twitch}}{\text{highest volitional } P_m \text{ during maneuver}}$$

To ensure supramaximal stimulation of the phrenic nerves, three additional twitches were performed at 98% and 94% of the stimulator output (each group of three stimulations was preceded by a 5-s maximal inspiratory effort). Because of time restrictions, this was only done in the fatigued state after the race (see Discussion). A near plateau in $P_{m,tw}$ was observed in every participant, and no statistically significant difference was found between 98% and 100% of the stimulator output ($P = 0.57$), thereby indicating maximal recruitment of all motor nerves (see Discussion). This is similar to previous reports using the same protocol to test for supramaximal stimulation in our laboratory (37).

For $P_{m,tw}$, the average amplitude (baseline to peak) of 3–9 potentiated twitches as well as contraction time (i.e., duration from stimulation to the peak of $P_{m,tw}$) and the maximal rate of pressure development (i.e., the largest incline of the $P_{m,tw}$ response) were calculated. A twitch was rejected *post hoc* if the end-expiratory lung volume deviated from FRC by more than ±5% of vital capacity.

Assessment of Lung Function

Lung function was assessed according to current American Thoracic Society/European Respiratory Society guidelines (2) using a metabolic cart with a calibrated volume sensor (Quark b2; COSMED, Rome, Italy). Percent predicted values of lung function were calculated according to reference values (30).

Data Analysis and Statistics

For before-and-after race comparison, paired *t*-tests were conducted after analyzing for normal distribution (Shapiro–Wilk test). For data without normal distribution, a Wilcoxon signed rank test was applied. Statistical analyses were performed with

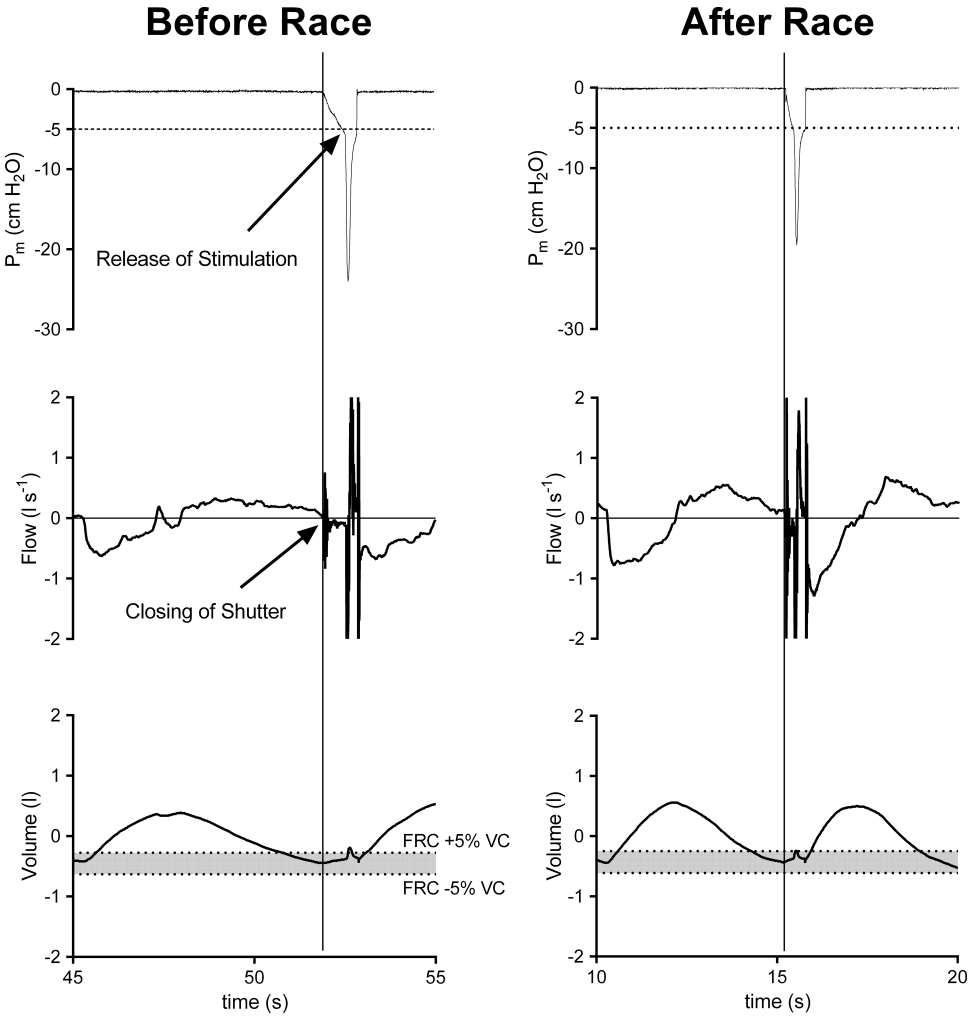

FIGURE 1—Raw data recordings of a representative subject showing pressure, flow, and volume during a single cervical magnetic stimulation obtained before and after the race. VC, vital capacity.

SPSS Statistics 19 (IBM Company, New York, NY). All data are shown as mean ± SD. The level of significance was set at $P < 0.05$ for all statistical comparisons.

RESULTS

Ultramarathon performance. Approximately 2500 runners participated, and 85% successfully finished the race (83% of the study participants finished). The average time to complete the race for participants in the present study was 20.1 ± 3.4 h (range, 13.8–25.8 h), resulting in an average velocity of 5.3 ± 0.9 km·h^{-1}. All participants were able to cover the final kilometer of the race (over a flat portion of the track) at a much higher pace (average, 12.1 ± 1.7 km·h^{-1}; range, 9.8–16.8 km·h^{-1}) than their respective average velocity.

Respiratory muscle strength. Average and individual changes in MIP, MEP, $P_{m,tw}$, and VA are displayed in Figure 2. One participant did not perform any respiratory strength measurement, three participants only performed volitional strength measurements (MIP and MEP), and three participants $P_{m,tw}$ could not be assessed appropriately after the race because of technical problems; thus, the number of participants varies slightly among parameters. Both MIP and MEP were significantly reduced ($P < 0.01$, $n = 22$) after the race, along with significant decrease in $P_{m,tw}$ ($P < 0.01$, $n = 16$) and a tendency for VA to be reduced ($P = 0.09$, $n = 16$). Twitch contraction time before (96 ± 13 ms) and after (94 ± 8 ms) remained unchanged ($P = 0.35$, $n = 16$), whereas maximal rate of pressure development after the race (578 ± 195 cm $H_2O \cdot s^{-1}$) was significantly lower than that before the race (702 ± 185 cm $H_2O \cdot s^{-1}$, $P < 0.01$, $n = 16$).

End-expiratory lung volume before cervical magnetic stimulation did not differ between measurements before and after the race, with an average change of 0.017 ± 0.075 mL ($P = 0.39$), corresponding to 0.5% ± 1.6% of FRC. The average within-session coefficient of variation (CV) for $P_{m,tw}$ was 7.1% ± 3.6%.

Lung function. Absolute values and relative changes in lung function parameters and maximal voluntary ventilation (MVV) are given in Table 2. One participant could not perform lung function measurements after the race because

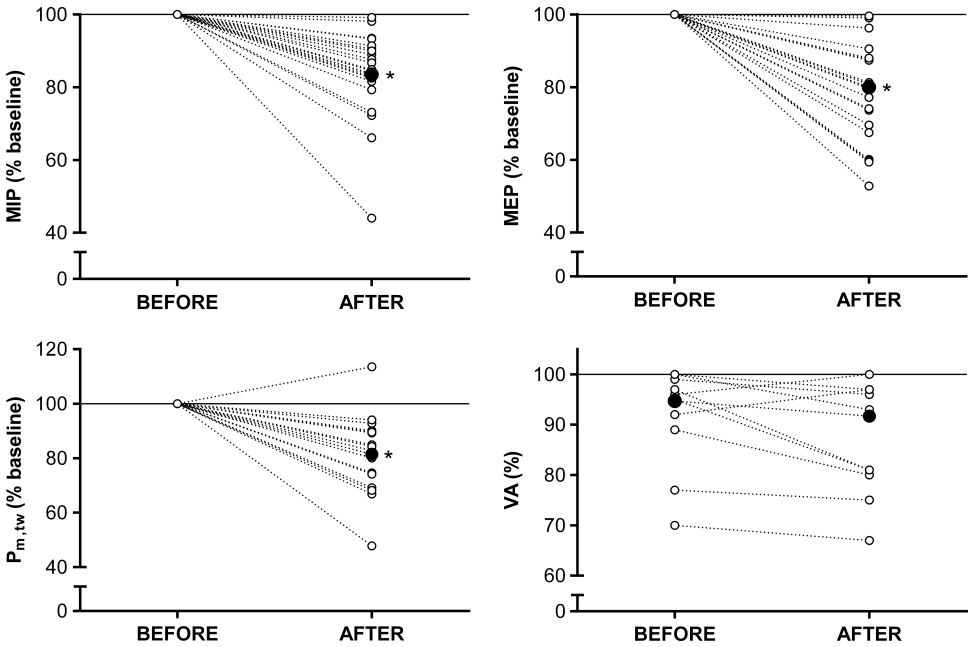

FIGURE 2—Individual changes in $P_{m,tw}$ (n = 16), volitional MIP (n = 22), MEP (n = 22), and VA (n = 16) from before (set at 100%) to after the race. *Open circles* represent individual data, whereas *closed circles* depict average values. *Significantly different from values before the race, $P < 0.01$.

of airway irritation. Apart from FVC, all lung function parameters were significantly reduced after the race ($P < 0.05$, n = 22). Reductions in variables of respiratory muscle strength and reductions in peak inspiratory flow (PIF), peak expiratory flow (PEF), and MVV were not correlated.

DISCUSSION

The main purpose of the present study was to investigate whether inspiratory and/or expiratory muscle fatigue would develop during an ultraendurance running competition and, if so, to what extent peripheral *versus* central mechanisms contribute to the loss of volitional strength. We found 1) that significant inspiratory and expiratory muscle fatigue developed as indicated by substantial reductions in MIP (−19%) and MEP (−21%), 2) that peripheral inspiratory muscle fatigue, i.e., loss in muscle contractility, contributed significantly to the decrease in volitional inspiratory muscle strength, as shown by reduction in $P_{m,tw}$ (−19%) whereas voluntary muscle activation only tended to decrease (−3%), and 3) that all flow-dependent variables of lung function assessments were significantly reduced. The present study provides, for the first time, nonvolitional measurements of inspiratory muscle strength (using cervical magnetic stimulation) before and after an extreme endurance running event, thereby offering new insights into neuromuscular consequences for the respiratory system in such exercise.

Neuromuscular Fatigue Induced by an Ultramarathon Mountain Race

The significant reduction in voluntary respiratory muscle strength (assessed by MIP and MEP) found in the present study is in contrast to findings obtained elsewhere, reporting no systematic change in MIP and MEP after ultraendurance competitions (19,39). This discrepancy may be explained by either the prolonged time between the end of the competition and the measurements or by an insufficient sample size in previous studies. In fact, Warren et al. (39) reported nonsignificant MIP reduction, although seven of 10 participants had reduced values after the race. Similarly, they reported large variability in the MEP reduction after the race, which was likely the cause for the decrease in MEP not reaching the level of statistical significance. When comparing the present findings with those found after marathon running, similar reductions in maximal voluntary respiratory muscle strength were observed (i.e., 15%–25%), thereby confirming the presence of respiratory muscle fatigue after endurance competitions of low-to-moderate intensities (6,21,31). Interestingly, both MIP and MEP reductions seem to be substantially

TABLE 2. Lung function parameters.

	FVC (L)	FEV_1 (L)	PEF ($L \cdot s^{-1}$)	MEF50% ($L \cdot s^{-1}$)	PIF ($L \cdot s^{-1}$)	MVV ($L \cdot min^{-1}$)
Before race	4.22 ± 0.88	3.78 ± 0.75	8.60 ± 1.81	4.96 ± 1.26	6.33 ± 2.09	149 ± 32
After race	4.11 ± 0.84	3.49 ± 0.78*	7.41 ± 1.98*	4.26 ± 1.42*	5.20 ± 1.72*	132 ± 34*
Percent reduction	−1.8 ± 11.3	−7.3 ± 11.6	−13.8 ± 13.4	−14.0 ± 17.8	−16.8 ± 12.0	−16.8 ± 12.0

Values are mean ± SD (n = 22).
*Significantly different from values before the race, $P < 0.05$).
MEF50%, mid expiratory flow at 50% of FVC.

larger in the present study than reductions seen for short-duration high-intensity exercise that are reported to be about 10% or less (e.g., (23). These results suggest that similar to locomotor muscle fatigue, the relation between the loss of volitional respiratory muscle strength and the increase in exercise duration follows an asymptotic relation reaching a plateau for respiratory muscle fatigue during running exercises with the length of marathon or longer races (26).

To elucidate the origin of global inspiratory muscle fatigue, cervical magnetic stimulation was performed before the race and within 1 h after completion. Surprisingly, only minor changes in VA were found after the race (approximately 3%), which contradicts our original hypothesis. This suggests that the contribution of central fatigue to the observed reduction in MIP was small. Bellemare and Bigland-Ritchie (3) were the first to introduce VA to estimate central components of diaphragm fatigue, and de Bruin et al. (8) confirmed that this technique may also be valid when applied to superimposed $P_{m,tw}$, similar to those applied in the present study. Bellemare and Bigland-Ritchie (4) also showed that central fatigue can occur in the diaphragm, as indicated by substantial reduction in VA after resistive breathing to exhaustion. However, they only investigated five individuals in that study and resistive breathing does not represent the load that inspiratory muscles are exposed to during exercise hyperpnoea. Therefore, direct comparison with our results seems difficult. To the best of our knowledge, no study has yet distinguished between central and peripheral components of inspiratory muscle fatigue after competitive endurance events. Using the superimposed twitch technique, the present data suggest that even after an ultraendurance race, respiratory muscle activation is well preserved. This is in contrast to previous results indicating substantial central fatigue in locomotor muscles (27,35). When comparing mechanisms of respiratory muscle fatigue in the present study with locomotor muscle fatigue in these latter studies, a potential difference in recovery time needs to be considered. In fact, Millet et al. (27) obtained knee extensor muscle strength approximately 20 min after the race whereas Temesi et al. (35) reassessed their subjects approximately 1 h after crossing the finishing line. Despite this difference in the period of potential recovery, both authors reported an average 19% reduction in VA, which may suggest that recovery of central fatigue is rather slow. In the present study, post-race measurements were performed approximately 1.4 h after the end of the competition on average, with no significant reduction in VA. Although this adds 24 min of recovery compared with that in the study of Temesi et al. (35), it seems reasonable to suggest that central fatigue of respiratory muscles was likely not much greater immediately after the race given that the recovery rate of respiratory muscles is similar to that of locomotor muscles. This is further supported by the fact that, in the present study, the reduction in VA did not correlate with the duration of recovery (data not shown). Therefore, other explanations should be considered for the different mechanisms of fatigue found in respiratory and locomotor muscles after ultramarathon competitions. These differences could be related to the load imposed on respiratory and locomotor muscles or differences regarding their intrinsic properties. This, and the level of central fatigue contributing to the post-race loss in MEP, remains to be investigated. As opposed to central fatigue, a significant amount of peripheral inspiratory muscle fatigue was observed, as highlighted by 19% reduction in $P_{m,tw}$. In 10 of 16 participants (i.e., 63%), a relevant amount of fatigue was detected, which was defined as $P_{m,tw}$ reduction exceeding 15%, i.e., 2 times the average within-session CV. This corresponds well to the prevalence of inspiratory muscle fatigue (approximately 72%) assessed by artificially induced twitch pressures after high-intensity exercise in our and other laboratories (17,34). Whether expiratory muscle fatigue also occurs at or distal to the neuromuscular junction remains to be investigated because we have not yet established a noninvasive measure of peripheral expiratory muscle fatigue, i.e., without using gastric balloon catheters. Therefore, we could not distinguish between peripheral and central expiratory fatigue in the present study. However, because both the muscles of inspiration and expiration share similar tasks during exercise, e.g., breathing and trunk stabilization, one could speculate that similar mechanisms were involved in the development of both inspiratory and expiratory muscle fatigue. This, however, remains to be tested.

Peripheral fatigue may either originate from reduced excitability (i.e., decrease in action potential propagation and/or transmission) or changes within the excitation–contraction coupling mechanism. Although not assessed in this study, the former is unlikely because altered M-wave characteristics have not been reported for fatigued inspiratory muscles in our or in other laboratories (17,37). Thus, it seems likely that peripheral fatigue measured approximately 1 h after the race was mostly due to impaired excitation–contraction coupling mechanisms (1). These cellular processes can be influenced by different metabolic factors, of which reduced muscle glycogen seems to be most relevant in light of the character of the race and the elapsed time until after-race measurements could be performed (29). This is based on animal studies showing that glycogen content in the diaphragm was substantially reduced after endurance-type exercise, which persisted for several hours (13). The cause of these changes in the intramuscular milieu is likely to be multifactorial. First, the level of ventilation itself needs to be considered. In fact, the average running velocity during the race was 5.3 $km \cdot h^{-1}$, suggesting rather modest levels of ventilation. However, short intervals of higher metabolic demand such as during steep inclines or during the final sprint possibly increased ventilation to levels known to affect respiratory contractility (e.g., (17)). In a population of trained runners, for instance, walking at 5 $km \cdot h^{-1}$ with 16% grade was accompanied by a ventilation of approximately 60 $L \cdot min^{-1}$ in normoxia, corresponding to the level of ventilation during running at approximately 11 $km \cdot h^{-1}$ (5).

On average, participants ran the final kilometer at 12 $km \cdot h^{-1}$ (range, 9.8–16.8 $km \cdot h^{-1}$), and in several stages of the race, they were exposed to moderate hypoxic conditions, which can both contribute to higher levels of ventilation and the development of respiratory muscle fatigue (36). Yet, we did not find any correlation of the velocity during the final kilometer and the reduction in $P_{m,tw}$.

An alternative explanation apart from ventilation may be found in the increased postural demand placed upon respiratory muscles during uphill and downhill running on uneven surfaces, such as that encountered during a mountain ultramarathon. Several lines of evidence exist suggesting that the diaphragm—for instance—is strongly involved in the stabilization of the trunk (12). Lastly, inflammatory agents could also affect muscle contractility and activation (40). Ultramarathons were shown to trigger a very pronounced systemic inflammatory response, which could then have detrimental effects on muscle contractility (27).

Changes in Lung Function after Ultramarathon Running

Only two studies have assessed the changes in lung function immediately after ultramarathon competitions, and results are conflicting. FVC was not altered in the present study, which is in line with the study of Warren et al. (39), whereas Mahler and Loke (22) found a 12% reduction after an 80- to 100-km race of markedly shorter duration (i.e., approximately 6–10 h) than that in the present study and, thus, higher exercise intensity. In the present study, FEV_1 (−7%), PEF (−14%), mid-expiratory flow at 50% of FVC (−14%), PIF (−17%), and MVV (−14%) all significantly decreased, which is mostly in line with previous findings (22,39).

Because of the nature of lung function assessment using volitional maneuvers, fatigue *per se* could have contributed to reductions in flow-dependent measures. However, none of the changes in MIP, MEP, and $P_{m,tw}$ correlated with changes in flow-dependent variables of lung function. However, the missing direct link between muscle fatigue and lung function reductions in this study should be interpreted with caution because static measures such as MIP and MEP (placed at one end of the muscle force–velocity curve) do not include changes in the potential to produce high shortening velocities as present during all flow-dependent maneuvers. The present data show, in fact, that the maximal rate of force development of the inspiratory muscles was significantly reduced. Thus, part of the reductions in dynamic lung function variables may well be associated with muscular fatigue *per se*.

Additionally or alternatively, impairment of lung function may also be influenced by other factors such as peripheral airway constriction and/or peribronchial edema. However, only reductions in FEV_1 greater than 10% are indicative of peripheral airway constriction (7), which was observed in only four of 18 participants in the present study (average, −7%), thus rendering this pathophysiology unlikely in the present study. Peribronchial edema, on the other hand, may have been present, as Miles et al. (24) showed that despite unchanged FVC, a mild transient subclinical edema was likely to be present after a marathon race, indicated by substantial reduction in pulmonary diffusing capacity that was, unfortunately, not assessed here. Thus, further investigations including techniques independent from the participant's effort are required to gain deeper insights into the potential presence of peripheral airway constriction and/or peribronchial edema in ultramarathon running.

Implications of Respiratory Muscle Fatigue for (Mountain) Ultramarathon Races

The observed reductions in $P_{m,tw}$ induced by cervical magnetic stimulation are likely to represent global inspiratory muscle fatigue rather than isolated diaphragm fatigue (32). In turn, global inspiratory muscle fatigue in healthy individuals has recently been shown to affect postural control by inducing a shift to a more rigid control strategy involving mainly the ankles, which is associated with decreased stability (16). Taking into account the massive reduction in calf muscle and quadriceps muscle strength after a similar ultramarathon race (27,38), it is tempting to speculate that with the occurrence of both respiratory and leg muscle fatigue, runners might be exposed to elevated risk of fall and injury especially when running on challenging undergrounds as present in mountain marathon races. This hypothesis, however, needs further investigation.

Methodological Considerations

Variation in respiratory muscle strength and lung function. The reproducibility of $P_{m,tw}$ measurements is a crucial element to the outcome of this study. Because of the study design, only within-session CV (on average, 7.1%) but not between-day CV could be assessed. However, unpublished data from our laboratory estimated between-day CV for $P_{m,tw}$ to be approximately 7.0%. Therefore, we are confident that the chosen 15% threshold (i.e., twofold CV) to detect a physiologically relevant reduction in $P_{m,tw}$ indicates true alterations in muscle contractility.

A factor contributing to this variability could reside in changes of lung volume at the time of stimulation, as it was shown that lung volume can substantially affect twitch pressure amplitude (14). However, end-expiratory lung volume was tightly controlled in the present study via continuous monitoring of the volume channel, thereby ensuring that the same lung volume was reached before each stimulation. If lung volume before stimulation deviated by more than ±5% from FRC, data were excluded *post hoc*. From before to after the race, lung volume before stimulation only changed by 0.02 L (range, −0.09 to 0.14 L), corresponding to 0.5% (range, −1.5% to 3.8%) on average. Using the equation provided by Hamnegård et al. (14), we would expect alterations in the twitch amplitude of −1 to +3%. Hence, we believe that differences in lung volume did not affect the outcome of the present study.

Moreover, circadian effects could theoretically have biased our findings because Fregonezi et al. (10) have shown differences of up to 3% for MIP and 10% for MEP between morning and afternoon measurements. After-race measurements of the present study were performed as soon as the race was finished, irrespective of the time of the day relative to the baseline measurements. However, after-race reductions in respiratory muscle strength here clearly outmatch reported diurnal variations. Theoretically, sleep deprivation could also contribute to reduction in respiratory muscle strength, but observations after a 20-h race do not speak in favor of such an effect (34). In addition, for lung function parameters, potential confounding effects of measurements at different times in the circadian rhythm and the presence of sleep deprivation should be considered as potential confounders. However, as for respiratory muscle strength, the differences in lung function variables exceeded the reported effects of the circadian rhythm and sleep deprivation (33).

CONCLUSIONS

From the present findings, we conclude that 1) both inspiratory and expiratory muscle fatigue occur after a mountain ultramarathon and that 2) inspiratory muscle fatigue mostly results from peripheral changes while central mechanisms seem to be of much less importance. The latter is in contrast to existing data on locomotor muscle fatigue and suggests distinctly different profiles of neuromuscular fatigue between locomotor and respiratory muscles after an ultraendurance event. Further investigations should be performed to clarify the role of peripheral and central mechanisms in the development of inspiratory and expiratory muscle fatigue and their potential link with altered postural control and performance during these types of competition.

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Samuel Verges and Christina M. Spengler contributed equally to this study.

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